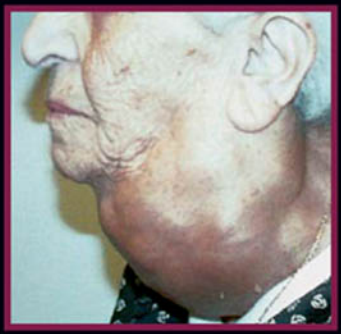
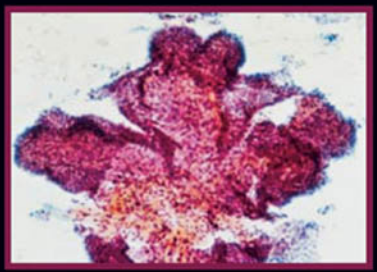
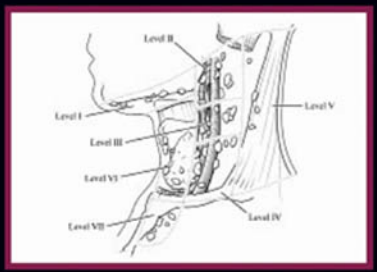
Endocrine Tumors







CLARK
DUH
PERRIER
JAHAN

American Cancer Society®

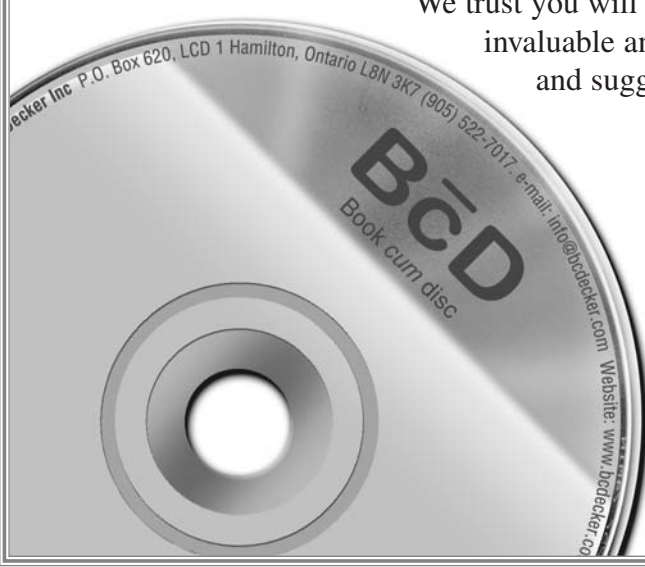
Every Decker book is accompanied by a CD-ROM.

The disc appears in the front of each copy, in its own sealed jacket. Affixed to the front of the book is a distinctive BcD sticker **"Book *cum* disc."**

The disc contains the complete text and illustrations of the book, in fully searchable PDF files. The book and disc are sold *only* as a package; neither are available independently, and no prices are available for the items individually.

BC Decker Inc is committed to providing high-quality electronic publications that complement traditional information and learning methods.

We trust you will find the book/CD package invaluable and invite your comments and suggestions.



Brian C. Decker
CEO and Publisher

American Cancer Society

Atlas of Clinical Oncology

Published

Blumgart, Fong, Jarnagin	*Hepatobiliary Cancer (2001)*
Cameron	*Pancreatic Cancer (2001)*
Carroll, Grossfeld	*Prostate Cancer (2002)*
Char	*Tumors of the Eye and Ocular Adnexa (2001)*
Clark, Duh, Jahan, Perrier	*Endocrine Tumors (2003)*
Eifel, Levenback	*Cancer of the Female Lower Genital Tract (2001)*
Ginsberg	*Lung Cancer (2002)*
Grossbard	*Malignant Lymphomas (2001)*
Ozols	*Ovarian Cancer (2003)*
Pollock	*Soft Tissue Sarcomas (2001)*
Posner, Vokes, Weichselbaum	*Cancer of the Upper Gastrointestinal Tract (2001)*
Prados	*Brain Cancer (2001)*
Shah	*Cancer of the Head and Neck (2001)*
Silverman	*Oral Cancer (1998)*
Silverman	*Oral Cancer, 5th Edition (2003)*
Wiernik	*Adult Leukemias (2001)*
Willett	*Cancer of Lower Gastrointestinal Tract (2001)*
Winchester, Winchester	*Breast Cancer (2000)*

Forthcoming

Droller	*Urothelial Tumors (2003)*
Fuller, Seiden, Young	*Uterine and Endometrial Cancer (2003)*
Raghavan	*Germ Cell Tumors (2003)*
Richie, Steele	*Kidney Tumors (2004)*
Volberding	*Viral and Immunological Malignancies (2004)*
Yasko	*Bone Tumors (2004)*

American Cancer Society

Atlas of Clinical Oncology

Editors

Glenn D. Steele Jr, MD
Geisinger Health System

Theodore L. Phillips, MD
University of California

Bruce A. Chabner, MD
Harvard Medical School

Managing Editor

Ted S. Gansler, MD, MBA
Director of Health Content, American Cancer Society

American Cancer Society

Atlas of Clinical Oncology

Endocrine Tumors

Orlo H. Clark, MD
Vice-Chairman, Department of Surgery
Chief, Department of Surgery
University of California, San Francisco
Mt. Zion Medical Center
San Francisco, California

Quan-Yang Duh, MD
Professor, Department of Surgery
University of California, San Francisco
Veterans Affairs Medical Center
San Francisco, California

Nancy D. Perrier, MD
Assistant Professor, Department of Surgery
Wake Forest University Medical Center
Winston-Salem, North Carolina

Thierry M. Jahan, MD
Assistant Professor, Department of Medicine
University of California, San Francisco
San Francisco, California

2003
BC Decker Inc
Hamilton • London

BC Decker Inc
P.O. Box 620, LCD 1
Hamilton, Ontario L8N 3K7
Tel: 905-522-7017; 1-800-568-7281
Fax: 905-522-7839; 1-888-311-4987
E-mail: info@bcdecker.com
www.bcdecker.com

03 04 05 06 / GSA / 9 8 7 6 5 4 3 2 1

ISBN 1–55009–134–4
Printed in Spain

Sales and Distribution

United States
BC Decker Inc
P.O. Box 785
Lewiston, NY 14092-0785
Tel: 905-522-7017; 800-568-7281
Fax: 905-522-7839; 888-311-4987
E-mail: info@bcdecker.com
www.bcdecker.com

Canada
BC Decker Inc
20 Hughson Street South
P.O. Box 620, LCD 1
Hamilton, Ontario L8N 3K7
Tel: 905-522-7017; 800-568-7281
Fax: 905-522-7839; 888-311-4987
E-mail: info@bcdecker.com
www.bcdecker.com

Foreign Rights
John Scott & Company
International Publishers' Agency
P.O. Box 878
Kimberton, PA 19442
Tel: 610-827-1640
Fax: 610-827-1671
E-mail: jsco@voicenet.com

Argentina
CLM (Cuspide Libros Medicos)
Av. Córdoba 2067 – (1120)
Buenos Aires, Argentina
Tel: (5411) 4961-0042/(5411) 4964-0848
Fax: (5411) 4963-7988
E-mail: clm@cuspide.com

Japan
Igaku-Shoin Ltd.
Foreign Publications Department
3-24-17 Hongo
Bunkyo-ku, Tokyo, Japan 113-8719
Tel: 3 3817 5680
Fax: 3 3815 6776
E-mail: fd@igaku-shoin.co.jp

U.K., Europe, Scandinavia, Middle East
Elsevier Science
Customer Service Department
Foots Cray High Street
Sidcup, Kent
DA14 5HP, UK
Tel: 44 (0) 208 308 5760
Fax: 44 (0) 181 308 5702
E-mail: cservice@harcourt.com

Singapore, Malaysia,Thailand, Philippines, Indonesia, Vietnam, Pacific Rim, Korea
Elsevier Science Asia
583 Orchard Road
#09/01, Forum
Singapore 238884
Tel: 65-737-3593
Fax: 65-753-2145

Australia, New Zealand
Elsevier Science Australia
Customer Service Department
STM Division
Locked Bag 16
St. Peters, New South Wales, 2044
Australia
Tel: 61 02 9517-8999
Fax: 61 02 9517-2249
E-mail: stmp@harcourt.com.au
Web site: www.harcourt.com.au

Mexico and Central America
ETM SA de CV
Calle de Tula 59
Colonia Condesa
06140 Mexico DF, Mexico
Tel: 52-5-5553-6657
Fax: 52-5-5211-8468
E-mail: editoresdetextosmex@prodigy.net.mx

Brazil
Tecmedd
Av. Maurílio Biagi, 2850
City Ribeirão Preto – SP – CEP: 14021-000
Tel: 0800 992236
Fax: (16) 3993-9000
E-mail: tecmedd@tecmedd.com.br

Preface

Surgical endocrinology or endocrine surgical oncology is an important component of general surgery and in some areas of head and neck surgery. As reported in Richard Welbourne's book *History of Endocrine Surgery*, the term "endocrine" is from the Greek *endo*, meaning within, and *kpiveiv*, meaning "separate," documenting the relationship of endocrine surgery and general surgery. Endocrine glands and tumors often make and secrete hormones; "hormone" is a term derived from the Greek word "to excite." Theodur Kocher and Theodor Bilroth contributed much to general surgery in the late nineteenth and early twentieth centuries. Many of their writings and medical contributions concerned thyroid surgery.

Today endocrine surgeons traditionally operate on patients with tumors of the thyroid, parathyroid, and adrenal and endocrine pancreas, as well as on carcinoid or neuroendocrine tumors of the gastrointestinal tract. Virtually all organs of the body, including gastrointestinal tracts, heart, kidney, and skin, secrete hormones, so endocrine surgery could include all of general surgery.

During the past decade, there have been numerous advances in our understanding of the etiology of endocrine tumors, the ability to identify some endocrine tumors such as medullary thyroid cancer, multiple endocrine neoplasia (MEN) type II, and MEN type I by screening family members of these patients for *RET* or *MENIN* mutations, respectively. This enables these individuals to know whether they are at risk of developing these tumors. In some individuals prophylactic treatment can then be done before cancer develops.

Blood testing for tumor markers and hormones such as thyroglobulin, calcitonin, gastrin, serotonin, and chromogranin also helps with tumor diagnosis and for follow-up care. Provocative testing of patients with possible tumors with calcium, pentagastrin, and recombinant thyroid-stimulating hormone helps to unmask or identify occult tumors, as do various localization tests.

Advances in preoperative tumor localization tests and intraoperative parathyroid hormone testing have resulted in a dramatic change in the surgical approach to patients with primary hyperparathyroidism. More epidemiologic and clinical information is also available that provides evidence-based medicine supporting parathyroidectomy even in "asymptomatic" patients with mild hypercalcemia. Osteopenia and osteoporosis are now two of the most common indications for parathyroidectomy in patients with primary hyperparathyroidism.

Major advances have also occurred both in our understanding of how to select patients with incidentally discovered (incidentalomas) adrenal tumors, for operation, and in the surgical treatment of patients with adrenal incidentalomas. Laparoscopic adrenalectomy has become the treatment of choice for patients with small to moderate (less than 6 cm) adrenal tumors.

The current book is by experts in the field of endocrine surgery and provides up-to-date information on the management of patients with endocrine and neuroendocrine tumors.

Orlo H. Clark, MD
January 2003

Dedication

The editors would like to dedicate this book on endocrine tumors to our families, teachers, and colleagues, especially Ms. Kate Poole, who helped us to prepare this volume. We are indebted to the outstanding and experienced endocrine surgeons who have written up-to-date, timely, and informative chapters. We appreciate the guidance of Brian Decker and his staff and the American Cancer Society for their patience and advice.

This page intentionally left blank

Contents

This page intentionally left blank

Contributors

Maha Al Fehaily, MD
Department of Surgery
University of California, San Francisco
San Francisco, California
Andrenocortical Carcinoma, Cushing's Syndrome

Osamah Alsanea, MD, FACS
Department of Surgery
King Faisal Specialist Hospital & Research Center
Riyadh, Saudi Arabia
Benign Disorders of the Thyroid Gland

Michael Sean Boger, PharmD
Department of Surgery
Wake Forest University Medical Center
Winston-Salem, North Carolina
Benign Primary Tumors,
Benign Secondary Tumors

Milana B. Boukhman, MD
Department of Emergency Medicine
Harvard University, Beth Israel Hospital
Boston, Massachusetts
Insulinomas

Laurent Brunaud, MD
Department of Digestive, Visceral and Endocrine Surgery
University of Nancy
Nancy, France
Neuroendocrine Tumors of the Gastrointestinal System

W. Keat Cheah, MBBS, FRACS
Department of Surgery
National University Hospital
Singapore
Adrenal Incidentaloma

Orlo H. Clark, MD
Department of Surgery
University of California, San Francisco
San Francisco, California
Benign Disorders of the Thyroid Gland, Medullary Thyroid Cancer, Benign Secondary Tumors, Insulinomas, Neuroendocrine Tumors of the Gastrointestinal System

Michael J. Demeure, MD
Department of Surgery
University of Arizona
Tucson, Arizona
Endocrine Tumors of the Pancreas

Gerard M. Doherty, MD
Department of Surgery
University of Michigan
Ann Arbor, Michigan
Multiple Endocrine Neoplasia Type I

James P. Dolan, MD
Department of Surgery
Oregon Health and Science University
Portland, Oregon
Gastrinoma (Zollinger-Ellison Syndrome)

Quan-Yang Duh, MD
Department of Surgery
University of California Veterans Affairs Medical Center
San Francisco, California
Primary Hyperaldosteronism, Andrenocortical Carcinoma, Cushing's Syndrome, Adrenal Incidentaloma

Paul A. Fitzgerald, MD
Department of Medicine
University of California, San Francisco
San Francisco, California
Pheochromocytoma and Paraganglioma

Francis S. Greenspan, MD, FACP
Department of Medicine and Radiology
University of California, San Francisco
San Francisco, California
Differentiated Thyroid Carcinomas

Steven R. Hunt, MD
Department of Surgery
Washington University
St. Louis, Missouri
Multiple Endocrine Neoplasia Type II Syndromes

Thierry M. Jahan, MD
Department of Medicine
University of California, San Francisco
San Francisco, California
Anaplastic Thyroid Carcinoma,
Parathyroid Carcinoma

Electron Kebebew, MD
Department of Surgery
University of California, San Francisco
San Francisco, California
Medullary Thyroid Cancer

Keh-Chuan Loh, MD, FACP, FRCP
Department of Medicine
National University of Singapore
Singapore
Differentiated Thyroid Carcinomas

Theodore R. Miller, MD
Department of Pathology
University of California, San Francisco
San Francisco, California
Differentiated Thyroid Carcinomas

Jeffrey F. Moley, MD
Department of Surgery
Washington University
St. Louis, Missouri
Multiple Endocrine Neoplasia Type II Syndromes

Jeffrey A. Norton, MD
Department of Surgery
University of California, San Francisco
San Francisco, California
Gastrinoma (Zollinger-Ellison Syndrome)

Jennifer Braemar Ogilvie, MD
Department of Surgery
University of California, San Francisco
San Francisco, California
Anaplastic Thyroid Carcinoma,
Parathyroid Carcinoma

Nancy D. Perrier, MD
Department of Surgery
Wake Forest University Medical Center
Winston-Salem, North Carolina
Benign Primary Tumors,
Benign Secondary Tumors

Wen T. Shen, MD
Department of Surgery
University of California, San Francisco
San Francisco, California
Primary Hyperaldosteronism

Fatma Tatar, MD
Department of Surgery
University of California, San Francisco
San Francisco, California
Benign Secondary Tumors

Chloe Wagner, MD
Department of Surgery
Oregon Health and Science University
Portland, Oregon
Multiple Endocrine Neoplasia Type I

1

Benign Disorders of the Thyroid Gland

OSAMAH ALSANEA, MD, FACS
ORLO H. CLARK, MD

The thyroid gland, the largest endocrine organ, weighs about 20 g. It develops from an evagination in the base of the tongue at the foramen cecum and descends anterior to the larynx via the thyroglossal duct; the latter usually disappears or remains as the pyramidal lobe. Congenital anomalies result from persistence of the thyroglossal duct or abnormal descent of the thyroid gland[1]:

1. *Persistent thyroglossal duct anomalies*. In some patients, the epithelium of the thyroglossal cyst may persist as a fistula or a blind-ended cyst usually located above the thyroid cartilage. Thyroglossal duct cysts, however, may present as midline structures from the base of the tongue to the suprasternal notch. Excision of the fistula or cyst should include resection of the midsection of the hyoid bone to avoid recurrence (Sistrunk operation). About 1% of thyroglossal duct cysts contain a focus of papillary thyroid cancer and about 25% of these patients have thyroid cancer elsewhere in the thyroid gland. The thyroid may also fail to descend and may result in a sublingual thyroid gland. Some patients with sublingual thyroids are hypothyroid, and the thyroid tissue may become calcified (Figure 1–1). The pyramidal lobe hypertrophies in patients with Graves' disease, multinodular goiter, or Hashimoto's thyroiditis and can usually be palpated in the central neck at the level of the cricothyroid membrane.
2. *Heterotopic thyroid tissue.* Some patients have small masses of normal thyroid tissue (usually about 1 cm in size) in the central neck that are of no clinical consequence. When ectopic thyroid tissue is found in the lateral neck, it is almost always metastatic thyroid cancer in lymph nodes. Malignant transformation can rarely arise in heterotopic thyroid tissue and is managed by excision of the mass.

The mature thyroid gland is composed of two lateral lobes connected via an isthmus that may connect to a pyramidal lobe (Figure 1–2). Fibrous septae divide each lobe into pseudolobules formed of follicular arrangements of single layers of cuboidal epithelial cells surrounding colloid-filled lumens. Thyroid function is regulated by a feedback loop that includes the thyrotropin-releasing hormone, which is released by the hypothalamus to stimulate the anterior pituitary to secrete thyroid-stimulating hormone (TSH).

TSH binds a surface receptor on the follicular cells in the thyroid gland and results in activation of

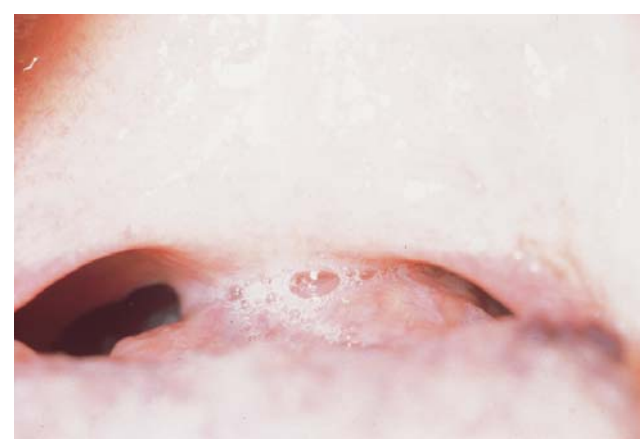


Figure 1–1. A calcified lingual thyroid (covered by saliva) is seen at the base of the tongue in a young infant.

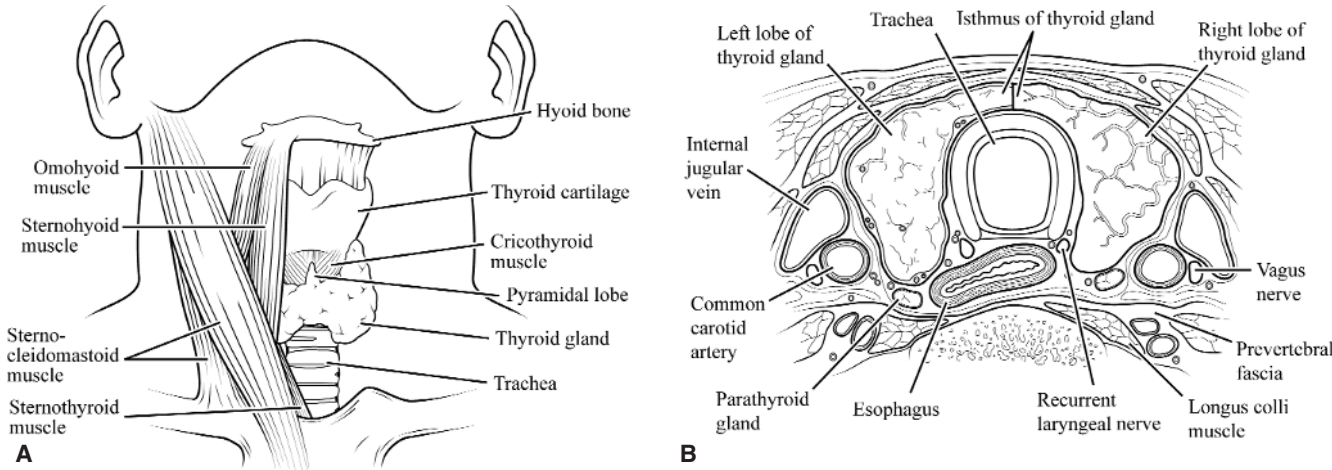


Figure 1–2. The normal thyroid gland is composed of two lateral lobes connected via an isthmus. *A*, The pyramidal lobe, a remnant of the caudal end of the thyroglossal duct, extends cranially from the isthmus of the thyroid gland. Reproduced with permission from Greenspan FS, Gordon JS. Basic and clinical endocrinology. 5th ed. Norwalk (CT): Appleton and Lange; 1997. *B*, A cross-section view of the anterior portion of the neck at the level of T1, showing the thyroid relations. Reproduced with permission from Linder HH. Clinical anatomy. Norwalk (CT): Appleton and Lange; 1989.

several signal transduction pathways: the cyclic adenosine monophosphate–mediated activation of a protein kinase A system is responsible for increased hormone production and, to a lesser extent, increased growth, and the phospholipase C–mediated activation of the protein kinase C system is primarily responsible for cellular growth.

The follicular cells of the thyroid gland synthesize and secrete thyroxine (T_4) and, to a lesser extent, triiodothyronine (T_3), the more active hormone. T_3 is predominantly produced by the extrathyroidal conversion of T_4 to T_3 (Figure 1–3) in the peripheral tissues by the action of 5′-deiodinase on T_4. A TSH-stimulated thyroid gland secretes relatively more T_3.

Normal thyroid hormone formation depends on normal levels of TSH and an adequate but not excessive supply of iodine (150 to 500 µg per day). Iodine is absorbed in the gastrointestinal tract after being reduced to iodide. Thyroid cells normally take up about 25% of the absorbed iodide through a sodium-iodide symporter. Iodide is oxidized and incorporated into tyrosine molecules of thyroglobulin via a thyroid peroxidase enzyme, which also couples monoiodinated and deiodinated tyrosines to form T_3 or T_4 (Figure 1–4). Thyroglobulin is then exocytosed and stored as colloid. Endocytosis of colloid droplets followed by proteolysis of thyroglobulin leads to release of thyroid hormones into the capillaries.

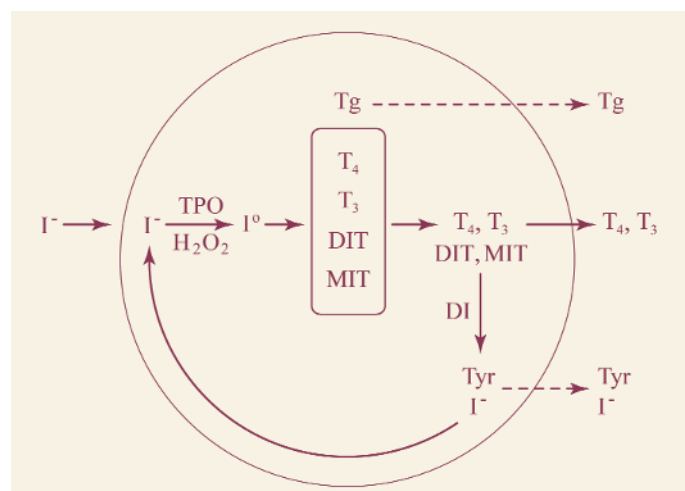


Figure 1–3. Thyroid hormone synthesis in a thyroid follicle. DI = deiodinase; DIT = diiodotyrosine; H_2O_2 = hydrogen peroxide; I^- = iodide ion; I^0 = active I; MIT = monodiodotyrosine; T_3 = triiodothyronine; T_4 = thyroxine; Tg = thyroglobulin; TPO = thyroidal peroxidase; Tyr = tyrosine;. Reproduced with permission from Greenspan FS, Gordon JS. Basic and clinical endocrinology. 5th ed. Appleton and Lange; 1997.

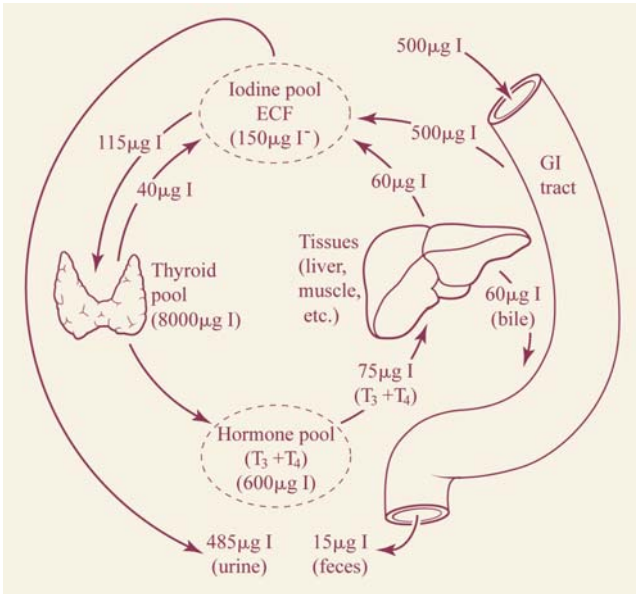


Figure 1–4. Iodine metabolism: the values are representative of those that might be found in a healthy subject ingesting 500 μg of iodine a day. The actual iodine intake varies considerably among different individuals. GI = gastrointestinal; T_4 = thyroxine; T_3 = triiodothyronine; I = iodine; ECF = extracellular fluid. Reproduced with permission from Greenspan FS, Gordon JS. Basic and clinical endocrinology. 5th ed. Appleton and Lange; 1997.

Abnormalities of the thyroid gland develop because of disorders of thyroid function or because of hyperplastic or neoplastic growth.[2]

GOITER

A goiter refers to any increase in the size of the thyroid gland as a result of excessive growth (Figure 1–5). Goiters may be diffuse or nodular and nodules may be solitary or multiple and functioning or nonfunctioning. Most goiters are multinodular, but solitary nodules are not uncommon.

Multinodular Nontoxic Goiter

Multinodular nontoxic goiter (MNG) is the most common disease of the thyroid gland, affecting as many as 90% of the population in iodine-deficient (-endemic) areas. In the United States, about 5% of the population are affected, and the incidence of MNG is approximately 0.1 to 1.5% per year, which translates into 250,000 new cases annually. Women are five times more frequently affected than men. Goiters may reach a considerable size and could extend into the substernal region in 0.2 to 10%. Substernal goiters form 4% of all mediastinal tumors. Most substernal goiters are located anteriorly, and only 1% of them are totally intrathoracic.[3] Virtually all (about 99%) of substernal goiters may be removed via a cervical incision. This may not be possible when the substernal component is malignant, where there is no thyroid tissue in the neck, and when the patient has had previous thyroid surgery.

Several theories have been suggested to explain the pathogenesis of MNG. Fluctuation in iodine intake causes repeated cycles of growth stimulation-inhibition owing to variation in the TSH level.[4] Iodine-deficient thyroid tissue is more growth responsive to TSH than is iodine-sufficient thyroid tissue.[5]

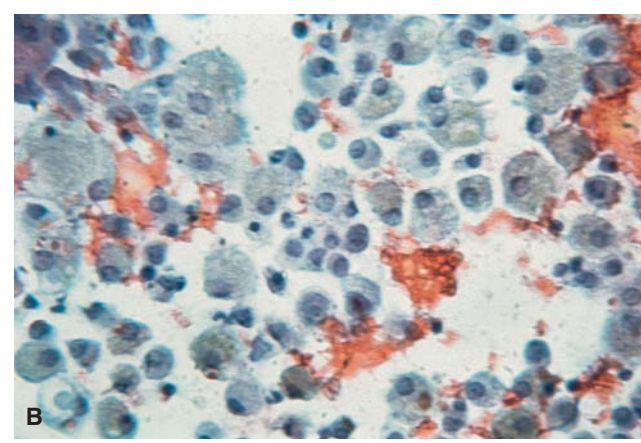


Figure 1–5. An asymptomatic patient presents with a swelling in the central neck that moves with deglutition. *A*, The goiter is classified as World Health Organization stage II. *B*, Photomicrograph of a fine-needle aspirate from the goiter reveals normal cellularity, abundance of colloid, and no signs of atypia (hematoxylin and eosin; ×400 original magnification).

Dyshormonogenesis, goitrogens whether natural or in the form of medications such as lithium, and radiation result in goiters in some patients. Furthermore, a gene linked to the familial form of MNG has been mapped to the short arm of chromosome 14.[6]

Many patients with MNG are asymptomatic, but some may present with local pressure symptoms exerted by the goitrous gland on neck structures such as the trachea or the esophagus.[7] Rarely, hoarseness would result from acute stretching of the recurrent laryngeal nerve by the goitrous gland, but when a patient has a thyroid nodule and recurrent laryngeal nerve palsy, thyroid cancer is most likely. A positive Pemberton's sign (facial flushing and dilation of the jugular veins owing to decreased venous drainage from the head and neck on raising the arms above the head) should raise suspicion of a substernal extension (Figure 1–6). An inspiratory stridor indicates tracheal compression, and flow loop studies can be done to confirm this diagnosis. The World Health Organization (WHO) classification of goiter in Table 1–1 is helpful to describe the size of the thyroid gland (Figure 1–7).

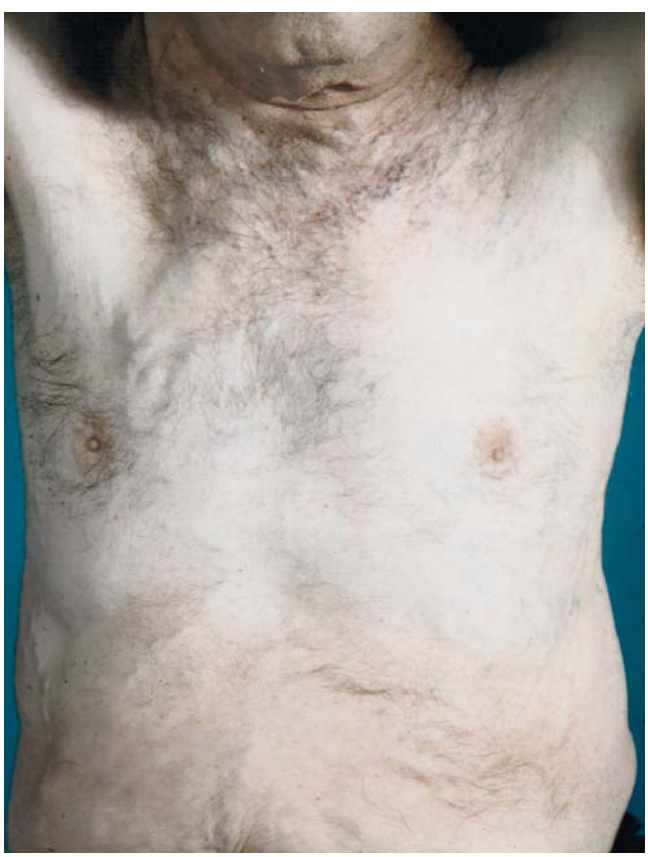


Figure 1–6. Pemberton's sign of facial plethora is demonstrated by asking the patient to raise both arms above the head, obstructing the venous drainage from the head and neck at the thoracic inlet.

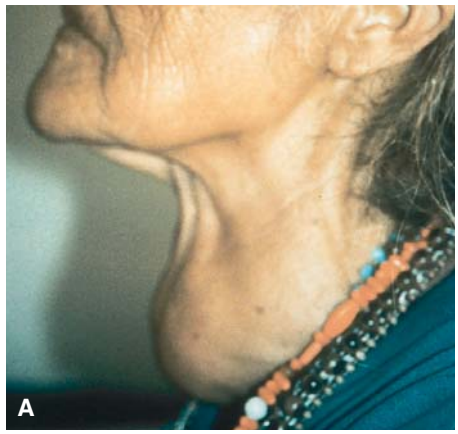
Table 1–1. WHO CLASSIFICATION OF GOITER

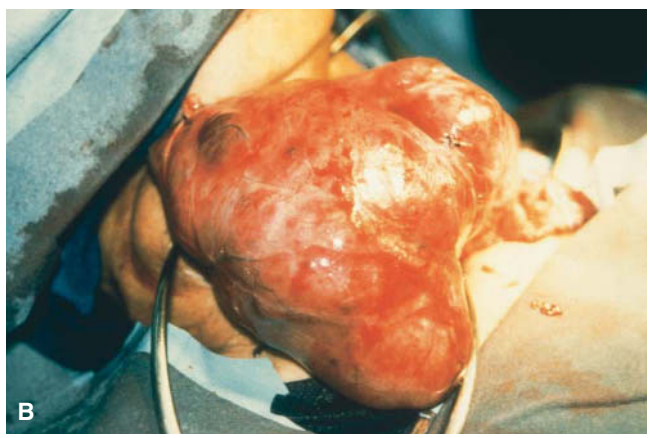
Stage	Description
0-A	No goiter
0-B	Goiter detected by palpitation but not visible when the neck is extended
I	Goiter is palpable and visible only with neck extension
II	Goiter is visible in normal position
III	Larger goiter seen at a distance

WHO = World Health Organization.

Most multinodular goiters are asymptomatic and are noted because of a swelling in the thyroid area. Patients with goiters should be questioned about a family history of familial thyroid cancer or radiation exposure. Patients should be asked if they have any local symptoms such as pain, hoarseness, a change in voice or dysphagia, or systemic symptoms of hyper- or hypothyroidism. A serum TSH level should be obtained to determine whether the patient is euthyroid, hypothyroid (elevated TSH), or hyperthyroid (suppressed TSH). The latter occurs in patients with autonomous hyperfunctioning nodules. Testing of thyroid function is especially important in elderly patients who may have apathetic hyperthyroidism to avoid the detrimental effect of untreated thyrotoxicosis on the cardiovascular system and bones.

Ultrasonographic examination of the neck and thyroid gland often reveals many subclinical nodules, even in patients thought to have a solitary nodular goiter. Patients with multinodular goiters are less likely to have cancer than are patients with solitary nodules, although dominant nodules arising in MNG carry nearly the same risk of malignancy as those arising in normal glands. In a patient with a dominant or solitary nodule, fine-needle aspiration (FNA) for cytologic examination is the most cost-effective method to determine whether the nodule is benign, suspicious, or malignant. Computed tomography and magnetic resonance imaging (MRI) are not usually needed, except in some patients with substernal goiters and to help plan the extent of the surgical operation (Figure 1–8). Radioiodine scanning is rarely indicated, except in patients with cytologic evidence of follicular neoplasms because thyroid cancer is rare when the nodules are hot or autonomous.





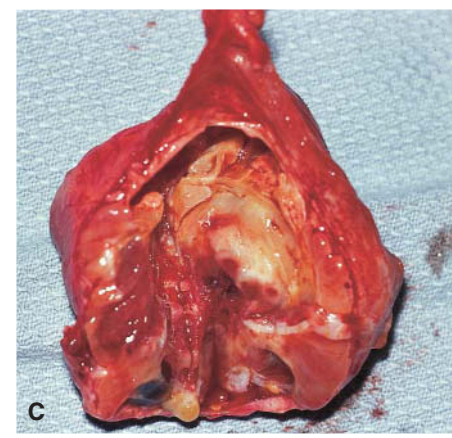


Figure 1–7. The patient presented with a long-standing swelling in the lower part of the neck. History revealed increasing neck discomfort in the recent past. *A*, Note the multinodular appearance of a World Health Organization stage III goiter. *B*, Multiple nodules are seen in the total thyroidectomy specimen. *C*, A multilocular cyst was deroofed to show areas of necrosis and hemorrhage.

Patients with endemic goiter benefit from iodine or thyroid hormone replacement. However, they should be followed carefully as some may develop jodbasedow (iodine-induced) hyperthyroidism. T_4 should be used to reduce blood TSH levels to the low normal range in patients with an elevated TSH. Treatment with thyroid hormone to lower TSH levels works better in patients with diffuse or small goiters or nodules than in patients with larger nodules. The target TSH level should be 0.1 to 1.0 mU/L in young patients and about 1.0 mU/L in older patients. Although treatment with thyroid hormone appears to decrease goiter size in about 25 to 50% of patients, it also appears to prevent some goiters from growing.[8]

Surgical therapy is indicated in patients with local symptoms, lesions proven or suspicious for being malignant on FNA, recurrent cysts, history of familial nonmedullary thyroid cancer or irradiation, patient anxiety, and an enlarging lesion while on thyroid hormone and for cosmetic reasons (Figure 1–9). We recommend surgery in most patients with substernal goiters, even in the absence of symptoms, because most patients are likely to develop symptoms in the future when the gland enlarges, and some patients develop acute respira-

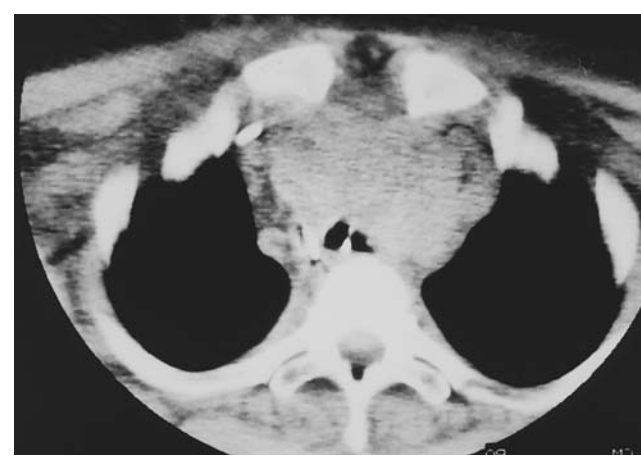


Figure 1–8. Chest computed tomographic scan in a patient with a substernal goiter and significant stridor. Note that the gland is compressing the airway down to the level of the carina.

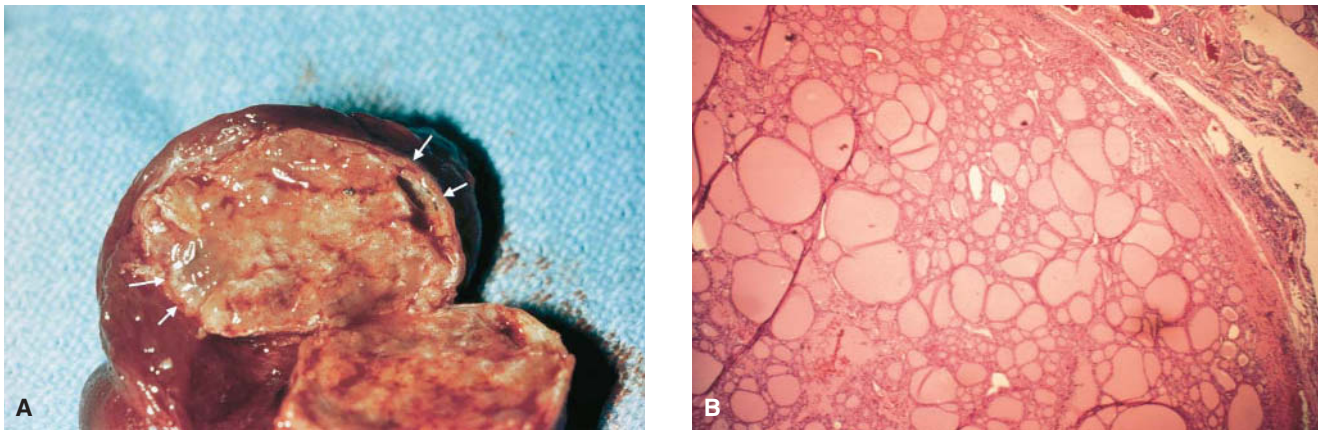


Figure 1–9. A hemithyroidectomy specimen. *A*, Note the calcific solitary benign thyroid nodule, which was bivalved to show the eggshell benign calcification (*arrows*). *B*, Photomicrograph of the specimen revealed a well-defined nodule. The follicles have abundant colloid and flat cuboidal epithelium. Note the cystic spaces surrounding the nodule (hematoxylin and eosin; ×40 original magnification).

tory distress with growth of the goiter (Figure 1–10). Furthermore, cytologic evaluation of the substernal component is not possible. Flow loop studies are useful in these patients.

One must be aware that it may be difficult to intubate a patient with a large goiter. Awake and fiberoptic intubation may be necessary. Vocal cord function should be assessed in all patients with a voice change and in patients who have had previous neck surgery. Hypothyroidism should be diagnosed and treated because of the increased risk of anesthesia. For most patients, we recommend total lobectomy on the side with the dominant nodule and subtotal lobectomy on the contralateral side, leaving a small thyroid remnant (1 to 5 g) in patients with MNG (Hartley-Dunhill operation).

Recurrence and postoperative hypothyroidism depend on the amount and functional quality of remaining tissue. Some surgeons prefer to perform total thyroidectomy to minimize the risk of recurrence. Although we sometimes do total thyroidectomy in such patients, we do not believe that this approach should be accepted for all patients as it slightly increases the risk of long-term complications. The complications of a bilateral thyroidectomy, whether total or subtotal, for MNG, including hypoparathyroidism and recurrent laryngeal nerve injury, should not exceed 2% (Figure 1–11). As already mentioned, about 98% of substernal goiters can be removed through a cervical incision. Rarely, median sternotomy might be needed to remove the entire gland. As mentioned, this is more likely in patients who have had previous thyroid operations, those with invasive thyroid cancers, and those whose entire thyroid gland is in a substernal position. When an occult focus of papillary thyroid cancer is detected in the removed specimen, no further surgical treatment is usually necessary. Some clinicians treat poor-risk patients with radioactive iodine (RAI) rather than by surgical removal. It should be mentioned that most patients, including elderly patients, are well enough to go home within 23 hours of thyroidectomy. RAI ablation can cause acute thyroiditis and may increase thyroid swelling, resulting in acute obstructive symptoms.[9]

Thyroid Adenoma

Follicular or Hürthle cell neoplasms account for about 20% of all thyroid nodules in the United States, and about 20% of these nodules are malignant. These are usually solitary nodules composed of hypercellular arrangements of follicular or Hürthle cells with a surrounding capsule. Most thyroid adenomas are follicular adenomas and are classified into micro- or macrofollicular and a rare embryonal variant. Other less likely adenomas include the Hürthle cell adenoma and the very rare papillary adenoma. It may be difficult if not impossible to differentiate between a Hürthle cell adenoma and a carcinoma cytologically. Histologic features, including capsular and vascular invasion, are used to identify malignant nodules (Figures 1–12 and 1–13).

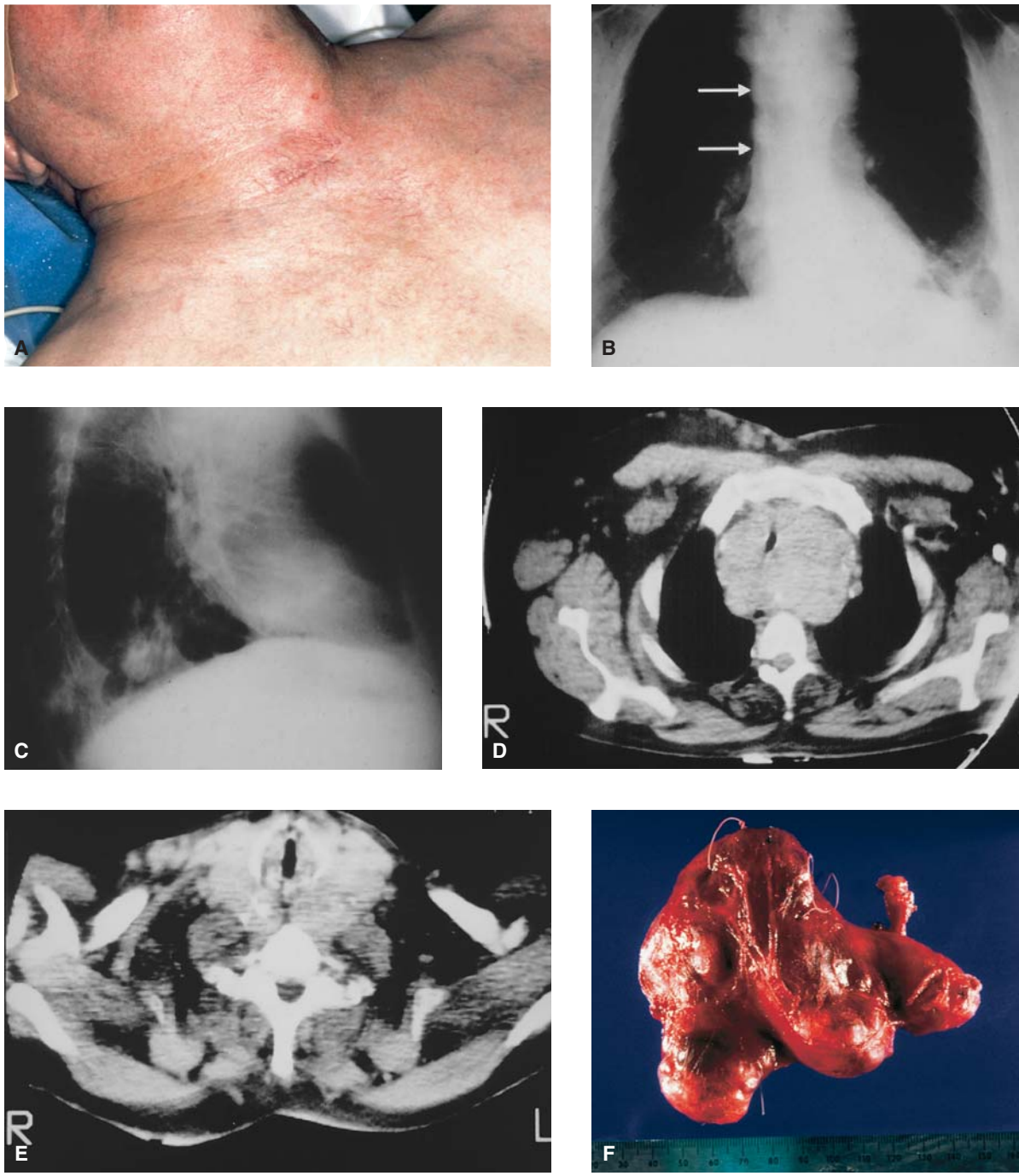


Figure 1–10. A patient presented with worsening inspiratory stridor and discomfort in the lower neck several years after thyroidectomy for multinodular goiter. *A*, Prominent venous collaterals secondary to superior vena caval obstruction by a recurrent substernal goiter. *B*, A posteroanterior radiographic view of a chest shows absence of the superior vena cava from the cardiac silhouette (*arrows*). *C*, A lateral radiographic view of the chest shows a mass in the superior mediastinum. *D*, Chest computed tomographic (CT) scan reveals tracheal compression by the retrosternal goiter. *E*, Neck CT scan shows that the goiter extends to the level of the thyroid cartilage, causing airway compression. Awake intubation under fiberoptic laryngoscopy is the safest way to intubate this patient. *F*, Gross appearance of the goiter. Note the prominent nodularity.

Most thyroid nodules are first identified on routine physical examination and are asymptomatic. Occasionally, a nodule may become acutely enlarged and cause acute pain secondary to bleeding within the nodule. Patients who develop toxic adenomas usually display classic signs of thyrotoxicosis without the

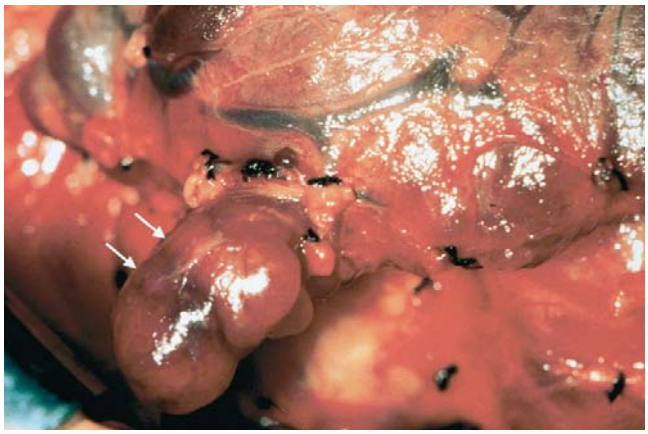


Figure 1–11. Zuckerkandl's tubercle (*arrows*) represents a lateral protrusion from the thyroid lobe at the level of the cricoid cartilage. The recurrent laryngeal nerve usually passes posterior or dorsal to it before it reaches the ligament of Berry to enter into the larynx. The upper parathyroid gland may be at the end of this tubercle.

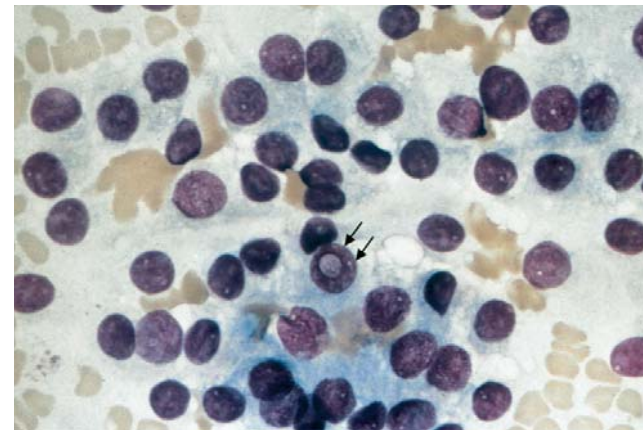


Figure 1–12. Photomicrograph of a fine-needle aspirate from a solitary nodule shows ground-glass appearance of the nuclei and pseudoinclusions, which represent acidophilic well-demarcated invagination of the cytoplasm into the nucleus. These features, best demonstrated in follicular cells near the center of the slide (*arrows*), document that this is a follicular variant of papillary carcinoma rather than a follicular neoplasm (hematoxylin and eosin; ×400 original magnification).

extrathyroidal manifestations of Graves' disease. Only about 1% of hot nodules are malignant (Figure 1–14).

For patients with follicular or Hürthle cell neoplasms by cytologic examination, we recommend total thyroid lobectomy. Frozen section is of limited value in differentiating a follicular adenoma from follicular carcinoma or Hürthle cell adenoma from Hürthle cell cancer. Frozen section is more helpful when one suspects that a neoplasm with follicular architecture might be a follicular variant of papillary thyroid cancer. Any adjacent lymph nodes should be removed and examined by frozen section if the lymph nodes look abnormal. Preoperatively, we tell patients with follicular and Hürthle cell neoplasms that about 10% will require a completion thyroidectomy, removing the contralateral lobe, if cancer is diagnosed in the thyroid gland. In patients with toxic nodular goiter and thyrotoxic symptoms, hemithyroidectomy treats the problem successfully.

THYROTOXICOSIS

Thyrotoxicosis is a clinical syndrome that results from exposure to increased levels of circulating thy-

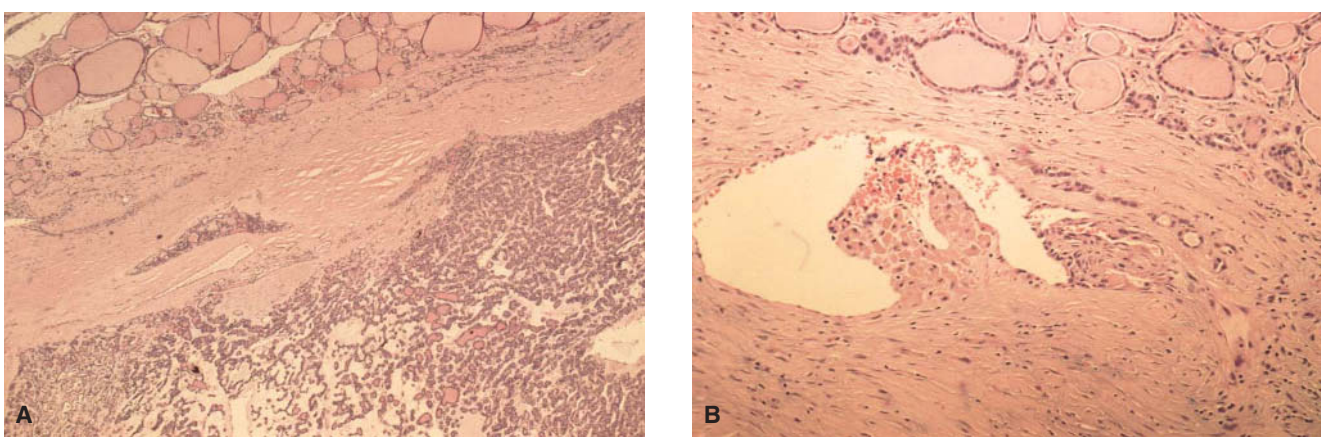
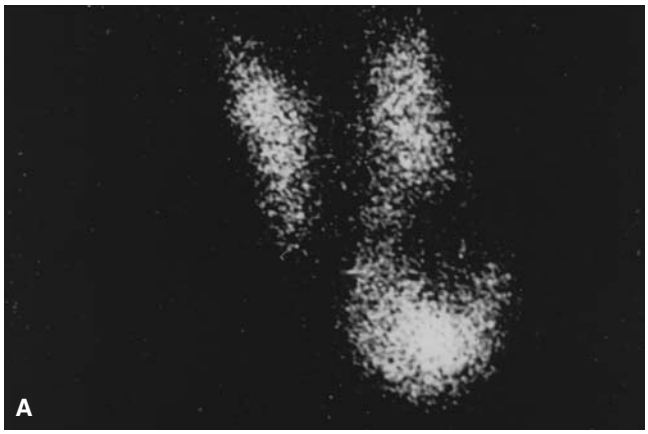
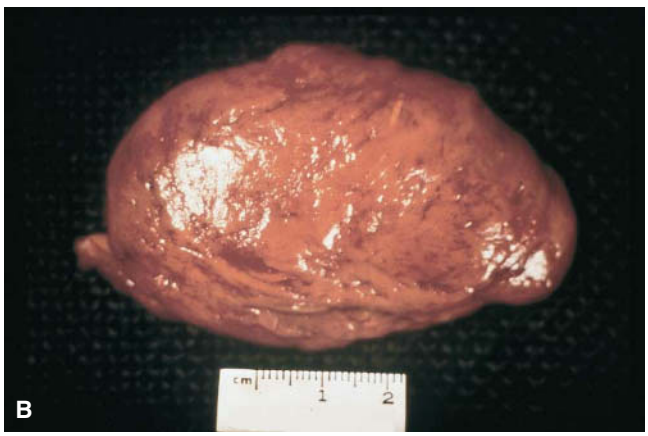


Figure 1–13. In follicular neoplasms, cytology and frozen section examinations are of limited to no value in differentiating between follicular adenoma and adenocarcinoma. Permanent histology with the demonstration of capsular or vessel invasion is necessary to diagnose cancer. *A*, Photomicrograph showing invasion into but not through the capsule consistent with an atypical follicular adenoma. *B*, Photomicrograph revealing vascular invasion into a capsular venule. It appears as a tumor thrombus attached to the wall of the blood vessel and is consistent with follicular adenocarcinoma (hematoxylin and eosin; ×40 original magnification).





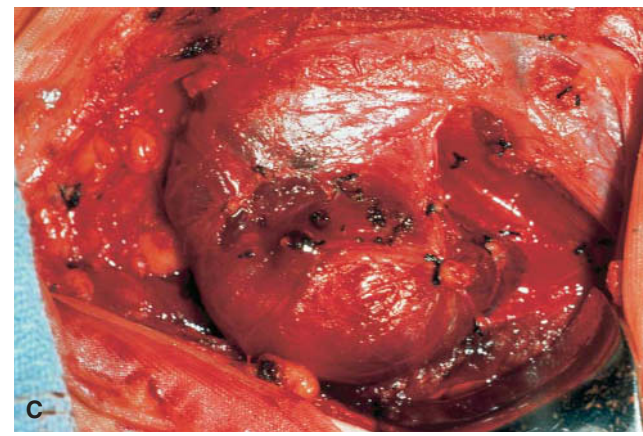


Figure 1–14. Nuclear scanning can be helpful in a patient with a follicular neoplasm. *A*, A "cold" nodule has a 20% chance of being malignant, whereas a "hot" or "autonomous" thyroid nodule is rarely malignant. *B*, A hemithyroidectomy specimen of a follicular neoplasm. Note the smooth outer surface of the neoplasm. *C*, In contrast to *B*, the irregular appearance of a benign solitary nodule presenting as part of a multinodular architecture is demonstrated here.

roid hormone, which results in an exaggerated autonomic response. Major causes of thyrotoxicosis are listed in Table 1–2.

Graves' Disease

Graves' disease is an autoimmune disease of the thyroid gland that results in a diffuse goiter and overproduction of thyroid hormones (Figure 1–15). Patients sometimes develop a characteristic ophthalmopathy and dermopathy as part of the extrathyroidal autoimmune process. Graves' disease is more common in women of child-bearing age (ie, the third and fourth decades of life). The disease has a bimodal distribution with a smaller peak between 11 and 16 years of age. About 5% of patients with Graves' disease develop thyroid nodules, of which 20% are malignant.

The etiology of Graves' disease remains unclear. Possible explanations include impaired humoral mediated immunity that results in overproduction of different immunoglobulins such as the thyroid-stimulating immunoglobulins (TSIs) or antibodies that are capable of binding TSH receptors, which, in turn, stimulate the thyroid gland to grow and produce excessive amounts of T_3 and T_4. Antibodies against thyroperoxidase have also been isolated and result in lymphocytic infiltration of the thyroid gland. In addition, high antibody titers against *Yersinia enterocolitica* in Graves' disease patients suggest cross-reactivity between the bacteria and the TSH receptors. Recently, linkage analysis has confirmed two chromosomal susceptibility loci (14q31 and 20q11.2) that may explain the strong family predisposition in Graves' disease patients, but precipitating factors such as hormonal changes seen in puberty and pregnancy or psychological stress may initiate the disease in susceptible individuals.

The clinical manifestations of Graves' disease are summarized in Table 1–3. The goiter is usually symmetric and firm, and there is often a bruit. About 15% of patients, especially the elderly, pre-

Table 1–2. CAUSES OF HYPERTHYROIDISM

Cause	Relative Frequency	Characteristics
Increased thyroid hormone production (increased iodine uptake)		
Graves' disease	60–85%	Ophthalmopathy, dermopathy, increased uptake
Plummer's disease	5–15%	Elderly, solitary or multiple palpable nodules clinically or on scan with variable uptake
TSH-secreting pituitary tumors	Very rare	Elevated alpha subunit TSH, CNS manifestations
Functional thyroid cancer metastasis	Very rare	Clinically evident
Trophoblastic disease (choriocarcinoma or molar pregnancy)	Very rare	Elevated HCG
Decreased thyroid hormone production (decreased iodine uptake often with increased release)		
Thyroiditis	5–25%	Pain, tenderness, low uptake
Thyroiditis factitia	Uncommon	Absent goiter, low uptake, intentional from eating raw thyroid
Struma ovarii	Very rare	Decreased thyroid but increased ovarian uptake

CNS = central nervous system; HCG = human chorionic gonadotropin; TSH = thyroid-stimulating hormone.

sent with normal-size thyroid glands. Some patients present with apathetic thyrotoxicosis and appear to be clinically hypothyroid rather than hyperthyroid. Apathetic hyperthyroidism is more common in patients with Plummer's disease than in patients with Graves' disease. All patients with new-onset atrial fibrillation should have a blood test for TSH and T_3.

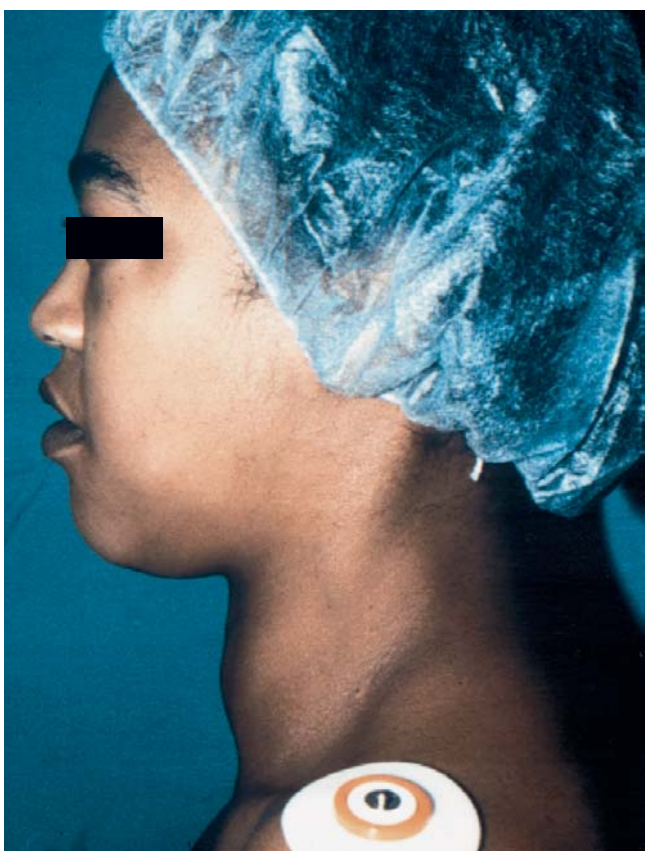


Figure 1–15. A profile of a patient with Graves' disease. Note the classic appearance of a smooth diffuse enlarged goiter.

Noninfiltrative eye signs such as lid retraction or staring gaze result from sympathetic overstimulation of the levator palpebre superioris muscle and disappear with successful treatment. Infiltrative ophthalmopathy results from mucopolysaccharide deposition and cellular infiltration of the orbit and ocular muscles. It causes acutely swollen inflamed red eyes that sometimes become ulcerated, leading to loss of visual acuity. Muscle involvement results in lid lag, squint with double vision. Infiltrative dermopathy, pretibial myxedema, is defined as plaques or confluent areas of violacious pretibial induration. Uncommonly, pretibial myxedema may arise many years after the onset or treatment of the disease (Figure 1–16).

A classic triad of tachycardia with palpitation, weight loss, and heat intolerance is usually diagnostic of Graves' disease in a patient with a diffuse goiter. The goiter is usually symmetrically enlarged, with a smooth rubbery consistency. Elevated T_3 and T_4 and reduced TSH levels confirm the diagnosis and establish a baseline for follow-up. High antibody titers against TSH, also called TSI, are present in about 80% of patients with Graves' disease. A radionuclide uptake scan may be unnecessary, but it is essential if one suspects subacute thyroiditis; the

Table 1–3. MANIFESTATION OF THYROTOXICOSIS

Symptoms	Signs
Nervousness and sweating	Tachycardia
Palpitation	Diffuse goiter
Fatigue	Skin changes
Weight loss	Tremor
Heat intolerance	Bruit
Dyspnea	Noninfiltrative eye signs*
Visual symptoms	Heart disease
Diarrhea	Infiltrative dermopathy*
Menstrual disturbance	Atrial fibrillation
Pathologic fractures	Osteoporosis

*Extrathyroidal manifestation specific to Graves' disease.

scan would reveal increased uptake in Graves' patients (Figure 1–17) and low uptake in the thyroid bed in patients with thyroiditis. Furthermore, Plummer's disease and toxic adenoma have a characteristic appearance on a radionuclide scan with increased uptake in the nodule and suppression of the rest of the thyroid gland (Figure 1–18).

Ideally, successful treatment should aim at prompt restoration and maintenance of a euthyroid state with minimal complications and reasonable cost. Surgical treatment and radioactive ablation have been superior to medical therapy in avoiding recurrence. Indicators of a favorable response to medical treatment include the following:

- A small thyroid gland
- Reduction in the goiter size with medical treatment
- Biochemical euthyroidism with normalization of TSH
- Decreased antibody titers

Medical Treatment

Medical treatment is most effective as definitive treatment in patients with small diffusely toxic goiters or T_3 thyrotoxicosis. It is also used for preparation prior to treatment with surgery or radioidine and for those who refuse other modalities of therapy. The incidence of relapse correlates inversely with the duration of therapy in some but not all investigations, in which as many as 65% of the patients relapse after a year of medical therapy, and even after 4 years of treatment, around 25% relapse once the medications

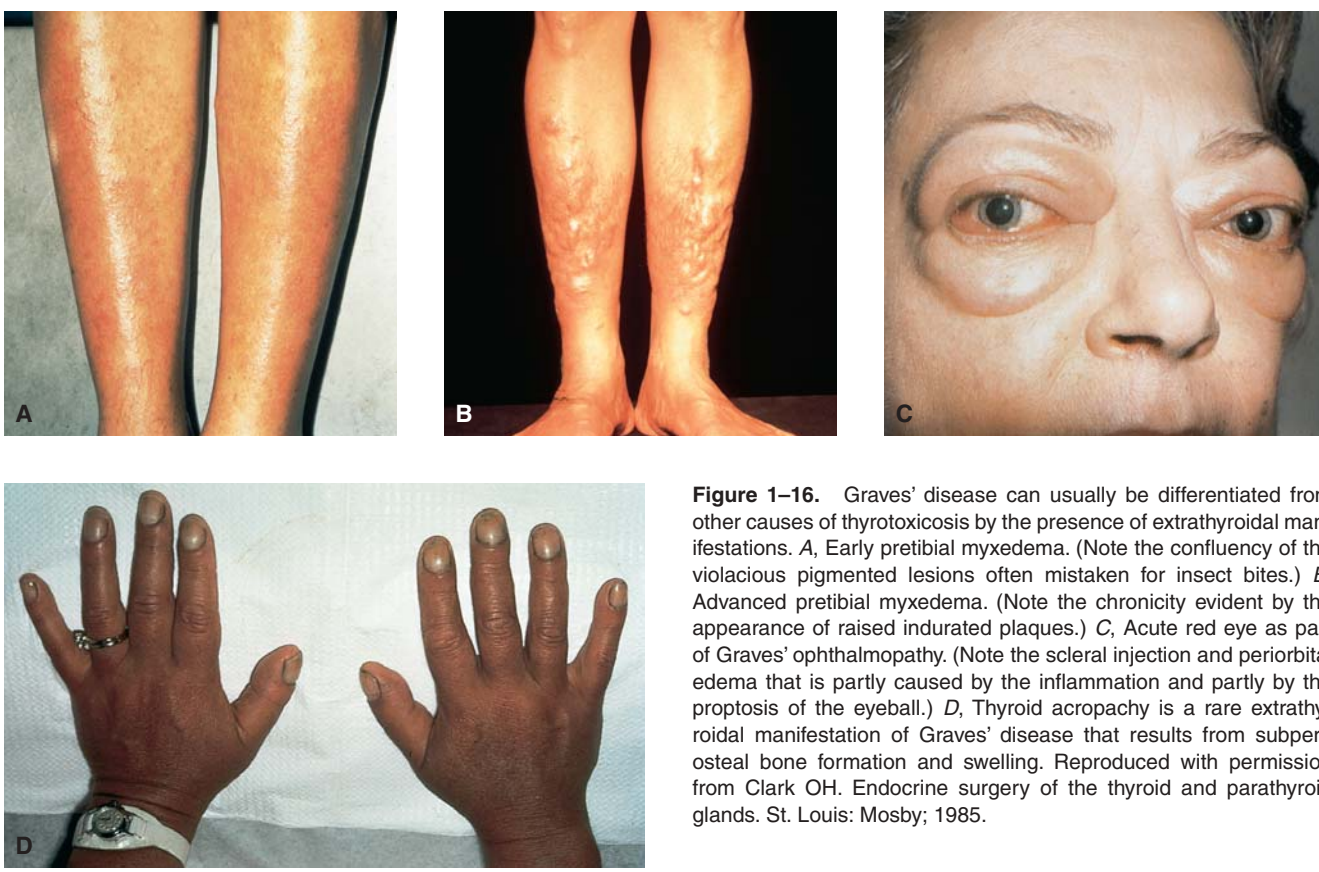


Figure 1–16. Graves' disease can usually be differentiated from other causes of thyrotoxicosis by the presence of extrathyroidal manifestations. *A*, Early pretibial myxedema. (Note the confluency of the violacious pigmented lesions often mistaken for insect bites.) *B*, Advanced pretibial myxedema. (Note the chronicity evident by the appearance of raised indurated plaques.) *C*, Acute red eye as part of Graves' ophthalmopathy. (Note the scleral injection and periorbital edema that is partly caused by the inflammation and partly by the proptosis of the eyeball.) *D*, Thyroid acropachy is a rare extrathyroidal manifestation of Graves' disease that results from subperiosteal bone formation and swelling. Reproduced with permission from Clark OH. Endocrine surgery of the thyroid and parathyroid glands. St. Louis: Mosby; 1985.

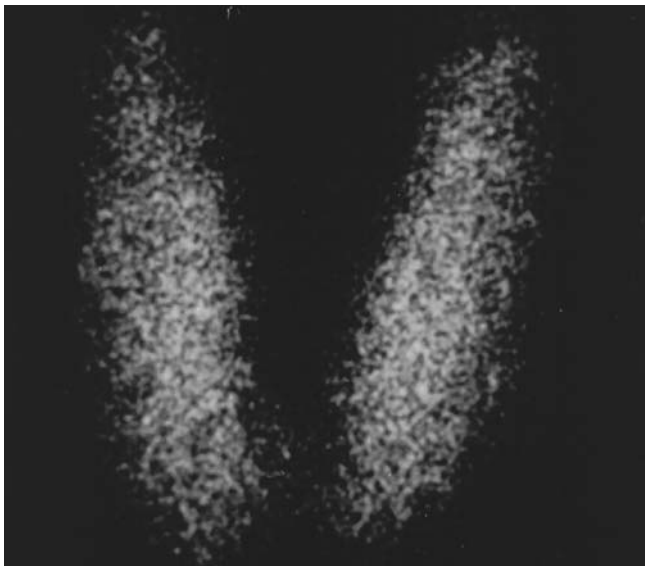


Figure 1–17. A radionuclide scan shows diffusely increased uptake in Graves' disease.

are stopped. Medical treatment is therefore usually recommended for patients with small goiters and for preparing patients for definitive thyroablative therapy by surgery or RAI.

Thionamide derivatives such as propylthiouracil or methimazole (Tapazole) medications inhibit the thyroperoxidase enzyme and decrease thyroid hormone formation. They become effective 1 to 2 weeks after initiating therapy. Side effects of these antithyroid medications may occur soon after initiating treatment and range from mild hypersensitivity with skin rash in about 3% of patients to a potentially fatal agranulocytosis in about 0.5% of the patients. A white blood cell count must be obtained in any patient who develops fever or sore throat while taking thionamides. Iodides inhibit organic binding and block hormone release. They are valuable in preparing patients for surgery and for patients with thyroid storm. Propranolol suppresses the exaggerated sympathetic response in patients with hyperthyroidism and reduces the peripheral conversion of T_4 to T_3. When used preoperatively, it is reported to reduce the vascularity of the thyroid gland. Glucocorticoids can also be used to decrease the peripheral conversion of T_4 to T_3.

Surgical Treatment

Prior to any surgical operation, patients must be rendered euthyroid, preferably using a thionamide medication. An iodide preparation should be administered beginning 10 days prior to thyroidectomy to decrease the vascularity of the gland (Figure 1–19). Some surgeons recommend only iodide or propranolol to prepare patients for thyroidectomy. This treatment should be done for 10 to 14 days preoperatively. We recommend thyroidectomy for the following:

- Patients with local compressive symptoms
- Patients with coexistent malignancy or suspicious thyroid nodules

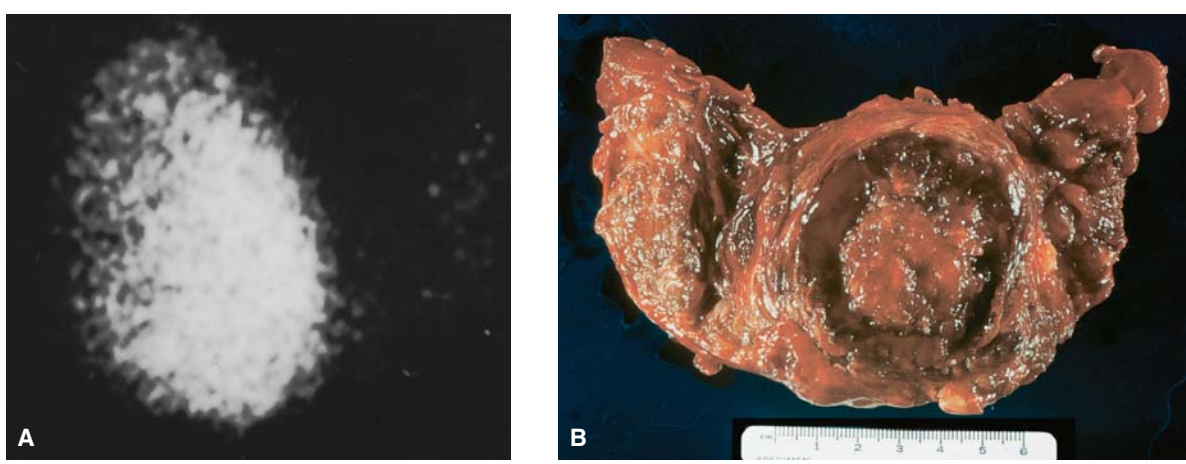


Figure 1–18. Toxic adenoma (Plummer's disease) is suspected in thyrotoxic patients who have prominent thyroid nodules and no extrathyroidal manifestations. *A*, Classic appearance of a toxic adenoma on nuclear scanning as a hot nodule with a suppressed contralateral lobe. *B*, Gross appearance of a bivalved toxic adenoma in the center of the thyroid gland. Note the very vascular and well-demarcated nodule.

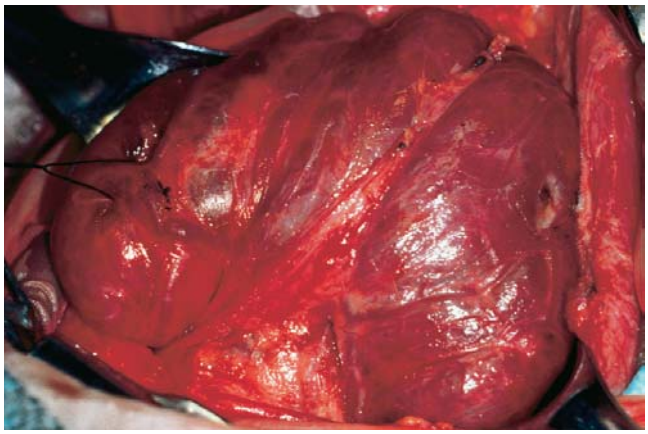


Figure 1–19. Graves' disease glands are usually very vascular. This vascularity decreases when patients are treated with antithyroid medications, β-blockers, and iodide preparations.

- Pregnant women not easily controlled on low doses of antithyroid medications
- Children (Figure 1–20)
- Patients with large goiters or low uptake
- Patients who need rapid remission
- Patients who are noncompliant or who developed serious side effects from medical treatment

For pregnant patients, thyroidectomy should be done during the second trimester and RAI must be avoided. Women who wish to get pregnant within a year of treatment are also best treated by surgery.

Many, but not all, experts recommend total thyroidectomy for patients with severe ophthalmopathy or associated malignancy (Figure 1–21) and for patients who have had a life-threatening complication from medications or their Graves' disease. For most patients, we prefer the Hartley-Dunhill operation, in which a total lobectomy is performed on one side and a subtotal lobectomy is performed on the contralateral side. The size of the remnant is around 4 to 5 g in adults and 2 to 3 g in children to avoid recurrence. A euthyroid state is achieved in 50% of adult patients. The incidence of hypothyroidism depends on the size of the thyroid remnant, the length of follow-up, and the definition of hypothyroidism. Unfortunately, there are no other reliable predictors of recurrent hyperthyroidism or progression to hypothyroidism. The complication rate of total or subtotal thyroidectomy should not exceed 2%, including hypoparathyroidism, recurrent laryngeal nerve injury, hematoma, and the less significant complications such as wound infection and keloid formation.

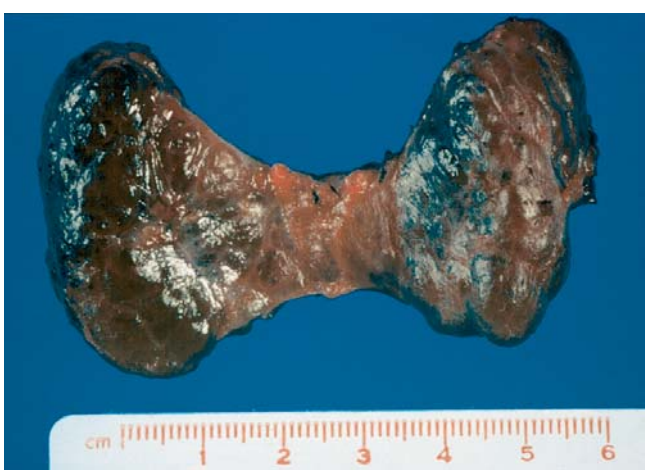


Figure 1–20. The thyroid gland from a 13-year-old adolescent girl suffering from Graves' disease reveals diffuse symmetric enlargement. The dark appearance is secondary to increased vascularity within the substance of the thyroid gland. This patient failed medical therapy and underwent a successful near-total thyroidectomy.

Radioactive Iodine Ablation

RAI is the most frequently used treatment in the United States for adult patients with Graves' disease.

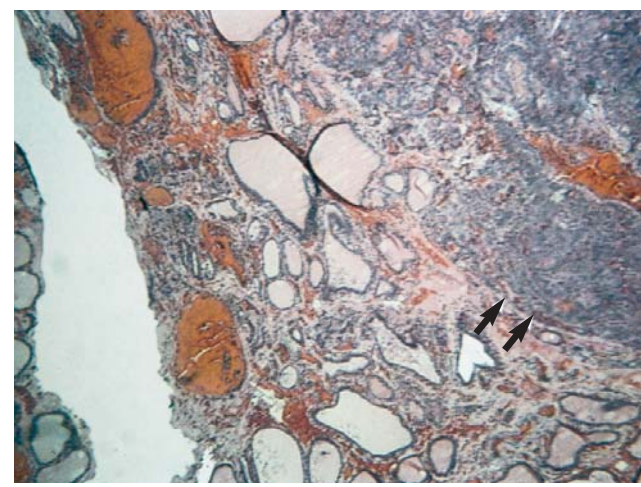


Figure 1–21. Photomicrograph shows a focus of malignancy (*arrows*) in a patient with Graves' disease. Hyperplastic tall columnar epithelial cells with basal nuclei line the follicles with some papillary infoldings. Although not very prominent in this case owing to preoperative treatment, the scalloped pattern at the edge of the colloid is the result of active reabsorption of colloid. A focus of papillary thyroid carcinoma is seen in the left upper corner. These occult tumors are thought to be of little clinical significance. However, patients who present with thyroid cancer and Graves' disease may have more aggressive tumors (hematoxylin and eosin; ×40 original magnification).

It is preferred in older patients with moderate hyperthyroidism and small or moderate-size (< 50 g) goiters. As mentioned, RAI is contraindicated in pregnant or lactating women, in children, and in patients with large retrosternal goiters. About 20% of patients require a second dose to control their disease depending on the initial dose administered. For most patients with Graves' disease, the choice between surgery and RAI depends on the advantages and disadvantages of each treatment. Several issues need to be considered in making this choice. RAI has a 6-week to 3-month latency before the patient becomes euthyroid; during this time, patients must continue to receive medical therapy. It is important to prevent hypo- or hyperthyroidism post-RIA in patients suffering from Graves' eye disease because both of these states lead to worsening of the Graves' ophthalmopathy. In patients with clinically apparent eye disease, glucocorticoid administration should be used prior to treatment with RAI or surgery. Initially, the percentage of patients who develop hypothyroidism after RAI treatment depends primarily on the dose used. Some patients may develop transient hypothyroidism 2 months post-RAI. In most reports, about 50% will develop permanent hypothyroidism within 1 year. The remaining patients develop hypothyroidism at a rate of 2 to 3% per year over the following years, with a 70% incidence at 10 years. Eventually, almost all patients develop hypothyroidism after treatment with RAI.

Treatment of Ophthalmopathy

Clinically detectable ophthalmopathy is seen in a third of patients with Graves' disease, but, luckily, only about 1 to 5% develop severe ophthalmopathy. When questioning the patient, it is important to determine whether the eyes are worse in the morning on awakening or at night. For the former, one should elevate the head of the bed, tape the eyes shut while sleeping, and apply methylcellulose eye drops. For the latter, one should avoid irritants such as smoking, wind, and sunshine. Eye drops are again useful. In some patients, a diuretic may be used to decrease the swelling. Lateral tarsorrhaphy is helpful in some patients with Graves' ophthalmopathy who have exophthalmos. Protecting the cornea from dryness and relieving eye discomfort is essential. In patients with severe inflammation, prednisone may be used alone or in combination with cyclosporine. Retrobulbar external irradiation (2,000 rad) over a period of 2 to 3 weeks may help during the acute phase. Patients who develop signs of optic nerve compression or strabismus may require retrobulbar corrective surgery.

Thyrotoxic Storm

Thyrotoxic storm is an uncommon but life-threatening complication of Graves' disease in which there is an exaggerated autonomic and systemic response. Patients present with high fever, hypotension, marked weakness, altered mentation, cardiovascular collapse, and shock as a result of failure to regulate vital functions in a state of extreme hypermetabolism. Precipitating factors include diabetic ketoacidosis, infection, and trauma, including surgery in untreated patients with Graves' disease. Thyroid hormone levels are elevated, and a radioiodine scan is likely to show very high tracer uptake. Management includes

- treatment with intravenous fluids, oxygen, and rapid cooling with a cooling blanket in an intensive care unit. Aspirin should not be used because it decreases binding of proteins to thyroid hormone.
- treatment with an iodide preparation such as ipodate sodium that decreases thyroid hormone secretion.
- propylthiouracil, which is superior to methimazole because it prevents the peripheral conversion of T_4 to T_3.
- intravenous or oral propranolol, which can block the sympathetic response and prevent peripheral conversion of T_4 to T_3.
- glucocorticoids, which should be used to prevent adrenal exhaustion and block the conversion of T_4 to T_3.[10]

Multinodular Toxic Goiter (Plummer's Disease)

Hyperthyroidism may be attributable to one or more autonomous functioning thyroid nodules. If the nodules are of sufficient size to secrete excessive levels of T_3 and T_4, the remaining gland will be suppressed and the patient will become thyrotoxic.[11] Plummer's

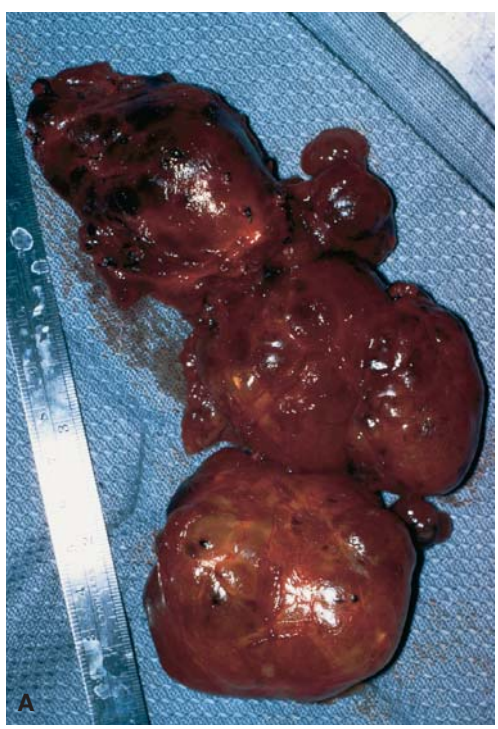
disease generally affects elderly patients. Patients with Plummer's disease often have milder symptoms than patients with Graves' disease, and there may be a longer history. Plummer's disease patients are more likely to have a greater weight loss, mood depression, cardiac disease with atrial fibrillation, and muscle wasting. Extrathyroidal manifestations of Graves' disease rarely or never occur in patients with Plummer's disease.

The recognition of hyperthyroid symptoms is rather difficult because the manifestations of Plummer's disease are usually mild in a patient with a long-standing history of multinodular goiter and apathetic hyperthyroidism. The diagnosis is usually confirmed by documenting elevated levels of thyroid hormones or a suppressed TSH level. It is important to measure T_3 in these patients owing to a higher incidence of T_3 thyrotoxicosis. Antibodies against TSH and thyroperoxidase are usually absent. Scanning reveals one or more areas of increased uptake and suppressed areas between them. Surgery is the ideal treatment for Plummer's disease (Figure 1–22) because

- patients have nodules that may not resolve after radioactive iodine ablation;
- uptake is often relatively low, requiring high doses of radioiodine, almost twice that given to Graves' disease patients for successful treatment; and
- the thyroid tissue adjacent to the thyroid nodule receives about 2,000 rads, which is in the carcinogenic range.[12–14]

TSH-Secreting Pituitary Tumors

TSH-secreting pituitary adenoma is a rare but important cause of thyrotoxicosis (Figure 1–23). Excessive secretion of TSH by the pituitary stimulates the thyroid gland to grow and produce excess thyroid hormone. The goiter is usually relatively small. A TSH-secreting pituitary adenoma should be suspected in a patient with high TSH and elevated thyroid hormone levels. An MRI scan of the pituitary in a patient with an elevated alpha subunit of TSH and hyperthyroidism confirms the diagnosis. Such patients are treated by a transsphenoidal approach to remove the tumor. External irradiation is used when the tumor is invasive after excision or as definitive therapy. Finally, medical therapy with a somatostatin analogue can be effective to control TSH secretion or the thyroid hormone production can be controlled by antithyroid drugs. Rarely, a



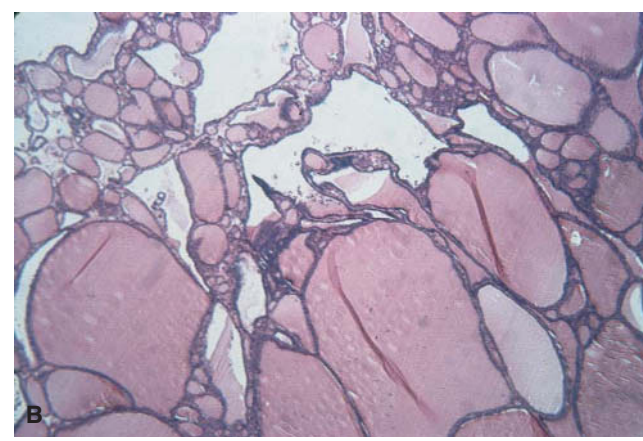


Figure 1–22. Patients with Plummer's disease are about 10 years older than patients with Graves' disease. Plummer's disease is also relatively common in older patients with multinodular goiters. *A*, A T_3 thyrotoxic multinodular goiter from one lobe in a patient with recurrent goiter. The gland weighed 180 g. (Normal thyroid glands weigh 20 g on average.) Note the increased vascularity of the gland. *B*, Photomicrograph of the specimen in *A* shows several small hyperplastic follicles in the background of a typical colloid goiter with multiple cystic spaces and large follicles with flat cuboidal epithelia (hematoxylin and eosin; ×40 original magnification).

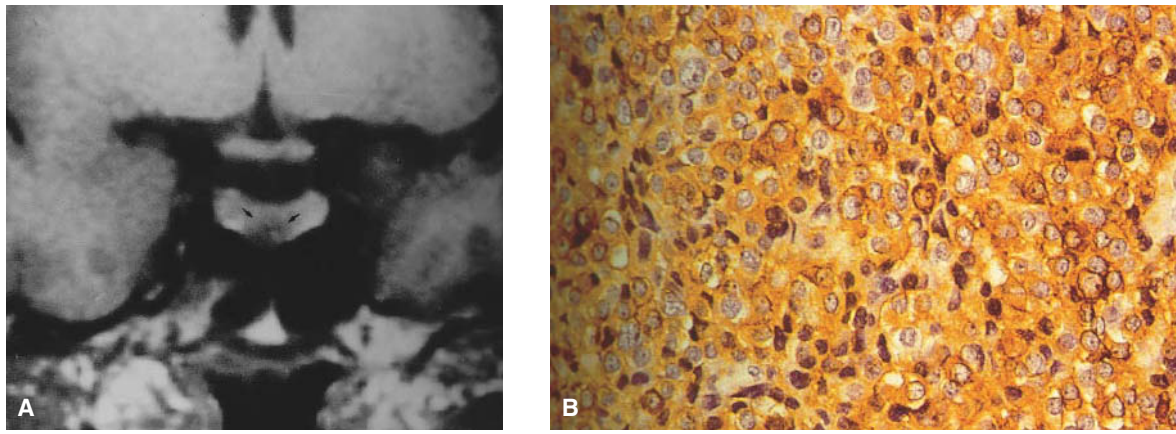


Figure 1–23. Thyroid-stimulating hormone (thyrotroph) adenomas are among the rarest types of pituitary tumors. *A*, Coronal T_1-weighted image reveals a 5 mm centrally located adenoma associated with focal deformity in the floor of the sella turcica. Their appearance is similar to other adenomas except that they are more frequently centrally located. Reproduced with permission from Atlas SW. Magnetic resonance imaging of the brain and spine. New York: Raven Press; 1991. *B*, Photomicrograph of a thyrotroph adenoma reveals round to angular cells that contain abundant immunoreactive hormone (immunoperoxidase stain) (hematoxylin and eosin; ×100 original magnification). Reproduced with permission from Damjanov I, Linder J. Anderson's pathology. 10th ed. St. Louis: Mosby-Yearbook; 1996.

patient may need a total thyroidectomy to treat the thyrotoxic manifestations.[15]

Functional Metastases of Follicular Thyroid Cancer

Sizable masses of metastatic follicular thyroid cancer may produce excessive quantities of thyroid hormones, resulting in hyperthyroidism. Treatment is usually palliative, with debulking surgery and RAI ablation to decrease thyroid hormone levels (Figure 1–24). Antithyroid medications may also be necessary.

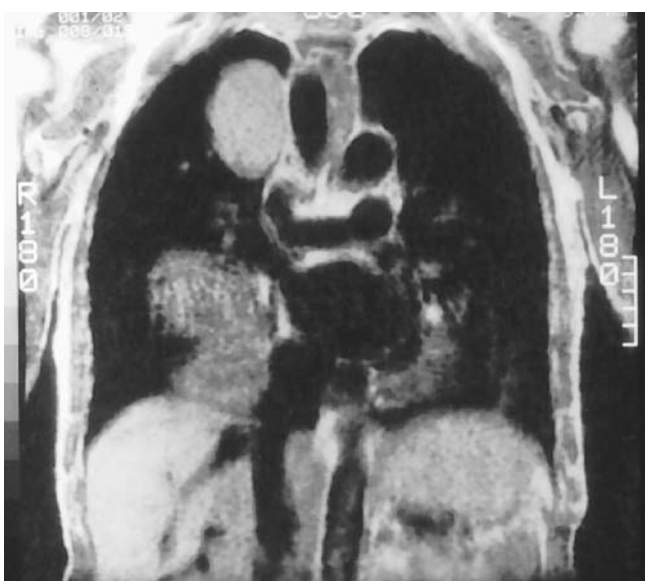


Figure 1–24. Disseminated metastases of follicular carcinoma are usually in lungs or bones as seen in this coronal magnetic resonance image.

Trophoblastic Disease

There is abundant evidence that the human chorionic gonadotropin hormone (HCG) is a weak TSH agonist. An increased HCG level in trophoblastic disease (choriocarcinoma or molar pregnancy) stim-

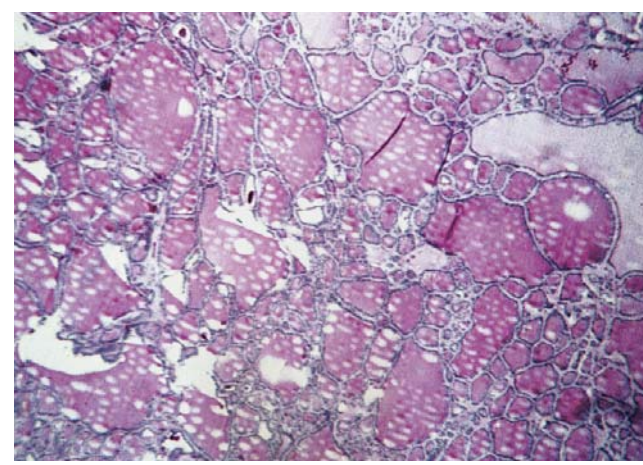


Figure 1–25. Photomicrograph of the jodbasedow effect following iodine loading in a goiter patient. Note the hyperplasia and scalloping of the follicles consistent with increased activity (hematoxylin and eosin; ×40 original magnification).

Table 1–4. CLASSIFICATION OF THYROIDITIS

Disease	Onset	Etiology
Suppurative	Acute	Bacterial
de Quervain's	Subacute	Viral
Hashimoto's	Chronic	Autoimmune
Riedel's	Chronic	Idiopathic

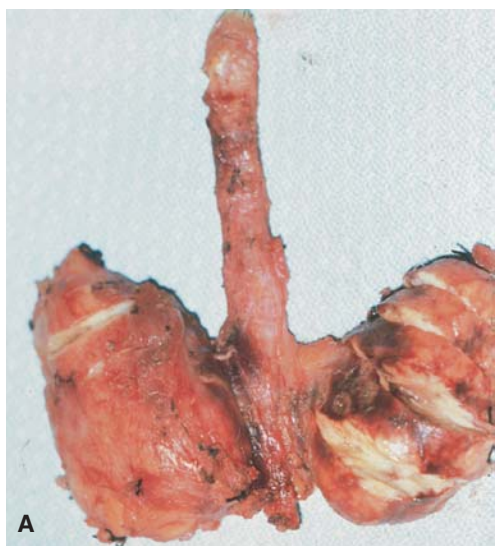
ulates the thyroid gland, causing thyrotoxic manifestations proportional to the level of HCG. Evacuation of the molar pregnancy or effective chemotherapy of the choriocarcinoma cures the hyperthyroidism. Some of these patients require symptomatic treatment with β-blockers.[16]

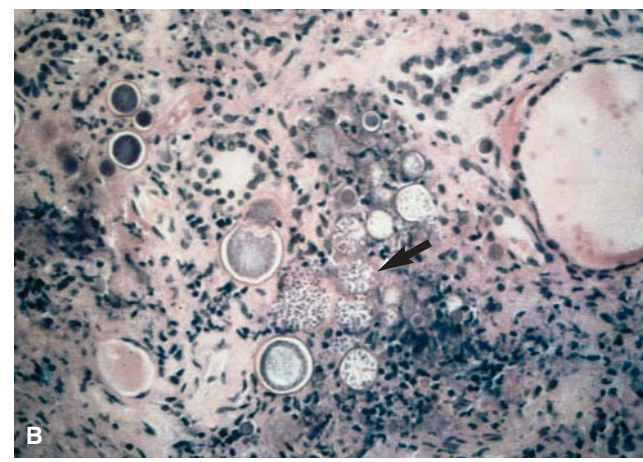
Jodbasedow Effect

Iodine-induced hyperthyroidism, jodbasedow hyperthyroidism, occurs following iodine replacement in patients with goiters in iodine-deficient areas and following iodine loading. Typically, the patient who has had a nonfunctioning nodular goiter presents with tachyarrhythmia or heart failure after being given an iodine-containing radio contrast agent or being treated with amiodarone. Increased urinary iodine concentrations and low radioiodine uptake in the thyroid gland confirm the diagnosis. In mild cases, antithyroid medications are used. Potassium perchlorate given as 200 mg four times a day can prevent iodine uptake and block thyroid hormone formation.[17] Occasionally, these patients require dialysis or emergency thyroidectomy (Figure 1–25).

THYROIDITIS

Thyroiditis represents a variety of infectious and autoimmune inflammatory diseases of the thyroid and can be classified based on onset and pathogenesis, as in Table 1–4.[18]





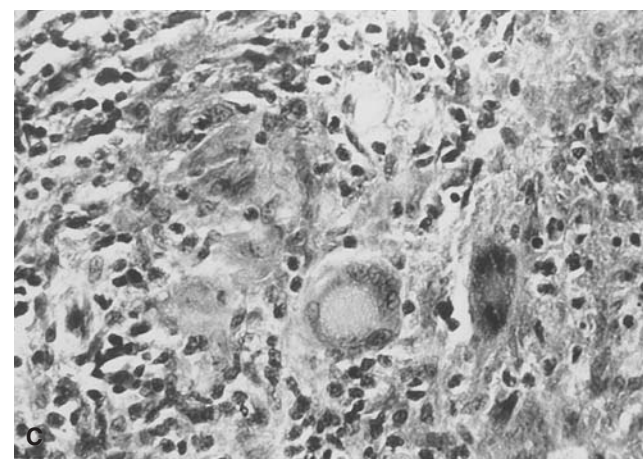


Figure 1–26. Suppurative thyroiditis is usually an acute disease that results from bacterial infections, but, on rare occasions, tuberculosis and fungi may infest the thyroid gland. *A*, Coccidioidomycosis thyroiditis in a patient on long-term corticosteroids for systemic vasculitis. Linear cuts were made in the thyroid tissue to show evidence of central necrosis. Note the large pyramidal lobe that is also involved. *B*, Photomicrograph of the specimen in *A* showing a necrotic area of the thyroid gland formed by mature spherules of *Coccidioides immitis* filled with endospores (*arrow*) (hematoxylin and eosin; ×100 original magnification). *C*, Photomicrograph of tuberculous thyroiditis reveals multiple giant cells and acid-fast bacilli (hematoxylin and eosin; ×250 original magnification).

Acute Suppurative Thyroiditis

Although the thyroid gland is very resistant to infection, bacterial and very rarely fungal infections have been reported. Patients present with fever and erythema overlying a tender swollen gland. Isolation of the organism in FNA establishes the diagnosis and guides appropriate antimicrobial therapy. Organisms include staphylococcus, streptococcus, pneumococcus, salmonella, and bacteroides. Fungus and tuberculosis have been reported rarely (Figure 1–26).[19,20] Some patients may need drainage of the abscess and, very rarely, thyroidectomy. FNA or occasionally open biopsy is also helpful to rule out an undifferentiated thyroid carcinoma with extensive necrosis. Some patients with thyroid neoplasms that rapidly infiltrate the thyroid can cause a pseudothyroiditis. This can also occur in patients with amyloidosis of the thyroid gland. In children with acute thyroiditis, the presence of a piriform fossa sinus must be excluded by a barium swallow of the pharynx.[21] Recently, ultrasonography and esophagography have been used successfully in detecting this congenital anomaly.[22] The sinus must be excised to avoid recurrence.

Subacute Granulomatous (de Quervain's) Thyroiditis

Subacute or de Quervain's thyroiditis frequently follows an upper respiratory viral infection and has been associated with human leukocyte antigen (HLA)-B35.

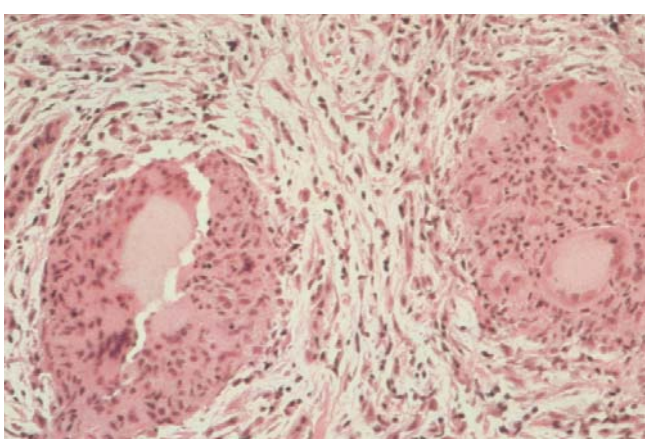


Figure 1–27. Photomicrograph of granulomatous thyroiditis showing foreign-body giant cells surrounding a colloid follicle. Note the fibrosis and squamous metaplasia that resulted from the chronicity of the illness (hematoxylin and eosin; ×100 original magnification).

Although autoantibodies and lymphocytic infiltration of the thyroid gland have been detected in some patients, they are thought to represent a secondary phenomenon.[23] The thyroid gland is enlarged, painful, edematous, and severely tender, although some patients may have no pain (painless thyroiditis).[24] Microscopic features include foci of chronic inflammation and foreign-body giant cells that surround follicles and engulf colloid. An elevated sedimentation rate and a marked decrease in radioiodine uptake characterize this disorder, which is self-limited (Figure 1–27). However, some patients may need symptomatic therapy with aspirin and nonsteroidal anti-inflammatory medications during the initial hyperthyroid state and may occasionally need corticosteroids to suppress the inflammation and control the pain.[25] Some experts recommend treating these patients with thyroid hormone once the thyrotoxicosis resolves, although most patients are euthyroid.

Hashimoto's Thyroiditis

Chronic lymphocytic thyroiditis was first recognized by Hashimoto in 1912 (Figure 1–28). Hashimoto's thyroiditis is an organ-specific autoimmune disease that affects about 15% of the women in the United

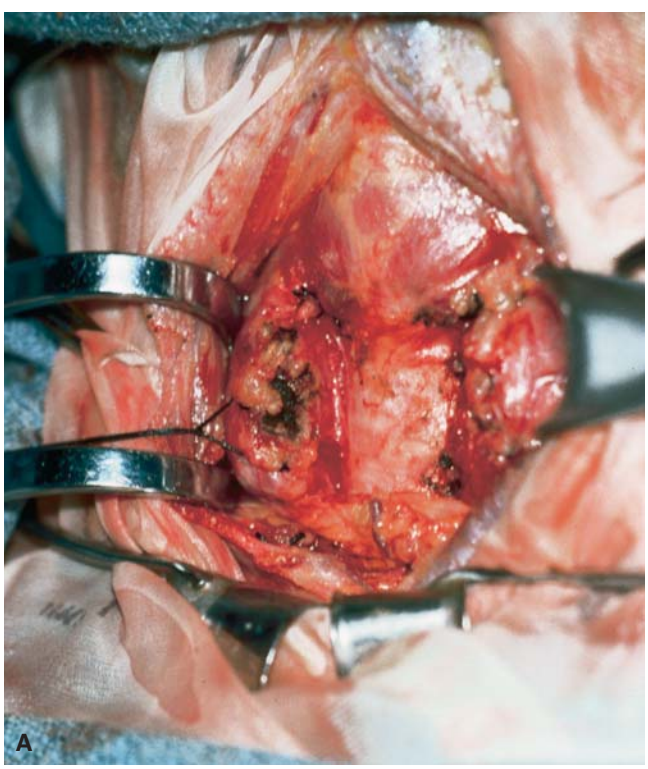
Figure 1–28. Hakaru Hashimoto. Reproduced with permission from Welbourn RB. The history of endocrine surgery. New York: Praeger; 1990.

States and Japan. It is about nine times more common in women than in men. Hashimoto's thyroiditis usually presents clinically between the third and fifth decade of life and can occur in combination with other autoimmune disorders such as Addison's disease and pernicious anemia (Schmidt's syndrome), as well as with diabetes mellitus. HLA association (DR3, 5, and B8), in addition to a preponderance of familial cases, has been reported. Hashimoto's thyroiditis is differentiated from other autoimmune disorders of the thyroid gland by the intensity of lymphocytic infiltration that destroys the thyroid follicles with the formation of lymphoid germinal centers. Autoantibodies are formed against the thyroglobulin and thyroid peroxidase. It is the most common cause of hypothyroidism in nonendemic goiter areas. There is no direct evidence of an increased risk of thyroid cancer in Hashimoto's thyroiditis patients, but the incidence of cancer in reported series ranged between 0.5 and 21%.[26] Also, patients with Hashimoto's thyroiditis are at an increased risk of developing thyroid lymphoma. Patients with Hashimoto's thyroiditis and papillary thyroid cancer are reported to have fewer recurrences and improved survival, although our studies suggest that this may be because they have other good risk factors (young age, female gender, and a small primary tumor).

Hashimoto's thyroiditis is mostly an asymptomatic disease, although about 20% of patients may develop hypothyroidism, which may be the only clinical clue to the presence of Hashimoto's thyroiditis. Typically, those patients present with lethargy, weight gain, cold intolerance, coarse skin, and menorrhagia. Most patients have a small firm goiter (Figure 1–29). About 5% of the patients may present with or develop hyperthyroidism (hashitoxicosis) (Figure 1–30). Occasionally, the thyroid gland may cause compressive symptoms.

Most patients have positive titers to thyroperoxidase, whereas nearly half have antithyroglobulin antibodies and about 15% have elevated TSI levels. Radionuclide scanning often reveals reduced, patchy uptake, although scanning with radioiodine is usually unnecessary. FNA should be performed on dominant nodules to rule out coexistent malignancy.

During the acute initial phase, patients may need symptomatic treatment with antithyroid medications or β-blockers. T_4 replacement therapy is indicated in patients with large goiters and those patients with low normal T_4 and/or elevated TSH levels. Surgery



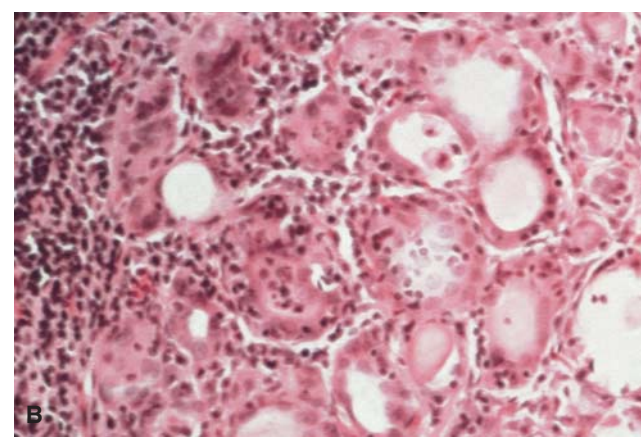
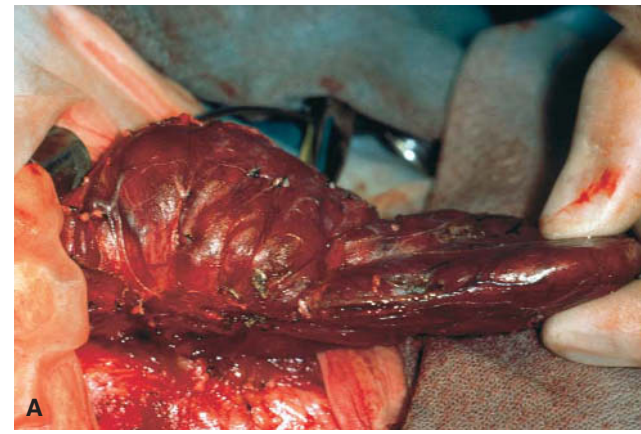
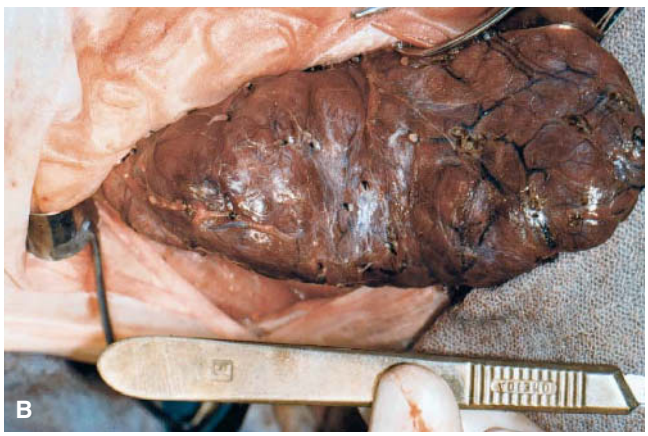


Figure 1–29. Hashimoto's thyroiditis is a chronic autoimmune thyroid disorder that may cause compressive symptoms. *A*, A 50-year-old patient underwent an isthmectomy to remove a benign nodule that had caused pressure symptoms over the trachea immediately below the larynx, which is also seen covered by the cricothyroid muscles. Note the typical pale appearance of the gland as a result of replacing the thyroid follicles with lymphoid tissue. *B*, Photomicrograph of Hashimoto's thyroiditis shows extensive infiltration with mature lymphocytes and oxyphilic changes in the follicular epithelium (hematoxylin and eosin; ×100 original magnification).





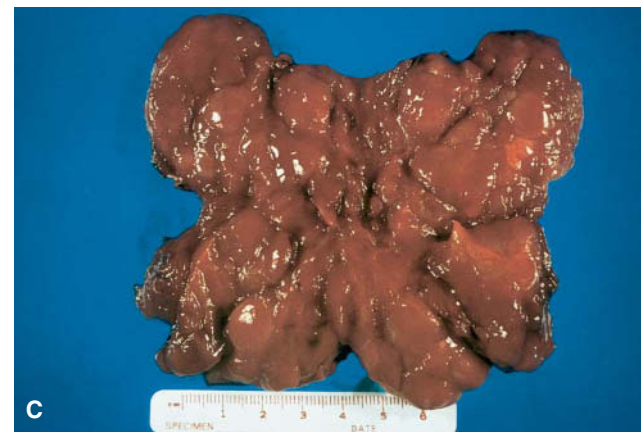


Figure 1–30. Hashimoto's thyroiditis is the most common cause of hypothyroidism in nonendemic areas. It is occasionally associated with hyperthyroidism. *A*, Patient underwent total thyroidectomy for a rapid increase in the growth of a Hashimoto's gland. Instead of the usual pale appearance, this gland has a dark appearance owing to increased vascularity of active thyroid tissue. *B*, Another case of atypical Hashimoto's thyroiditis with rapid growth evident by an enlarged dark thyroid gland. Both patients in *A* and *B* were diagnosed to have combined Hashimoto's and Graves' disease, a condition referred to as hashitoxicosis. *C*, The gland in *B* was bivalved. Note the multinodular appearance of the gland. No evidence of malignancy was seen.

is indicated when there are persistent local symptoms and when malignancy cannot be excluded.

Riedel's Thyroiditis

Patients who have Riedel's thyroiditis, a very rare condition, have an infiltrative dense fibrotic reaction secondary to idiopathic chronic inflammation. It results in a rock-hard and fixed thyroid gland highly suspicious of malignancy. The fibrotic process extends into the perithyroidal soft tissues and skeletal muscle with complete obliteration of the thyroid capsule (Figure 1–31). This process may involve other organs, resulting in synchronous sclerosing mediastinitis, pseudotumor of the orbit, or retroperitoneal fibrosis. It is more prevalent among women. Patients may complain of hoarseness, dyspnea, or dysphagia, but it rarely causes pain. FNA is needed to exclude malignancy.[27] When the aspirate is acellular, as is usually the case, then a core or opened biopsy becomes necessary to exclude malignancy.

The disease has a very favorable prognosis. Once the diagnosis is confirmed, surgical treatment is limited to debulking to diminish the goiter size in symp-

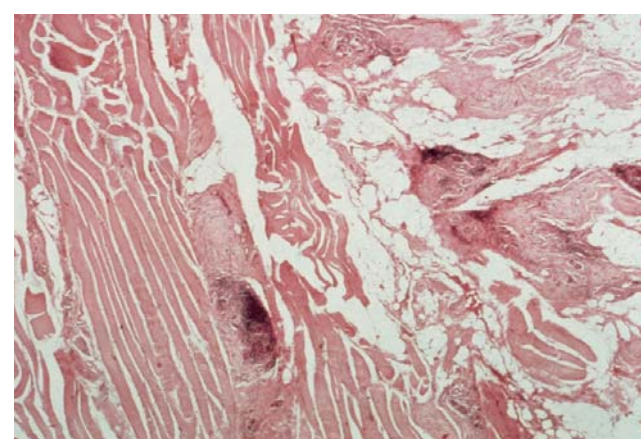


Figure 1–31. Riedel's thyroiditis is characterized by chronic inflammation and extensive fibrosis that replaces the entire thyroid gland with loss of all anatomic planes. Note that the invasion extends into the skeletal muscles, which usually raises suspicion of malignancy. However, the lack of atypical cells, mitosis, or vascular invasion on opened biopsy rules out thyroid cancer and confirms the diagnosis of Riedel's thyroiditis, which has a favorable prognosis (hematoxylin and eosin; ×40 original magnification).

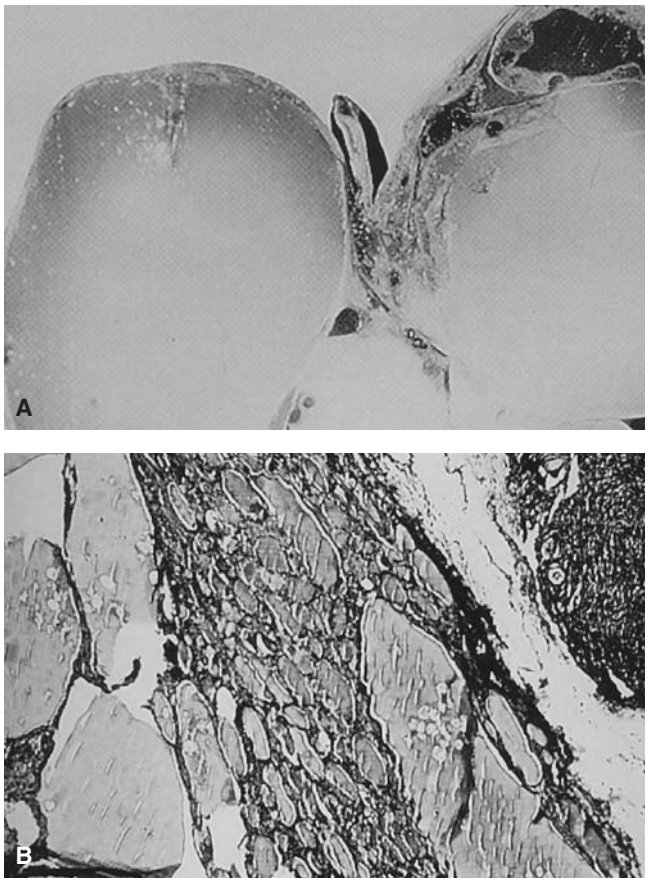


Figure 1–32. Struma ovarii results from the presence of thyroid tissue that becomes hyperactive in an ovarian teratoma. *A*, Typical gross appearance of a struma ovarii. Note that the tumor is composed almost entirely of thyroid tissue. Reproduced with permission from Rosai J. Ackerman's surgical pathology. 8th ed. Mosby-Yearbook; 1996. *B*, Photomicrograph of the specimen in *A* reveals relatively normal thyroid tissue except for some follicular dilatation. The thyroid tissue is surrounded by ovarian stroma consistent with the diagnosis of struma ovarii (hematoxylin and eosin; ×100 original magnification). Reproduced with permission from Rosai J. Ackerman's surgical pathology. 8th ed. S. Louis: Mosby-Yearbook; 1996.

tomatic individuals. Formal surgery is not possible because anatomic planes are not preserved in this disease. Corticosteroids have not been shown to be effective in diminishing the goiter size. Successful treatment with tamoxifen has been reported. Rarely, Riedel's struma, when bilateral, may result in both hypothyroidism and hypoparathyroidism.[27]

Thyroiditis Factitia

The deliberate intake of thyroid hormone, overdosage with thyroid hormone or from eating uncooked, fresh thyroid glands, can cause hyperthyroidism. Suspicion is key to diagnosis in thyrotoxic patients with a normal-size gland and low radioiodine uptake, especially if they or their relatives have had a history of intake of the thyroid hormone. A suppressed thyroglobulin level is also consistent with exogenous intake of thyroid hormone. Patients with factitious hyperthyroidism who take T_3 have suppressed T_4 levels. Treatment is to stop the intake of thyroid hormone with psychological therapy. Rarely, patients may acutely need sympathetic treatment with β-blockers.

Struma Ovarii

Struma ovarii is a thyroid hormone–secreting ovarian teratoma composed predominantly or exclusively of thyroid tissue (Figure 1–32). In these patients, RAI uptake occurs in the teratoma but not in the thyroid gland. Malignant transformation of the thyroid tissue in struma ovarii is uncommon and rarely recurs or metastasizes. This diagnosis is usually suspected in a patient with a pelvic mass and hyperthyroidism in the absence of goiter. It is confirmed by increased tracer uptake in the pelvis with a suppressed thyroid gland. Symptoms usually resolve with resection of the pelvic tumor. Occasionally, patients may need symptomatic treatment with antithyroid drugs. In malignant struma ovarii, radioactive iodine should be used following surgical excision and to treat the rare patient with recurrence or metastasis that cannot be removed surgically.[27]

REFERENCES

1. Leung AK, Wong AL, Robson WL. Ectopic thyroid gland simulating a thyroglossal duct cyst: a case report. Can J Surg 1995;38:87–9.
2. Cavalieri RR. Iodine metabolism and thyroid physiology: current concepts. Thyroid 1997;7:177–81.
3. Hedayati N, McHenry CR. The clinical presentation and operative management of nodular and diffuse substernal thyroid disease. Am Surg 2002;68:245–51.
4. Corvilain B, Van Sande J, Dumont JE, et al. Autonomy in endemic goiter. Thyroid 1998;8:107–13.
5. Bignell GR, Canzian F, Shayeghi M, et al. Familial nontoxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial nonmedullary thyroid cancer. Am J Hum Genet 1997;61:1123–30.
6. Hurley DL, Gharib H. Evaluation and management of multinodular goiter. Otolaryngol Clin North Am 1996;29: 527–40.

7. Trimarchi F, Benvenga S, Lo Presti VP, Vermiglio F. Endemic goiter. Curr Ther Endocrinol Metab 1997;6:101–7.
8. Baldini M, Gallazi M, Orsatti A, et al. Treatment of benign nodular goitre with mildly suppressive doses of L-thyroxine: effect on bone mineral density and on nodule size. J Intern Med 2002;251:407–14.
9. Clark OH, Duh Q-Y. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997.
10. Siegel RD, Lee SL. Toxic nodular goiter. Toxic adenoma and toxic multinodular goiter. Endocrinol Metab Clin North Am 1998;27:151–68.
11. Wahl RA, Rimpl I, Saalabian S, Schabram J. Differentiated operative therapy of thyroid autonomy (Plummer's disease). Exp Clin Endocrinol Diabetes 1998;106 Suppl 4:S78–84.
12. Moser E. Radioiodine treatment of Plummer's disease. Exp Clin Endocrinol Diabetes 1998;106 Suppl 4:S63–5.
13. So WY, Yeung VT, Chow CC, et al. TSH secreting pituitary adenoma: a rare cause of thyrotoxicosis. Int J Clin Pract 1998;52:62–4.
14. Hershman JM. Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. Thyroid 1999;9:653–7.
15. Henzen C, Buess M, Brander L. [Iodine-induced hyperthyroidism (iodine-induced Basedow's disease): a current disease picture]. Schweiz Med Wochenschr 1999;129:658–64.
16. Hamburger JI. The various presentations of thyroiditis. Diagnostic considerations. Ann Intern Med 1986;104:219–24.
17. Smilack JD, Argueta R. Coccidioidal infection of the thyroid. Arch Intern Med 1998;158:89–92.
18. Mondal A, Patra DK. Efficacy of fine needle aspiration cytology in the diagnosis of tuberculosis of the thyroid gland: a study of 18 cases. J Laryngol Otol 1995;109:36–8.
19. Bar-Ziv J, Slasky BS, Sichel JY, et al. Branchial pouch sinus tract from the piriform fossa causing acute suppurative thyroiditis, neck abscess, or both: CT appearance and the use of air as a contrast agent. AJR Am J Roentgenol 1996;167:1569–72.
20. Ahuja AT, Griffiths JF, Roebuck DJ, et al. The role of ultrasound and oesophagography in the management of acute suppurative thyroiditis in children associated with congenital pyriform fossa sinus. Clin Radiol 1998;53:209–11.
21. Sarlis NJ, Brucker-Davis F, Swift JP, et al. Graves' disease following thyrotoxic painless thyroiditis. Analysis of antibody activities against the thyrotropin receptor in two cases. Thyroid 1997;7:829–36.
22. Bianda T, Schmid C. De Quervain's subacute thyroiditis presenting as a painless solitary thyroid nodule. Postgrad Med J 1998;74:602–3.
23. Topuzovic N, Smoje J, Karner I. The therapeutic approach in subacute (de Quervain's) thyroiditis [letter; comment]. J Nucl Med 1997;38:1665.
24. Okayasu I, Fujiwara M, Hara Y, et al. Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and white and African Americans. Cancer 1995;76:2312–8.
25. Wan SK, Chan JK, Tang SK. Paucicellular variant of anaplastic thyroid carcinoma. A mimic of Riedel's thyroiditis. Am J Clin Pathol 1996;105:388–93.
26. Few J, Thompson NW, Angelos P, et al. Riedel's thyroiditis: treatment with tamoxifen. Surgery 1996;120:993–8; discussion 998–9.
27. Brenner W, Bohuslavizki KH, Wolf H, et al. Radiotherapy with iodine-131 in recurrent malignant struma ovarii. Eur J Nucl Med 1996;23:91–4.

2

Differentiated Thyroid Carcinomas

KEH-CHUAN LOH, MD, FACP, FRCP
THEODORE R. MILLER, MD
FRANCIS S. GREENSPAN, MD, FACP

The scope of this chapter is confined to differentiated thyroid follicular cell–derived carcinomas, which typically account for 80 to 95% of all thyroid cancers; for the purposes of the present discussion, the term differentiated thyroid carcinomas (DTCs) will be used. Papillary thyroid carcinomas (PTCs) account for about 75 to 90% of DTCs, the remaining 10 to 25% being follicular thyroid carcinomas (FTCs) or their variant, Hürthle cell carcinomas (HCCs).[1]

EPIDEMIOLOGY

Incidence, Mortality, and Prevalence

Although comprising less than 1% of clinically diagnosed malignancies, thyroid cancers are the most common endocrine neoplasms, and they kill more patients than all other endocrine malignancies combined. Approximately 19,500 new cases of thyroid cancer are diagnosed each year in the United States, resulting in 1,300 deaths annually. However, an estimated 500,000 patients have been treated effectively and are survivors of thyroid cancer.[2] Worldwide, the annual incidence rate varies from 0.5 to 10 per 100,000 population. The incidence of thyroid cancer increases with age in adults; the median age at diagnosis is 45 to 50 years, and thyroid cancer is two to four times as frequent in women as in men.[1,2]

Five to 36% of adults are reported to have occult thyroid carcinomas at autopsy. In contrast to clinically diagnosed malignant lesions of the thyroid, these are characteristically small (< 1 cm) and innocuous tumors that have become well recognized in recent years because of serial sectioning and thorough microscopic examination.

Risk Factors

Familial association is noted in only a minority of cases of DTC, as described in patients with Cowden disease (multiple hamartoma syndrome), Gardner's syndrome (adenomatous polyposis coli), and familial PTC.[3,4]

The only established environmental risk factor for PTC is radiation exposure to the thyroid in childhood. In subjects with a childhood history of external irradiation to the head and neck region, PTC typically develops after a latency period of at least 5 years, reaching its peak incidence at about 20 years and then declining gradually in incidence after another 20 years. Besides external irradiation, the Chernobyl nuclear accident proved that radioactive isotopes of iodine also have a direct tumorigenic effect on the thyroid. In Belarus and Ukraine, PTC develops mostly in children who were younger than 10 years old at the time of the accident, with onset noted as early as 4 years after exposure.[5]

The pathogenesis for FTC is unclear. Although it appears to be relatively more prevalent in countries where iodine intake is low, the overall incidence of DTC remains unchanged in these regions.

GENETICS

Recent advances in molecular biology have significantly improved our understanding of the genetics of

DTC. The genetic changes involved are likely to determine both the histologic appearance and the biologic behavior of the thyroid cancer. PTC appears to arise de novo within the thyroid gland as a result of receptor tyrosine kinase activation by *RET* or *NTRK1* gene rearrangement. Intrachromosomal inversion of the *RET* proto-oncogene (chromosome 10q11.2) has been reported in 10 to 70% of PTCs, being found most commonly in tumors arising after exposure to ionizing radiation. Four types of *RET* rearrangements have been observed, designated *RET/PTC1* to *RET/PTC4,* respectively (Figure 2–1). Constitutive *RET* activation occurs with these rearrangements, which is believed to play a direct role in carcinogenesis.[6] *RET/PTC* variants are found in less than half of PTCs in the adult population, whereas the prevalence is > 70% in children with radiation-induced PTC. Children with post-Chernobyl PTC showed a striking preponderance of the *RET/PTC3* gene and phenotypic association with a solid variant papillary tumor.[5]

In follicular neoplasms, a spectrum of increasingly severe chromosomal abnormalities is observed from benign to malignant lesions. Activation of the *RAS* oncogene is believed to be an early event in tumorigenesis, as observed in up to 40% of both follicular adenoma (FA) or FTC. Numerical and structural abnormalities have been demonstrated on chromosomes 3p, 7q, 10q, and 17p, which are likely targets for tumor suppressor gene inactivation (Figure 2–2). The loss of one or more putative tumor suppressor genes could be specific for FTC formation, or it might induce the transformation of benign adenoma to carcinoma. Structural chromosomal aberrations have been identified in 30% of FA, 60% of typical FTC, and 80% of HCC.[7]

In patients with DTC, tumor dedifferentiation may occasionally occur owing to inactivating mutations of the *P53* tumor suppressor gene, leading to the formation of anaplastic thyroid cancer.[8]

DIAGNOSIS

Most thyroid cancers present as asymptomatic thyroid nodules, of which 80 to 95% are benign hyperplastic nodules rather than true neoplasms.[9] Furthermore, most of the true neoplasms are benign adenomas rather than thyroid cancers. The task of identifying malignant nodules is therefore a challenge in itself as thyroid nodules are found in 5 to 10% of the population.

Among patients with palpable thyroid nodules, the history is usually not helpful in detecting underlying thyroid malignancy. Symptoms such as hoarseness of voice, dysphagia, or shortness of breath are uncommon and suggest advanced malignancy. However, an increased risk for malignancy is recognized in individuals with a history of ionizing radiation exposure in childhood, appearance of nodules at an age younger than 20 years or older than 60 years, and the male sex in general. Virtually all patients with DTC are clini-

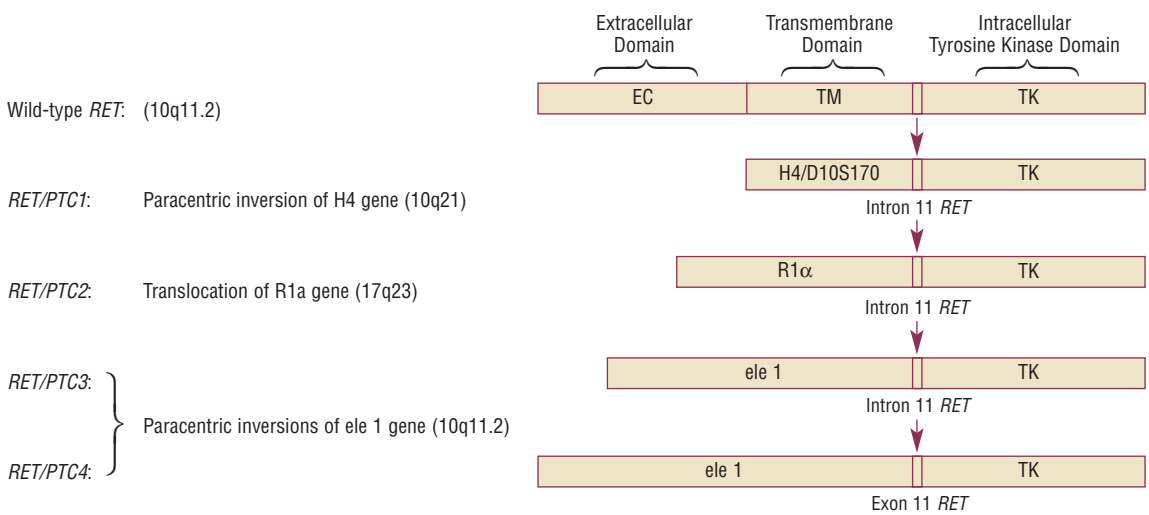


Figure 2–1. Schematic representation of the wild-type *RET* proto-oncogene and activated forms of *RET*/*PTC* rearrangements in human papillary thyroid carcinomas. *Arrows* indicate breakpoints in the *RET* proto-oncogene and site of fusion with the rearranged genes.

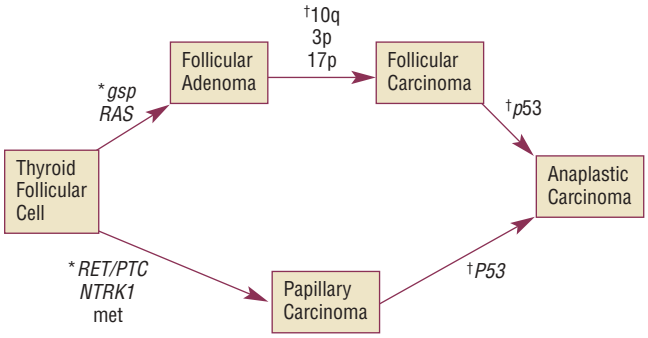


Figure 2–2. Proposed multistep tumorigenesis in differentiated thyroid carcinomas. *Oncogene activation; †tumor suppressor gene inactivation.

cally euthyroid and have normal serum thyrotropin (thyroid-stimulating hormone [TSH]) concentrations.[10]

The most cost-effective method for diagnosing malignant thyroid nodules is by fine-needle aspiration biopsy (FNAB). FNAB is reliable in identifying PTC (Figure 2–3); however, it does not distinguish FTC from benign FA (Figure 2–4). This is because the cytology obtained from FNAB of an FTC may be identical to that obtained from an FA, and the diagnosis of malignancy is based on the presence of capsular or vascular invasion on histologic examination of the surgical specimen (Figure 2–5). FNAB may yield one of four results (Figure 2–6): benign, malignant, suspicious, or insufficient yield. The management strategy may be summarized as follows: if the lesion is benign, the patient may be put on thyroxine (T_4) therapy to suppress TSH to a level just below normal, or the patient may simply be followed for evidence of growth or obstructive symptoms. If the lesion is malignant (PTC), the patient is referred for surgery. If the finding is suspicious for follicular or Hürthle cell

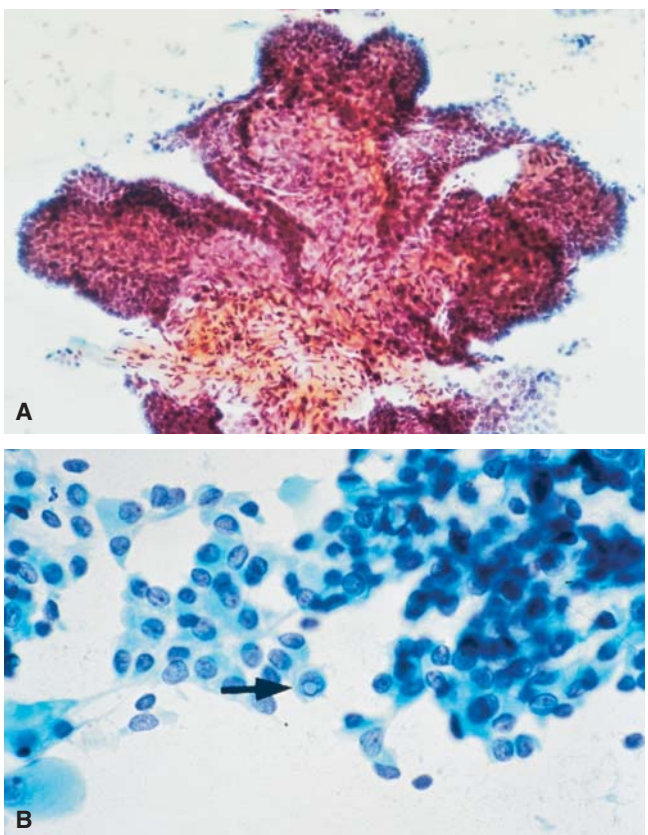


Figure 2–3. Fine-needle aspiration biopsy of a papillary thyroid carcinoma showing *A*, an example of papillary fronds with fibrovascular cores as seen on Papanicolaou-stained material (×20 original magnification); *B*, a nuclear inclusion in the center of the field (*arrow*) (Papanicolaou stain; ×40 original magnification).

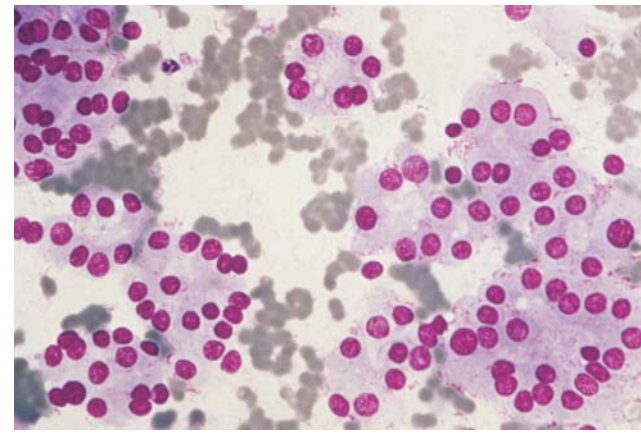


Figure 2–4. Fine-needle aspiration biopsy of a follicular neoplasm demonstrating numerous microfollicular structures and an absence of colloid (May-Grünwald/Giemsa stain; ×20 original magnification).

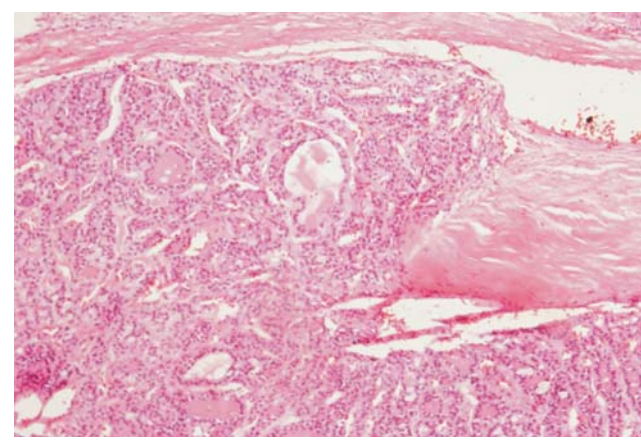


Figure 2–5. Photomicrograph showing a section through the capsule of a follicular carcinoma. A tongue of tumor is seen projecting into the capsule as well as into the lumen of a vessel (hematoxylin and eosin stain; ×20 original magnification).

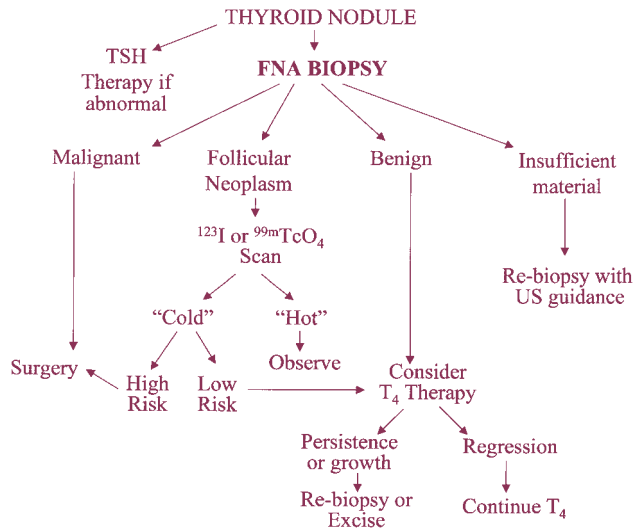


Figure 2–6. Algorithm for clinical approach to a thyroid nodule. FNA = fine-needle aspiration; TSH = thyroid-stimulating hormone; T_4 = thyroxine; US = ultrasound.

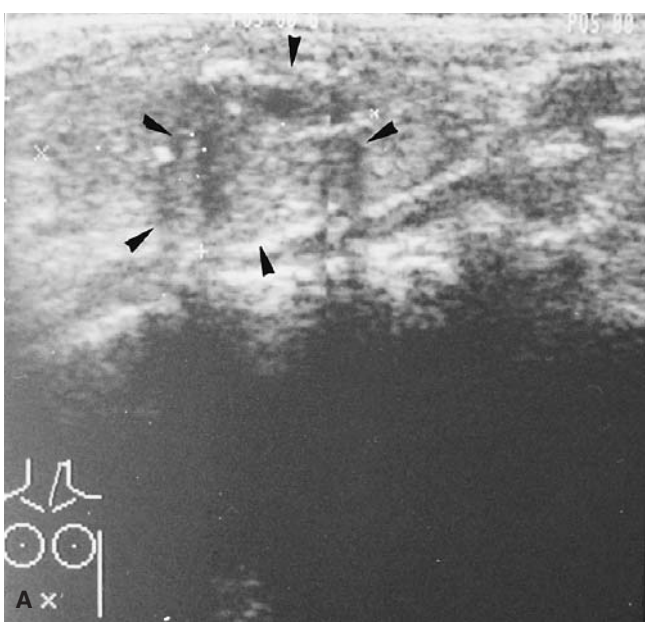
neoplasm, lobectomy is usually indicated to exclude malignancy, which may be found in 15 to 22% of such nodules. A repeat FNAB is necessary if there is insufficient material for diagnosis, and the use of thyroid ultrasonography may improve the yield in biopsy of deep-seated or mixed cystic nodules.[11]

When performed by an experienced operator and interpreted by a competent cytopathologist, the sensitivity of thyroid FNAB is 95 to 98% and the specificity is 97 to 99%.[9] False-negative results, usually from sampling or interpretive errors, and false-positive results are rare. FNAB is less reliable in patients who have been exposed to ionizing radiation or in patients with a family history of thyroid cancer because there is an increased frequency of both benign and malignant thyroid neoplasms in these patients.

Radionuclide thyroid scan may be used to determine the functional status of a nodule that has been interpreted as follicular neoplasm by FNAB, particularly in subjects who are reluctant to undergo surgery. Overall, only about 5% of all thyroid nodules are "hot" by radionuclide scanning; however, the incidence is somewhat higher among patients with follicular neoplasms. As "hot" nodules are rarely malignant, these patients, if euthyroid, can therefore be followed up medically rather than be treated surgically (Figure 2–7).

HISTOLOGIC FEATURES AND SUBTYPES

The usual PTC demonstrates an ill-defined margin indicating an invasive neoplasm. The cut surface is granular and may show cystic change. The tumor is firm to palpation and varies from white to tan. The microscopic defining features of this neoplasm are papillary formations and nuclear changes. Papillae are formed by a central fibrovascular stalk covered by neoplastic epithelium (Figure 2–8). The cytoplasm of the tumor cells is denser in quality than the cytoplasm of follicular lesions. The characteristic



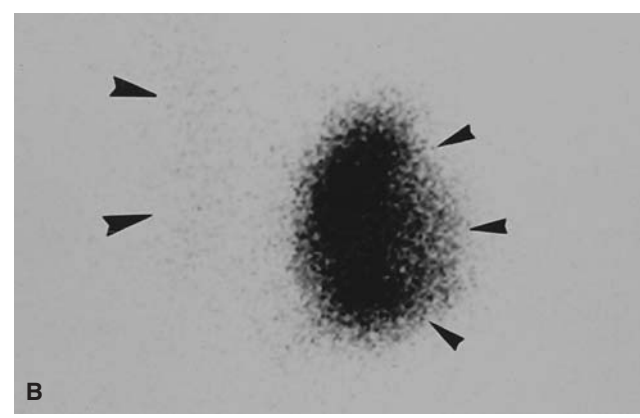


Figure 2–7. Patient with an autonomously functioning or "hot" thyroid nodule. *A*, Sonogram of thyroid showing a 3.6 × 2.1 cm mixed echogenic nodule (*arrowheads*) occupying almost the entire left lobe. *B*, Radioactive iodine (^{131}I) thyroid scan showing intense tracer uptake by the nodule (*small arrowheads*) with suppressed tracer uptake in the right lobe (*larger arrowheads*). Courtesy of E. S. Ang, MD, Department of Nuclear Medicine, Singapore General Hospital, Singapore.

nuclear changes include the clearing of chromatin, nuclear grooving, and nuclear cytoplasmic inclusions. A third useful marker of PTC is the finding of laminated calcific structures called psammoma bodies (see Figure 2–8). PTC is multicentric and bilateral in 20 to 30% of patients clinically; the incidence is as high as 50 to 80% on careful histologic studies. Patients with combined papillary and follicular elements are classified as PTC based on their biologic behavior. Tumor spread in PTC is nearly exclusively by lymphatics, and approximately 20 to 40% of adults and 60 to 90% of children have intraoperatively palpable lymphadenopathy.[12]

FTC is grossly similar to benign FA. The general shape is round and tan to brown with a solid cut surface. The tumor often has a grossly visible capsule that is thick and irregular. Microscopically, these tumors will show a solid pattern of neoplastic follicles that are best described as microfollicles. The lumens of these microfollicles will be very small to absent. Evaluation of the capsule will demonstrate penetration of the entire thickness with neoplastic cells mushrooming outward into the normal parenchyma. A more reliable sign of malignancy is the presence of vascular invasion (see Figure 2–5). The vessels that need to be examined are those located within the capsule or immediately outside it and not the vessels within the tumor proper. The cells of FTC have large round nuclei and fragile cytoplasm. A variant of this tumor, termed HCC (oxyphilic tumor or oncocytoma), consists of tumor cells that have abundant granular cytoplasm that stains pink on hematoxylin and eosin–stained material. The granular cytoplasm is the result of a cytoplasm that is filled with mitochondria (Figure 2–9).[13]

CLASSIFICATION AND STAGING

Based on risk group assignments, patients with DTC are generally separated into those with good to excellent prognoses versus those with poorer prognoses. This is important to guide the treatment strategy in order that patients with a low risk for cancer recurrence or death are managed in a less aggressive manner compared with those in the high-risk category.

Until recently, the proliferation of tumor staging systems for DTC led to much heterogeneity and difficulty in comparing the results across institutions. Therefore, acceptable rules for a staging system in DTC have been adopted by the American Joint Committee on Cancer (AJCC) and the Tumor-Node-Metastasis (TNM) Committee of the International Union Against Cancer (UICC) (Table 2–1). An interesting feature of the TNM staging system is the primacy of the patient's age at diagnosis: irrespective of the T and N categories, patients below 45 years and with no distant metastases have stage I disease, whereas those with distant metastases are classified as having stage II tumor. In patients aged 45 years and older, however, the staging system for papillary and follicular thyroid cancer follows the conventional paradigm and is similar to that adopted for patients with medullary thyroid

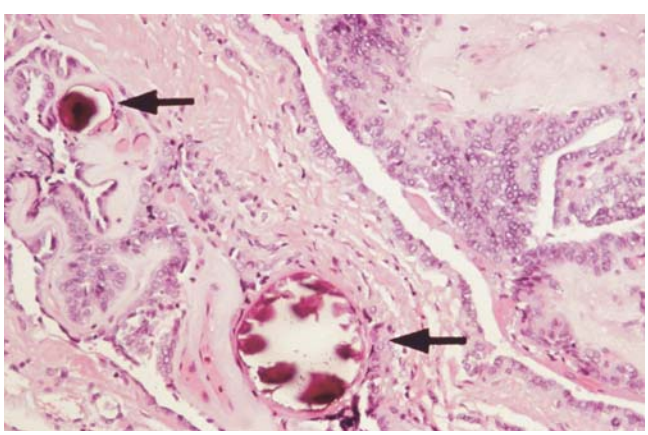


Figure 2–8. A histologic section of a papillary carcinoma demonstrating psammoma bodies (*arrows*) and fibrovascular stalks surrounded by epithelium (hematoxylin and eosin stain; ×20 original magnification).

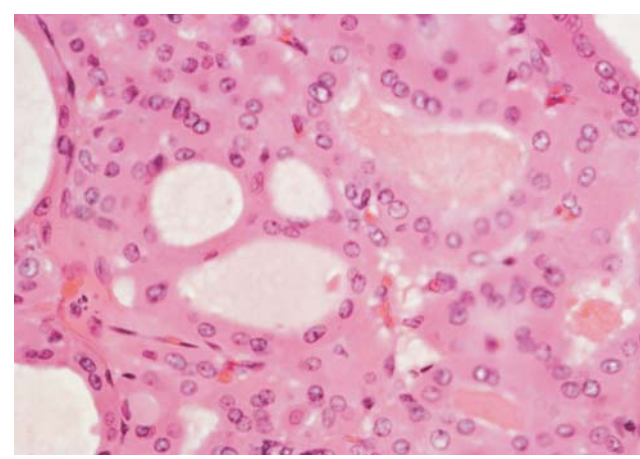


Figure 2–9. A histologic section of a Hürthle cell carcinoma. Note the abundant eosinophilic, granular cytoplasm (hematoxylin and eosin stain; ×20 original magnification).

Table 2–1. TNM STAGING ADOPTED BY THE AMERICAN JOINT COMMITTEE ON CANCER STAGE CLASSIFICATION FOR THYROID CANCER (2002 REVISIONS INCORPORATED)

	Papillary or Follicular			
Stage	Age < 45 yr	Age ≥ 45 yr	Medullary (any age)	Anaplastic (any age)
I	M0	T1	T1	—
II	M1	T2	T2	—
III	—	T3 or N1a	T3 or N1a	—
IVa	—	T4a or N1b	T4a or N1b	T4a*
IVb	—	T4b	T4b	T4b*
IVc	—	M1	M1	M1

T (primary tumor): T1 = ≤ 20 mm; T2 = 20–40 mm; T3 = > 40 mm; T4a = invasion of subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve; T4b = invasion of prevertebral fascia or encasement of carotid artery or mediastinal vessels.
N (nodal disease): N1a = metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes); N1b = metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes.
M (distant metastasis): M0 = no distant metastasis; M1 = distant metastasis.
*All anaplastic carcinomas are considered T4 tumors: T4a = intrathyroidal (surgically resectable) tumor; T4b = extrathyroidal (surgically unresectable) tumor.
Adapted from Green FL et al.[14]

cancer.[14] This reflects the more aggressive nature of differentiated follicular cell–derived thyroid cancers in older patients. Our DTC series clearly demonstrated different disease-free survival and cancer-specific survival rates, respectively, in patients from different TNM stages (Figures 2–10 and 2–11).[15]

Unfortunately, the setback in any tumor staging system for DTC is the fact that 20 to 30% of patients in the low-risk group will develop recurrence and a minority will die of thyroid cancer. It remains a formidable challenge to identify these individuals at the outset and to determine if aggressive initial treatment would impact on the final outcome.[10,15–19]

TREATMENT

The guiding principle in managing patients with DTC is to avoid either overaggressive treatment in a patient with an excellent prognosis or inadequate therapy for the unusual patient with a high risk of tumor recurrence and possible death from thyroid cancer. However, what constitutes the appropriate therapy in patients with DTC is still a subject of intense debate because no prospective randomized clinical trials exist and none are likely to be done. Given the slow progression and good prognosis of the disease, it is difficult to demonstrate a beneficial

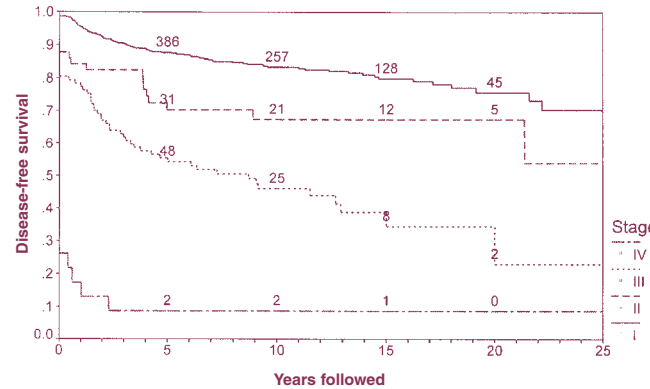


Figure 2–10. Disease-free survival curves for patients with differentiated thyroid carcinoma by pTNM staging ($p < .0001$ among all stages). Reproduced with permission from Loh KC et al.[15]

effect of therapy unless very large cohorts are studied over several decades.

THYROID SURGERY

Surgery is the primary treatment for DTC and should be performed by a surgeon with expertise in thyroid surgery. In the very low-risk patients with a single small focus of PTC (≤ 1.0 cm) confined within the thyroid lobe, a lobectomy and isthmusectomy may be adequate as most studies do not demonstrate better survival rates after a total or near-total thyroidectomy compared with a lobectomy plus an isthmusectomy. Because PTC is a potentially multicentric and bilateral disease, one should, however, recognize a small but significant long-term risk of local recurrence after unilateral lobectomy.[15,18]

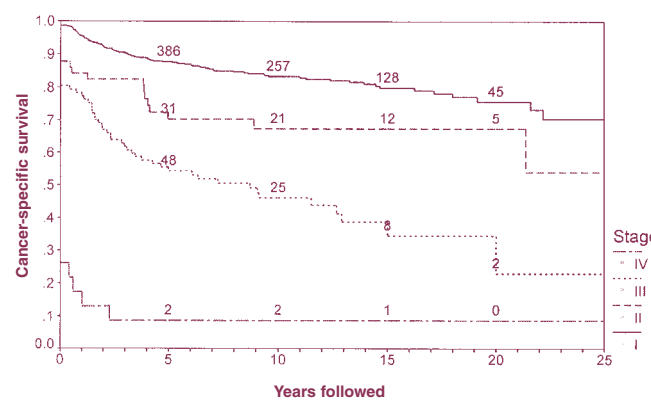


Figure 2–11. Cancer-specific survival curves for patients with differentiated thyroid carcinoma by pTNM staging ($p < .0001$ among all stages). Reproduced with permission from Loh KC et al.[15]

Conversely, most experts would agree to a total or near-total thyroidectomy in patients with multicentric or bilobar disease, locally invasive tumor, nodal or distant metastases, or history of ionizing radiation exposure in childhood. In patients with primary tumor size > 1 cm but without the above-mentioned adverse factors, a lobectomy plus an isthmusectomy is advocated by some, whereas a total or near-total thyroidectomy is practiced in most centers. We prefer the latter approach as total thyroidectomy in particular would facilitate postoperative total-body radioiodine scanning for local or distant metastatic disease and enhance the specificity of using serum thyroglobulin (Tg) as a tumor marker in follow-up. In centers lacking the surgical expertise or having > 1 to 2% complication rates of recurrent laryngeal nerve palsy or hypoparathyroidism, near-total thyroidectomy followed by radioiodine ablation of residual thyroid tissue is an acceptable option as current studies showed similar cancer-specific survival and recurrence rates, respectively.[10,16,17,19]

The initial surgical approach to patients with follicular neoplasms is different. As cytologic criteria are usually insufficient to diagnose malignancy, a thyroid lobectomy is the initial treatment for patients with suspected follicular or Hürthle cell neoplasms based on FNAB results. Unfortunately, the differentiation between benign and malignant lesions is also difficult using frozen-section examination. In most instances, the diagnosis of FTC or HCC can be established only with permanent section showing vascular or capsular invasion. Other than very low-risk patients with minimally invasive FTC in whom a lobectomy may be deemed adequate treatment, a completion total thyroidectomy should be performed in all other patients with FTC and in all patients with HCC. Reoperation is not associated with an appreciable increased risk of complications because the parathyroid glands and the recurrent laryngeal nerve on the side of the remaining thyroid lobe are in unviolated territory when a complete thyroid lobectomy has been performed as the initial procedure. All patients requiring reoperation should have their vocal cords evaluated before surgery to ensure that the cords are functioning normally.

Although there is considerable controversy concerning appropriate surgery for cervical lymph node metastases in patients with DTC, it is clear that the presence of initial nodal metastasis increases the risk of subsequent tumor recurrence in neck nodes. During thyroidectomy, we recommend looking for and removing all lymph nodes immediately adjacent to the thyroid tumor and medial to the carotid sheath as well as Delphian nodes in the cricothyroid membrane (Figure 2–12). Patients with palpable lymphadenopathy lateral to the carotid sheath should have a modified neck dissection with preservation of the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein. However, there is no convincing evidence to justify prophylactic multicompartmental neck dissection in patients with DTC, especially in the absence of palpable lymphadenopathy.[18]

ROLE OF RADIOACTIVE IODINE THERAPY

Radioactive iodine (^{131}I) therapy is well accepted as an adjunct to surgery for both ablation of postoperative thyroid remnants and treatment of metastatic

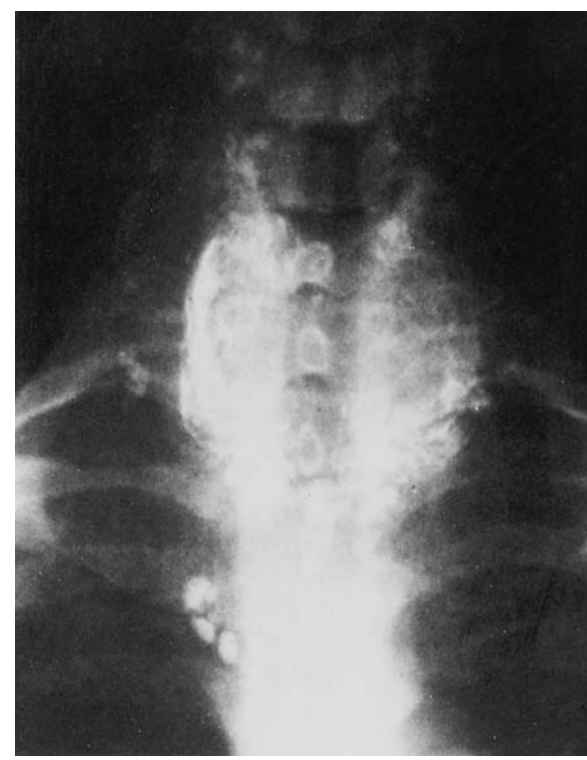


Figure 2–12. Radiograph of the neck and upper chest of a patient following injection of iodized oil (Lipiodol) into the thyroid gland. Note the flow of contrast laterally and downward along lymphatic channels. Courtesy of O. H. Clark, MD, Department of Surgery, University of California-San Francisco/Mount Zion Medical Center, San Francisco, CA.

disease. However, there is much debate on the selection of patients for postoperative ^{131}I remnant ablation among those who have undergone "potentially curative" surgery because radioiodine therapy may not alter the course of the disease in patients in the low-risk category. Nevertheless, postoperative remnant ablation affords the theoretical advantage to (1) destroy occult microscopic carcinoma cells within the thyroid remnant, (2) facilitate radioiodine scanning by the destruction of remaining normal thyroid tissue, and (3) improve the value of serum Tg measurements during follow-up.[20]

Among our series of patients with DTC with primary tumor > 1 cm in size, we found a twofold higher risk of tumor recurrence in the cohort who did not have postoperative adjuvant ^{131}I ablative therapy (Figure 2–13).[15] Most experts agree that the improved disease-free survival associated with ^{131}I remnant ablation provides sufficient ground to recommend ^{131}I ablation of residual thyroid tissue in most DTC patients who have undergone total or near-total thyroidectomy.[17,19] This is not indicated, however, in very low-risk category patients who are treated with lobectomy.

On the other hand, the role of adjuvant radioiodine therapy for patients with persistent or recurrent neck disease or distant metastatic lesions is less controversial (Figure 2–14). This is especially effective if the tumor is occult or microscopic and involves larger administered doses of ^{131}I, which necessitates

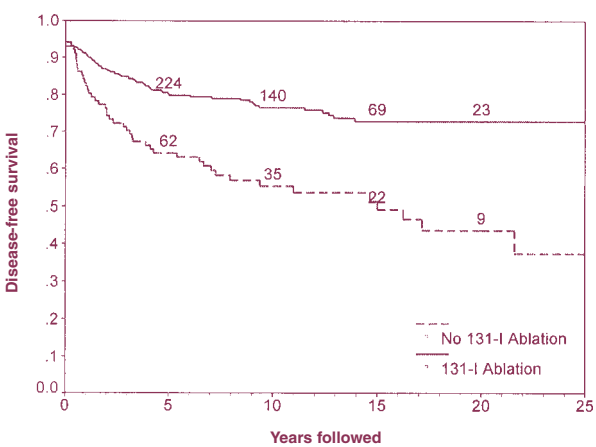


Figure 2–13. Disease-free survival in patients with differentiated thyroid carcinoma in whom the primary tumor size is > 1 cm, comparing the groups with and without postoperative radioactive iodine (^{131}I) ablation ($p < .0001$ between treatment groups). Reproduced with permission from Loh KC et al.[15]

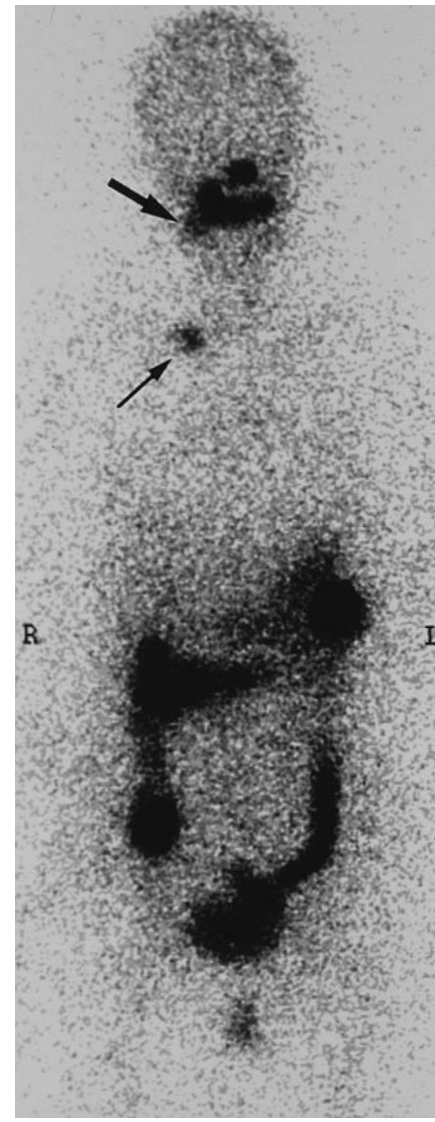


Figure 2–14. Total-body scan performed 72 hours after high-dose (200 mCi) radioactive iodine (^{131}I) therapy in a previously treated papillary thyroid carcinoma patient who developed nodal recurrence. Note the increased ^{131}I uptake in the right submandibular (*thick arrow*) and supraclavicular (*thin arrow*) regions, respectively. Courtesy of E. S. Ang, MD, Department of Nuclear Medicine, Singapore General Hospital, Singapore.

radiation isolation either in the hospital or at home. After total thyroidectomy, treatment with a therapeutic dose of ^{131}I (approximately 100 to 200 mCi) was associated with successful ablation of micrometastases in the lung in about 70% of patients, whereas when pulmonary metastases were identified on chest radiographs, curative ^{131}I ablation was achieved in only about 10% of patients (Figure 2–15). Microscopic bone metastases identified with ^{131}I total-

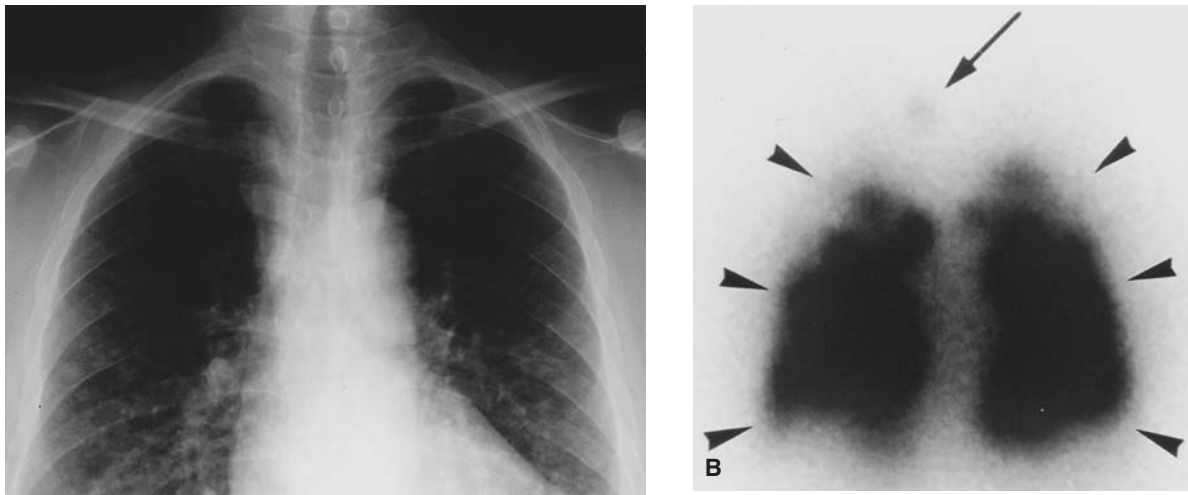


Figure 2–15. Widespread pulmonary metastases from papillary thyroid carcinoma. *A*, Plain chest radiograph showing bilateral micronodular lung metastases. *B*, Total-body scan performed 72 hours after high-dose (100 mCi) radioactive iodine (^{131}I) therapy showing intense and diffuse ^{131}I uptake in both lungs (*arrowheads*); faint ^{131}I uptake was noted in a supraclavicular lymph node (*arrow*), indicating metastatic nodal disease. Courtesy of E. S. Ang, MD, Department of Nuclear Medicine, Singapore General Hospital, Singapore.

body scanning, but not with radiography, could also be ablated in some patients with ^{131}I, whereas bone metastases visible on radiographs were rarely cured by ^{131}I ablation (Figures 2–16 and 2–17).

PRACTICAL ASPECTS OF RADIOACTIVE IODINE IMAGING AND THERAPY

Preparation of patients with thyroid hormone withdrawal and dietary iodine restriction is essential for optimal ^{131}I imaging or therapy. For patients currently on thyroid hormone suppression therapy, the T_4 is withdrawn for 4 to 6 weeks with a substitution of triiodothyronine (T_3) for 2 to 3 weeks. Then T_3 is discontinued and the patient is placed on a low-iodine diet (< 50 μg/d) for 1 to 2 weeks prior to the ^{131}I uptake and scan study. This regimen will allow 90% of patients to achieve a serum TSH concentration > 30 mU/L to stimulate iodide uptake by residual thyroid tissue.

At the University of California-San Francisco, an outpatient dose of 30 to 50 mCi ^{131}I is used to ablate residual thyroid tissue at 6 to 12 weeks after operation if focal uptake is detected in the thyroid bed on a 2 to 3 mCi ^{131}I diagnostic scan. Conversely, patients with residual tumor or distant metastases are treated with 100 to 200 mCi ^{131}I with radiation isolation either as outpatients or in the hospital. In either instance, a neck and body scan is obtained 1 week after the treatment dose of ^{131}I to detect additional areas of uptake that may suggest metastatic disease.

It usually takes 6 to 12 months after initial therapy for ^{131}I to achieve maximal effects. Serum TSH and Tg concentrations may be measured every 3 months during this period. The ^{131}I diagnostic scan is repeated at the end of the year after adequate thyroid hormone withdrawal and dietary iodine restriction. If there is uptake in the neck or the body or if serum Tg is > 5 ng/mL when the patient is hypothyroid, a repeat treatment with 100 to 200 mCi of ^{131}I should be given.

After the first negative ^{131}I scan, the patient may be followed periodically with a recombinant human TSH (rhTSH) protocol rather than T_4 withdrawal (see below).

THYROID HORMONE SUPPRESSION THERAPY

The rationale for thyroid-suppressive therapy in DTC is based on many studies showing that TSH, by bind-

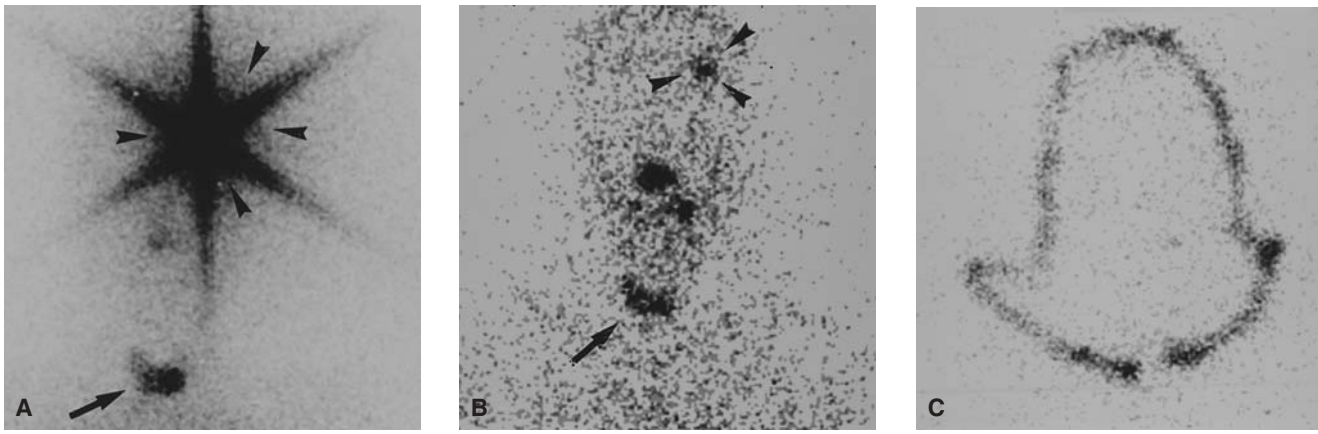


Figure 2–16. Patient with follicular thyroid carcinoma post–total thyroidectomy in whom an asymptomatic solitary left frontal bone metastasis was detected on low-dose ^{131}I diagnostic scan (not shown). *A*, Total-body scan performed 72 hours after high-dose (200 mCi) radioactive iodine (^{131}I) therapy showing avid ^{131}I uptake (*arrowheads*) in the left frontal bone and a lesser degree of ^{131}I in the thyroid remnant (*arrow*). *B*, A second dose of 200 mCi ^{131}I was administered 6 months later. Post-therapy scan now showed minimal ^{131}I uptake in the left frontal bone (*arrowheads*) as well as the thyroid remnant (*arrow*), indicating dramatic treatment response. *C*, Further diagnostic scan performed 6 months later showed no ^{131}I uptake in the skull or thyroid bed, indicating complete treatment response (outline of the patient's head and clavicles represented by the surface marker). Courtesy of E. S. Ang, MD, Department of Nuclear Medicine, Singapore General Hospital, Singapore.

ing to TSH receptors that are present in most tumors, exerts a trophic influence on thyroid tumor tissue. Traditionally, the goal of T_4 therapy has been complete suppression of pituitary secretion of TSH, as indicated by undetectable levels of serum TSH. With the increasing availability of the sensitive assays of TSH, meticulous titration of the level of TSH suppression has become possible. A basal serum TSH level of < 0.1 mIU/L has typically been considered equivalent to a nonresponse of TSH in a thyrotropin-releasing hormone (TRH) test, previously considered the hallmark for adequate TSH suppression in DTC. Recent studies have also addressed the concerns of accelerated bone turnover and cardiovascular abnormalities associated with long-term thyroid hormone suppression therapy.[21] Therefore, considerable debate has emerged on what is the acceptable degree of TSH suppression and whether the same degree of suppression is adequate for different patients.

Although controlled clinical studies are necessary to resolve the above controversy, experts generally agree that the goal of TSH suppression is < 0.1 mIU/L (closer to 0.01 mIU/L using third- or fourth-generation TSH assays) in patients deemed at risk for recurrence or mortality. Conversely, the degree of TSH suppression may be less stringent in the low-risk category, especially for PTC patients, with the goal for basal serum TSH within the 0.1 to 0.4 mIU/L range.[16,17]

OTHER ADJUVANT THERAPIES

External beam radiation therapy has been used with some success in tumors that do not concentrate ^{131}I, especially in patients with HCC or poorly differentiated tumors. It may also be used in conjunction with ^{131}I therapy postoperatively to treat patients who have gross evidence of local invasion that precludes complete surgical resection or to treat inoperable or metastatic lesions that concentrate ^{131}I poorly.

As the results of adjuvant chemotherapy in patients with DTC have been dismal, its use is restricted to those tumors that are surgically unresectable, unresponsive to ^{131}I therapy, and not amenable to external irradiation.

Potential therapeutic modalities currently being investigated include the use of cytokines, immunotherapy, and gene therapy.

FOLLOW-UP OF THYROID CANCERS

Although most patients survive DTC, lifelong follow-up is necessary because tumor recurrence is relatively common, and this may take many years to become clinically apparent. In our series of DTC patients followed up over a mean interval of 11.3 years, 20% of patients developed recurrence of tumor and 8.4% succumbed to the disease. When these data are plotted as cumulative survival curves

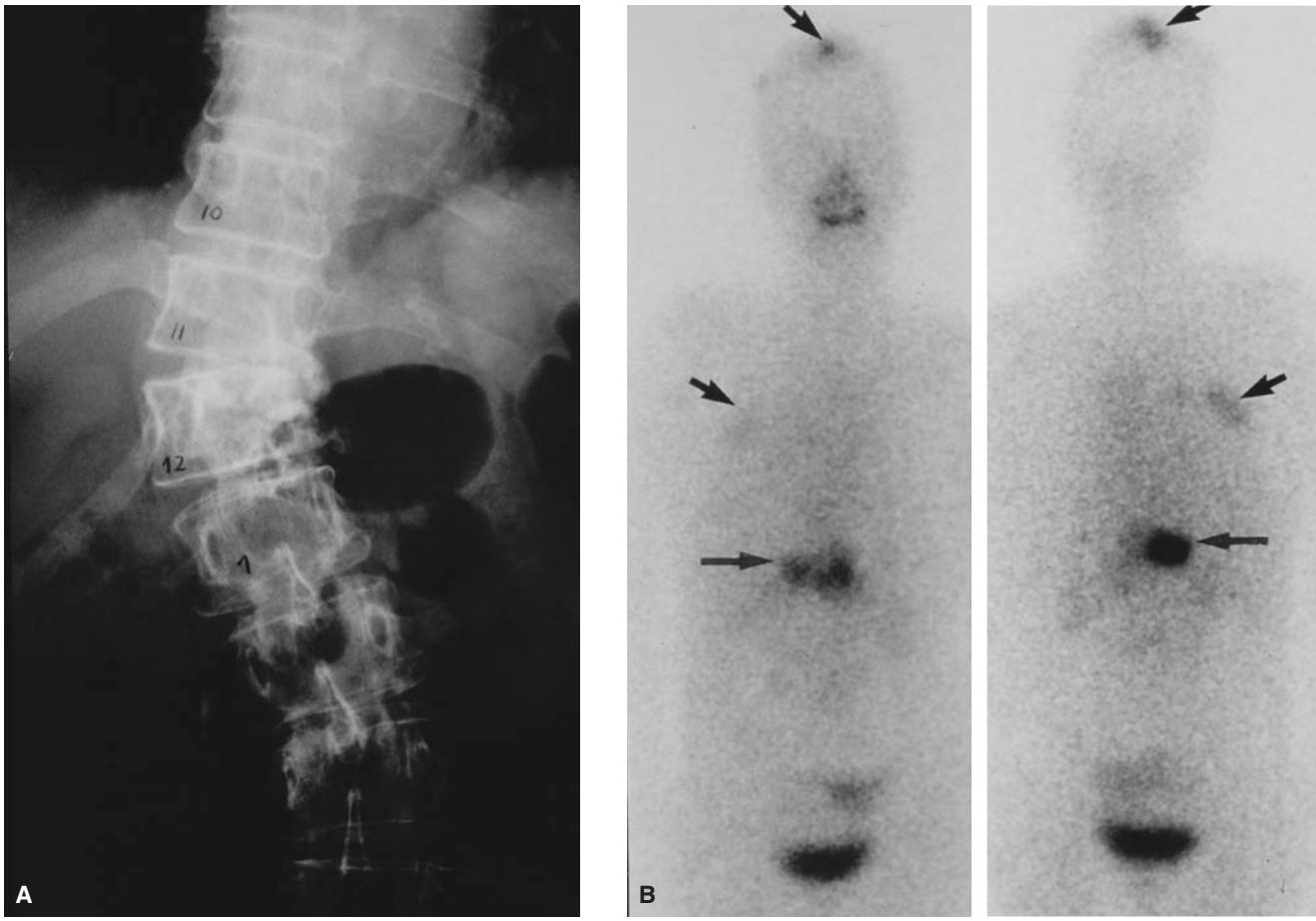


Figure 2–17. Papillary thyroid carcinoma with symptomatic bone metastases. *A*, Plain radiograph of the thoracolumbar spine showing partial destruction of T11 and T12 vertebral bodies, resulting in scoliosis. *B*, Total-body scan performed 72 hours after a high-dose (200 mCi) radioactive iodine (^{131}I) therapy showing intense ^{131}I uptake in vertebral bodies (*arrow*) and lesser degrees of ^{131}I uptake in the ribs and the skull (*shorter arrows*), indicating multiple sites of bony metastases. Unlike the case shown in Figure 2–15, this patient is unlikely to achieve complete treatment response. *B*, (1) anterior view, (2) posterior view. Courtesy of C. H. Goh, MD, Department of Nuclear Medicine, Singapore General Hospital, Singapore.

over 25 years by a Kaplan-Meier plot, the cumulative recurrence rate was about 40% and the cumulative cancer-specific death rate was about 20% (Figure 2–18).[15] These data are consistent with other reports and underscore the need for clinical judgment and individualization in follow-up strategy, recognizing that surveillance should not be discontinued but may be performed less frequently when a decade or more has passed with no evidence of relapse.[19,22]

ROLE OF RECOMBINANT HUMAN TSH

The recent availability of clinical grade rhTSH coincided with the cessation of the production of bovine TSH (bTSH). The latter was used clinically to stimulate ^{131}I uptake by metastatic thyroid cancer lesions; however, it had a number of side effects, which were sometimes severe. Clinical trials soon demonstrated that rhTSH is able to replace the need for patients with DTC to undergo T_4 withdrawal to have whole-body ^{131}I study and serum Tg testing, while eliminating the undesirable side effects of bTSH.[23] This compound has been approved by the US Food and Drug Administration for use as an adjunctive diagnostic tool for serum Tg testing and ^{131}I imaging in the follow-up of patients with DTC. However, it must be appreciated that there remains a small risk of missing a diagnosis of residual cancer or of underestimating the extent of disease with rhTSH-mediated testing and that thyroid hormone withdrawal testing remains the standard diagnostic modality, especially in high-risk patients.

The decisions whether to perform rhTSH-mediated testings and whether and when to withdraw a

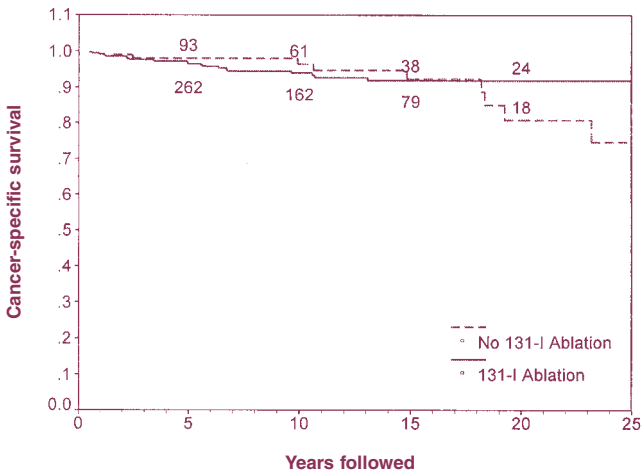


Figure 2–18. Cumulative survival curves by Kaplan-Meier plot for disease-free and cancer-specific survivals, respectively, in patients with differentiated thyroid carcinomas followed over a 25-year period. Reproduced with permission from Loh KC et al.[15]

patient from T_4 are complex and require individual judgment. After the first negative post–^{131}I therapy scan, and if the basal serum Tg is undetectable, we recommend the use of rhTSH for the second and subsequent scans to eliminate the need for T_4 withdrawal and the attendant morbidity associated with hypothyroidism. Patients will continue on T_4 treatment but will have to follow a low-iodine diet for 1 week prior to the study (Table 2–2). A positive scan or a rise in serum Tg to > 2 ng/mL is indicative of metastatic disease, which would require high-dose ^{131}I therapy.[24] For ^{131}I ablative therapy, the patient would require routine T_4 withdrawal preparation.

If the ^{131}I scan after rhTSH is negative, follow-up rhTSH studies can be done using serum Tg measurements alone. The protocol is the same as outlined in Table 2–2 except that the patient does not have to follow a low-iodine diet and no ^{131}I is administered. A rise in serum Tg > 2 ng/mL following rhTSH is an indication for a withdrawal scan and possible treatment with ^{131}I. The rhTSH-mediated Tg testing could be repeated annually for 3 to 5 years and thereafter at less frequent intervals.

For very high-risk patients, however, thyroid hormone withdrawal testing is currently the standard practice. This may be supplemented periodically with an ultrasonographic examination of the neck or spiral computed tomography or magnetic resonance imaging of the neck and chest to rule out metastases that do not pick up ^{131}I or synthesize Tg. Whole-body positron emission tomography (PET) scanning with ^{18}F-fluorodeoxyglucose (FDG) should be considered when tumor is suspected on the basis of high serum Tg levels but negative imaging studies.[25] Metastatic masses that do not pick up ^{131}I and are detected either with conventional imaging modalities or FDG-PET scanning may be amenable to surgical resection or external radiotherapy.

SERUM THYROGLOBULIN MEASUREMENT

Serum Tg determination after primary treatment of DTC is useful as a tumor marker to document recurrent disease on follow-up. However, current methods for serum Tg measurement remain technically challenging because significant assay interference may result from the presence of circulating thyroglobulin autoantibodies (TgAb), as noted in up to 25% of patients with DTC. To circumvent the problem, clinical studies are ongoing to detect Tg transcripts using a reverse transcriptase polymerase chain reaction technique on blood samples from patients with DTC.[26] As the presence of TgAb may invalidate Tg measurements, patients with positive TgAb may require periodic follow-up with thyroid ultrasonography, ^{131}I scans, or other imaging modalities. Nevertheless, postablation serum TgAb levels may be used to correlate directly with the presence or absence of tumor.[27] Because of assay variability, serial serum Tg measurements should be obtained using the same assay method.

Table 2–2. PROTOCOL FOR THE USE OF RECOMBINANT HUMAN THYROID-STIMULATING HORMONE IN THE FOLLOW-UP OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

Prestudy:	low-iodine diet (< 50 µg/d) for 1 wk
	L-Thyroxine therapy continued
Day 1:	blood for serum Tg and TSH
	Urine pregnancy test if indicated
	rhTSH 0.9 mg IM—first dose
Day 2:	rhTSH 0.9 mg IM—second dose
Day 3:	^{131}I 4 mCi PO
Day 5:	blood for serum Tg
	Neck and whole-body ^{131}I scan

Interpretation: a rise in serum thyroglobulin (Tg) > 2 ng/mL or a positive scan is an indication of persistent or recurrent tumor and requires further evaluation and treatment.
IM = intramuscularly; PO = orally; rhTSH = recombinant human thyroid-stimulating hormone; TSH = thyroid-stimulating hormone; ^{131}I = radioactive iodine.

The serum Tg result must be interpreted relative to the serum TSH value, that is, whether the patient is on or off T_4 treatment. Although the best time to obtain a serum Tg level is when the patient is hypothyroid in preparation for ^{131}I scanning, an increasing serial basal serum Tg measurement made on T_4 therapy is a useful indicator of tumor recurrence. Conversely, patients with undetectable basal serum Tg measurements may exhibit serum Tg elevations when serum TSH increases following T_4 withdrawal or exogenous TSH administration. The availability of rhTSH for clinical use has greatly improved the diagnostic sensitivity of serum Tg testing while on T_4 therapy.

SUMMARY

Recent advances in molecular biology have significantly improved our understanding of the genetics of DTC. PTC appears to arise from tyrosine kinase activation, whereas FTC develops from *RAS* activation followed by the inactivation of tumor suppressor gene(s). Over the last decade, FNAB has proven to be the most reliable and cost-effective method in selecting patients with thyroid nodules for surgery. The recent availability of clinical grade rhTSH as an adjunct diagnostic tool for serum Tg testing and ^{131}I imaging study represents yet another achievement in our management of patients with DTC.

Although treatment strategies for DTC have evolved through considerable controversy among thyroid experts because of the lack of prospective controlled studies, careful analysis of patients treated by well-defined methods now gradually proves the benefit of more aggressive initial tumor management. There is now a greater consensus among experts to treat most DTC patients, except for those in the very low-risk category, with total or near-total thyroidectomy and postoperative ^{131}I ablation of residual thyroid tissue, followed by long-term T_4 suppression of serum TSH concentrations. Similarly, the strategy for long-term tumor surveillance in patients with DTC remains unsettled. As data derived from controlled trials are unlikely to be available in the near future, management of patients with DTC should remain individually tailored with clinical decisions based on balancing the potential benefit and morbidity of any treatment modality.

REFERENCES

1. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A natinal cancer database report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. Cancer 1998;83: 2638–48.
2. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics 2001. CA Cancer J Clin 2001;51:15–36.
3. Box JC, Watne AL. Inherited syndromes of colon polyps. Semin Surg Oncol 1995;11:394–8.
4. Loh KC. Familial nonmedullary thyroid carcinoma: a meta-review of case series. Thyroid 1997;7:107–13.
5. Nikiforov YE, Rowland JM, Bove K, et al. Distinct pattern of *ret* oncogene rearrangements in morphologic variants of radiation-induced and sporadic thyroid papillary carcinomas in children. Cancer Res 1997;57:1690–4.
6. Bongarzone I, Butti MG, Coronelli S, et al. Frequent activation of ret protooncogene by fusion with a new activating gene in papillary thyroid carcinomas. Cancer Res 1994; 54:2979–85.
7. Grebe SK, McIver B, Hay ID, et al. Frequent loss of heterozygosity on chromosomes 3p and 17p without VHL or p53 mutations suggests involvement of unidentified tumor suppressor genes in follicular thyroid carcinoma. J Clin Endocrinol Metab 1997;82:3684–91.
8. Fagin JA, Matsuo K, Karmakar A, et al. High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. J Clin Invest 1993;91:179–84.
9. Gharib H. Changing concepts in the diagnosis and management of thyroid nodules. Endocrinol Metab Clin North Am 1997;26:777–800.
10. Schlumberger MJ. Papillary and follicular thyroid carcinoma. N Engl J Med 1998;338:297–306.
11. Greenspan FS. The role of fine-needle aspiration biopsy in the management of palpable thyroid nodules. Am J Clin Pathol 1997;108 Suppl 1:26–30.
12. Grebe SKG, Hay ID. Thyroid cancer nodal metastases: biologic significance an therapeutic considerations. Surg Oncol Clin North Am 1996;5:43–63.
13. Rosai J, Carcangiu ML, Delellis RA. Tumors of the thyroid gland. In: Rosai J, Sobin LH, editors. Atlas of tumor pathology. Washington (DC): Armed Forces Institute of Pathology; 1992. p. 1–335.
14. Greene FL, Balch CM, Page DL, et al, editors. American Joint Committee on Cancer (AJCC) cancer staging manual. 6th ed. New York: Springer-Verlag; 2002. p. 77–87.
15. Loh KC, Greenspan FS, Gee L, et al. pTNM classification for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J Clin Endocrinol Metab 1997;82:3553–62.
16. Singer PA, Cooper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. Arch Intern Med 1996;156:2165–72.
17. Hay ID, Feld S, Garcia M, et al. AACE clinical practice guidelines for the management of thyroid carcinoma. Endocr Pract 1997;3:60–71.
18. Tezelman S, Clark OH. Current management of thyroid cancer. Adv Surg 1995;28:191–221.
19. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thy-

roid cancer [published erratum appears in Am J Med 1995;98:215]. Am J Med 1994;97:418–28.
20. Wartofsky L, Sherman SI, Gopal J, et al. Therapeutic controversy: the use of radioactive iodine in patients with papillary and follicular thyroid cancer. J Clin Endocrinol Metab 1998;83:4195–203.
21. Greenspan SL, Greenspan FS. The effect of thyroid hormone on skeletal integrity. Ann Intern Med 1999;130: 750–8.
22. Gagel RF, Goepfert H, Callender DL. Changing concepts in the pathogenesis and management of thryoid carcinoma. CA Cancer J Clin 1996;46:261–83.
23. Ladenson PW, Braverman LE, Mazzaferri EL, et al. Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 1997;337:888–96.
24. Mazzaferri EL, Kloos RT. Is diagnostic iodine-131 scanning with recombinant human TSH (rhTSH) useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab 2002;87:1490–8.
25. Wang W, Larson SM, Fazzari M, et al. Prognostic value of [18F] fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab 2000;85:1107–13.
26. Ringel MD, Ladenson PW, Levine MA. Molecular diagnosis of residual and recurrent thyroid cancer by amplification of thyroglobulin messenger ribonucleic acid in peripheral blood. J Clin Endocrinol Metab 1998;83:4435–42.
27. Spencer CA, Takeuchi M, Kazarosyn M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin (Tg) measurement and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998;83:1121–7.

3

Medullary Thyroid Cancer

ELECTRON KEBEBEW, MD
ORLO H. CLARK, MD

Medullary thyroid cancer (MTC) is a relatively rare malignancy, accounting for 3 to 8% of all thyroid cancers; however, it is responsible for up to 14% of all thyroid cancer deaths.[1–3] In 1959, MTC was described as a unique clinical entity by Hazard and colleagues.[4] It is distinct from other thyroid carcinomas because it originates from parafollicular cells of the thyroid gland. Furthermore, MTC has a distinct clinical behavior, hereditary occurrence, and molecular biology. The tremendous advances and application of molecular medicine to patient care parallel the advances made in understanding the pathogenesis and genetics of MTC.[3] MTC has been recognized to occur in hereditary and sporadic forms because of the early contributions of Sipple. The introduction of fine-needle aspiration (FNA) cytology has allowed for accurate preoperative diagnosis of MTC, which has allowed for the selection of the appropriate initial extent of surgical resection preoperatively. Measurement of basal and stimulated serum calcitonin (a tumor marker for MTC) levels has been instrumental for screening patients at risk for hereditary MTC and remains indispensable in the surveillance of patients for persistent or recurrent MTC after initial treatment. More recently, the identification of the *RET* proto-oncogene, the gene responsible for hereditary MTC, has been effectively used to identify gene carrier status in affected families.[5–8] Clinically, genetic screening has allowed for the identification of at-risk individuals at a young age, leading to prophylactic treatment of these patients sometimes even before the development of any neoplasia.[7–9] Owing to these advances, the diagnosis and treatment of patients with MTC have improved immensely and have translated into improved patient outcome.[10]

EMBRYOLOGY, PHYSIOLOGY, AND PATHOLOGY

The parafollicular or C cells in the thyroid gland have a more distinct embryologic origin, phenotype, and function than the follicular cells of the thyroid gland. The C cells are derived from the neural crest cells that migrate during embryogenesis from the neuroectoderm (ultimobranchial pouch III) to reside adjacent to but outside the thyroid follicles. In a normal thyroid gland, C cells are infrequent and dispersed with no more than one to two C cells identified per high-power field. The largest concentration of C cells exists between the junction of the upper one-third and lower two-thirds of each thyroid lobe (Figure 3–1). This is the most common location where MTC or C-cell hyperplasia (CCH) develops in patients with hereditary MTC.

Although the function of C cells remains controversial, it has been shown that C cells regulate calcium hemostasis, albeit transiently, by affecting bone metabolism. Like most cells of neuroectodermal origin, C cells have an amine precursor uptake decarboxylase system. C cells secrete calcitonin, a small polypeptide 32 amino acids long, after post-translational modification. Calcitonin is secreted into the plasma and binds calcitonin receptors on the osteoclast cell surface to inhibit bone resorption. Calcitonin production in C cells is regulated at several levels: gene expression, post-transcription modification, and cellular secretion. Calcitonin expression in

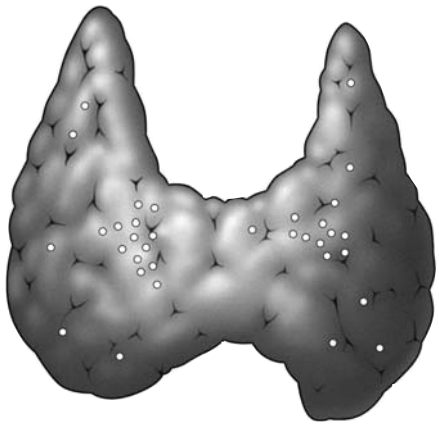


Figure 3–1. Distribution of parafollicular cells (C cells) in the thyroid gland. The highest concentration of C cells is in the area between the upper one-third and lower two-thirds of each thyroid lobe. This is the usual location where C-cell hyperplasia and medullary thyroid cancer (MTC) originate in patients with hereditary MTC.

the C cells can be inhibited by 1,25-dihydroxyvitamin D or glucocorticoids.[11–13] It can be enhanced by activation of the protein kinase A and protein kinase C intracellular pathways.[11–13] Calcium is the main physiologic, extracellular substance that regulates calcitonin secretion from C cells. Pentagastrin, β-adrenergic agonists, and growth hormone–releasing factor have also been found to regulate calcitonin secretion from C cells.[14–16] The increase in calcitonin secretion from C cells that occurs with calcium and pentagastrin stimulation (calcitonin stimulation test) has been clinically useful for screening patients at risk for hereditary MTC and for patient follow-up to detect persistent or recurrent MTC.[7,8,16] Calcitonin also may be secreted from Kulchitsky's cells of the lung, pituitary gland, thymus, hepatoma, and lung carcinoma or in benign liver disease. Although the calcitonin secreted by cells other than the C cells is usually procalcitonin, it is detected by most biochemical assays (immunochemical and radioimmunoassays).[3] Indeed, these other sources of calcitonin account for false-positive results of calcitonin basal and stimulated screening tests. Today, the commercial availability of genetic testing for the *RET* proto-oncogene mutations has eliminated some of the problems associated with biochemical calcitonin screening testing in patients at risk of developing MTC.

In sporadic MTC, a large unifocal tumor is usually found, whereas in the hereditary forms of MTC, the tumors are usually bilateral and multicentric, with or without CCH present. CCH in hereditary MTC is generally regarded as a premalignant lesion, but this is less clear for sporadic MTC (Figure 3–2). CCH is usually of monoclonal cell origin and may have a diffuse or nodular pattern. CCH usually develops where the greatest number of C cells reside in the thyroid gland. To identify CCH or microscopic MTC, it is important to take thin (1 to 5 μm) sections of the thyroid and perform a systematic complete histologic examination of the entire thyroid gland (Figure 3–3). Microscopic MTC is distinguished from CCH by invasion through the basement membrane of the thyroid follicle. Young patients undergoing preventive thyroidectomy, based on a positive genetic screening test, may only have CCH or no pathologic abnormality.[9] Nonspecific CCH may occur with chronic lymphocytic thyroiditis, multinodular goiter, follicular neoplasm, lymphomas, and papillary thyroid cancer.[17–20] In such a situation, CCH does not indicate a premalignant lesion.

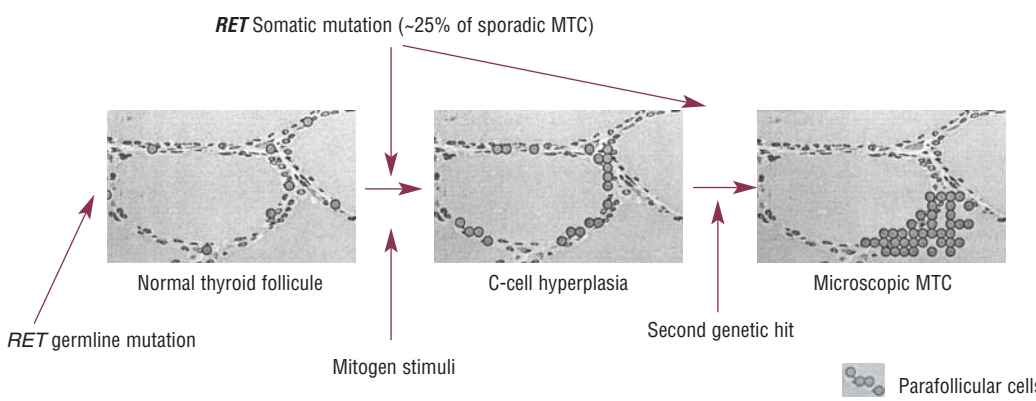


Figure 3–2. Multistep model for medullary thyroid carcinogenesis (MTC). Although C-cell hyperplasia is thought to progress to MTC in hereditary cases, this is less certain in sporadic MTC. In addition to *RET* mutations, a second genetic defect or mitogen stimuli probably contribute to the development of MTC.

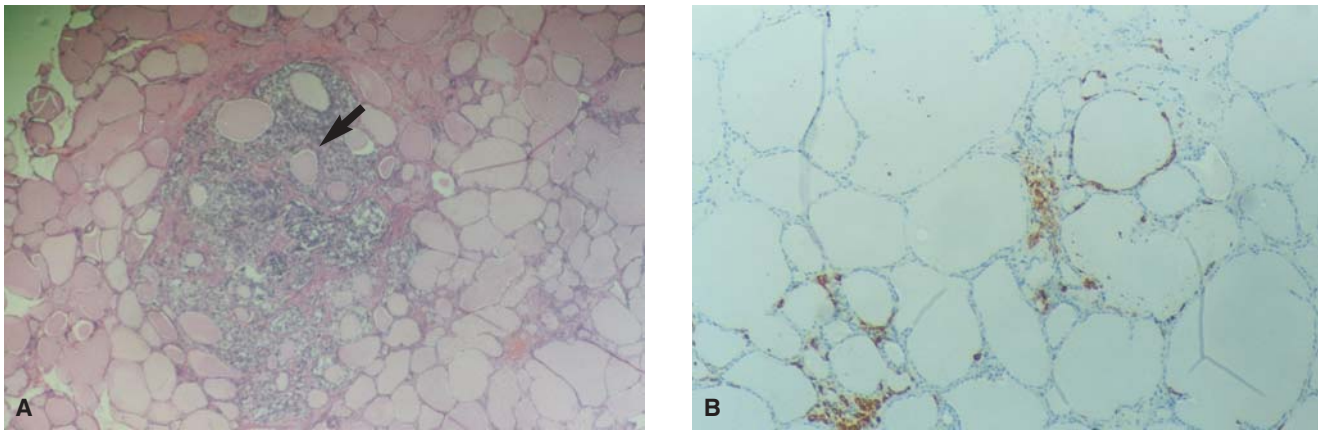


Figure 3–3. *A*, Microscopic medullary thyroid cancer on hematoxylin and eosin staining. *Arrow* shows thyroid follicles surrounded by C cells that have invaded beyond the basement membrane. *B*, Calcitonin immunohistochemistry of normal thyroid tissue section shows strong calcitonin immunoreactivity interspersed in the thyroid follicles. C-cell hyperplasia is diagnosed when one of the following criteria are fulfilled: (1) an increased number of diffusely scattered C cells (at least > 7 C cells per thyroid follicle), (2) cluster formation of C cells, or (3) C-cell density greater than 40 cells/cm^2 (hematoxylin and eosin, ×10 original magnification).

On gross examination, MTC usually has a whitish-tan color and is firm to hard on palpation. MTC has characteristic nestled spindle-shaped or polyglonal cells separated by fibrous septa on histologic examination (Figure 3–4). On routine hematoxylin and eosin staining, the cytoplasm has a granular eosinophilic appearance and the nuclei are hyperchromatic. An amyloid stroma is often present. The amyloid deposits result from the precipitation of the procalcitonin secreted by the tumor cells. In the past, MTC was referred to as an amyloid variant of anaplastic thyroid cancer. MTC could also be confused with papillary thyroid cancer when pseudopapillary structures were present. Sometimes it was also confused with Hürthle cell carcinoma because of the eosinophilic granular cytoplasm. MTC, however, now can be easily distinguished from other thyroid neoplasms by amyloid, calcitonin, thyroglobulin, and or carcinoembryonic antigen (CEA) immunocytochemistry (Figure 3–5).

MOLECULAR BIOLOGY OF MTC

Germline mutations in the *RET* proto-oncogene are responsible for hereditary MTC, and somatic point *RET* mutations have also been identified in some sporadic MTC (in about 25%).[3] The *RET* gene, located on chromosome 10q11.2, encodes a transmembrane receptor protein. The *RET* receptor belongs to the family of receptor tyrosine kinase proteins such as met, neu, and trk.[3] The *RET* receptor

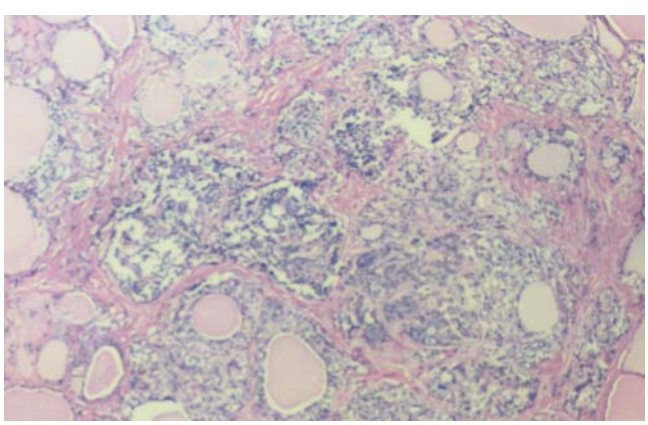


Figure 3–4. Medullary thyroid cancer on hematoxylin and eosin staining. Note the interspersed spindle and polyglonal cells separated by fibrinous septae (×10 original magnification).

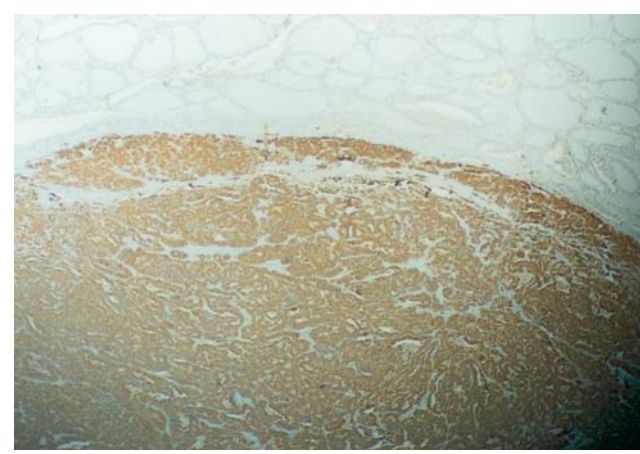


Figure 3–5. Calcitonin immunohistochemistry of medullary thyroid cancer with adjacent normal thyroid tissue.

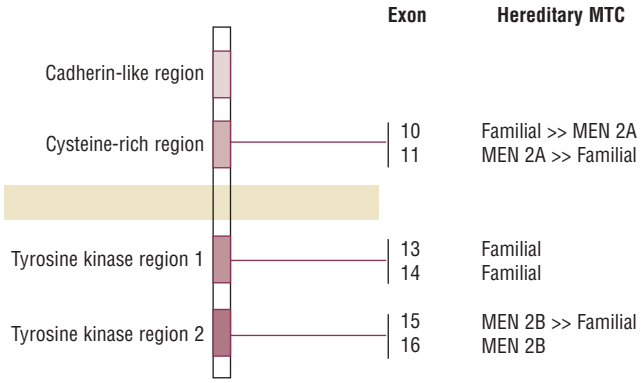


Figure 3–6. A schematic representation of the *RET* receptor and the exons in which codon point mutations have been identified for each type of hereditary medullary thyroid cancer (MTC). MEN = multiple endocrine neoplasia.

has (1) an extracellular domain with a cadherin-like domain and a proximal cysteine-rich region, (2) a transmembrane domain, and (3) a cytoplasmic tyrosine kinase region with two adjacent tyrosine kinase subdomains (Figure 3–6). The *RET* receptor functions as a multicomponent receptor with a complex of bound ligand, coreceptors anchored to the cell membrane by a glycosylphosphatidylinositol-linked protein and the receptor itself (Figure 3–7). Three ligands of the *RET* receptor have been described: glia-derived neurotrophic factor (GDNF), neurturin, and persephin.[21–26] These protein ligands share a 40% sequence homology.[21,22] Thus far, three coreceptors have been identified: growth factor receptors αl, α2, and α4. The coreceptor functions to increase *RET* receptor affinity for ligand binding.[21]

In general, *RET* is expressed in cells of neural crest origin and is low to absent in adult human tissue (ie, low in normal thyroid tissue). Its expression, however, is increased in neuroendocrine tumors such as MTC, pheochromocytoma, and parathyroid neoplasms. It has been proposed that germline point mutations in the *RET* proto-oncogene represent a "gain of function" in hereditary MTC and a "loss of function" in Hirschsprung's disease.[21] Activating *RET* point mutations in the cysteine-rich region in exons 10 and 11 accounts for most cases of familial MTC and multiple endocrine neoplasia (MEN) type IIA.[3] Point mutations in the tyrosine kinase domain occur almost exclusively in MEN type IIB. Other deletions, insertions, and missense mutations have also been described in the intracellular and extracellular regions of the *RET* receptor.

It has been documented in the wild-type *RET* receptor that GDNF binding induces *RET* receptor dimerization, which activates the intracellular tyrosine kinase and signal transduction.[25–27] Activating point mutations in the cysteine-rich extracellular region (exons 10 and 11) of *RET* commonly results in a loss of a cysteine residue, leading to disulfide bridge bond formation, resulting in the constitutive *RET* receptor dimerization and tyrosine kinase activation. Activating point mutations in the *RET* tyrosine kinase domain (exons 14 and 16), as occurs in MEN type IIB, appears to lead to modifications in the tyrosine kinase autocatalytic activity and substrate specificity. Several possible genotype-phenotype correlations have been observed in hereditary MTC. In families with MEN type IIA, the most common point mutation is in codon 634 (exon 10).[28] Importantly, in families with codon 634 mutations, pheochromocytoma and hyperparathyroidism are present in at least one member.[28] This, therefore, suggests that patients found to have codon 634 mutations should have rigorous screening for pheochromocytoma and hyperparathyroidism.

CLINICAL FEATURES OF MTC

Most patients with MTC present in the fourth decade of life.[10] Patients with sporadic MTC commonly present at an older age than patients with familial MTC and MEN type IIA. Most patients with MEN IIB are diagnosed within the first two decades of life.[10] The

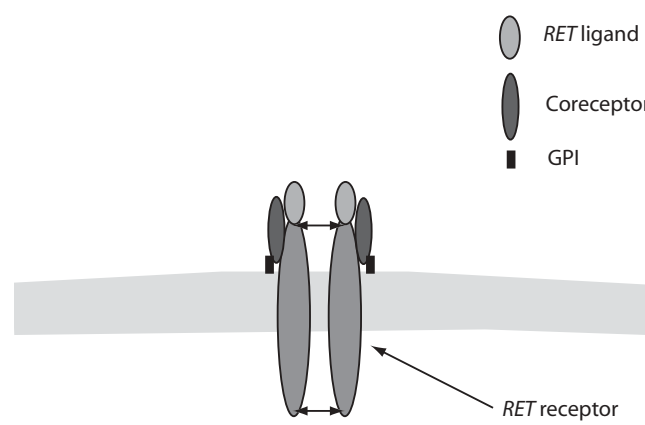


Figure 3–7. The *RET* multicomponent receptor: the transmembrane *RET* recepetor bound to a coreceptor (growth factor receptors α1, -2, -4) anchored to the cell membrane by glycosylphosphatidylinositol (GPI) and the ligand (glia-derived neurotrophic factor, neurturin, or persephin).

frequency of MTC is equal among both sexes, unlike other thyroid neoplasms, which have a female predominance. Almost all patients with sporadic MTC or index cases of familial MTC and MEN type IIA present with a thyroid mass, thyroid mass with cervical lymphadenopathy, and, less frequently, only cervical lymphadenopathy.[3,10] Regional lymph node metastases are common and occur in up to 75% of patients with clinically evident MTC.[29] Common sites of lymph node metastases are the central neck compartment lymph nodes: peritracheal and perithyroidal nodes (level VI cervical lymph nodes) (Figure 3–8). Lymph node metastases also occur to the lateral cervical compartment and upper mediastinum (levels II, III, IV, and VII) (see Figure 3–8). Because MTC usually occurs in the posterior-upper lobes of the thyroid gland, where most of the C cells reside, invasion into the trachea or recurrent laryngeal nerve or laterally into the jugular vein or carotid artery may be present. Rarely, patients with MTC may also present with diarrhea, flushing, or bone pain from tumor metastases or heavy tumor burden.[10] Distant metastases from MTC to the liver, bone, and lung occur with late presentation or after initial treatment in patients with persistent MTC. Unlike differentiated thyroid cancers of follicular cell origin, which trap radioiodine, localization of MTC distant metastases is difficult until gross disease has developed.

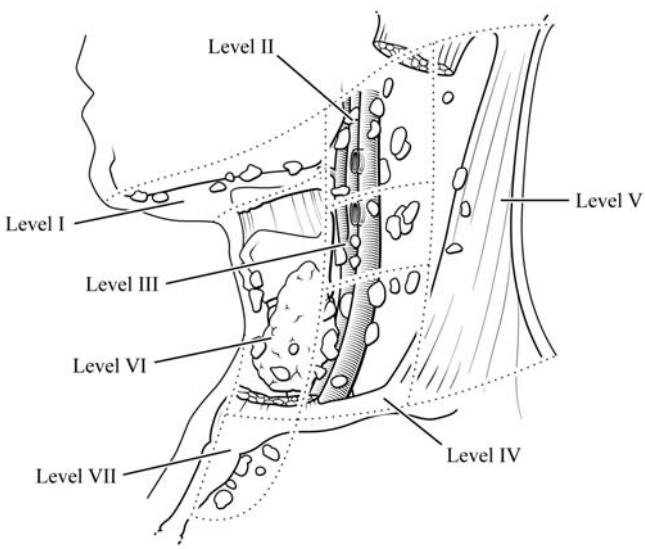


Figure 3–8. Cervical and mediastinal lymph node compartments. Level I = submental and submandibular nodes; level II = upper internal jugular chain nodes; level III = middle internal jugular chain nodes; level IV = lower internal jugular chain nodes; level V = spinal accessory and transverse cervical nodes; level VI = tracheoesophageal groove nodes and perithyroidal nodes; and level VII = infraclavicular and upper anterior mediastinal nodes (thymic).

Hereditary MTC has an autosomal dominant pattern of inheritance and accounts for 25 to 50% of all MTC cases. Almost all patients who are *RET* germline mutation carriers develop at least CCH by 30 years of age.[30] Familial MTC and MEN types IIA and IIB comprise the hereditary forms of MTC (Table 3–1). The MEN type IIA hereditary syndrome is composed of MTC, pheochromocytoma, and/or parathyroid neoplasms. About 50% of patients with MEN type IIA will develop pheochromocytoma, and up to 30% will develop hyperparathyroidism. Furthermore, some patients with MEN type IIA may have cutaneous lichen amyloidosis.[31,32] Patients with MEN type IIB have MTC with or without pheochromocytoma and typical phenotypic features. These phenotypic features include mucosal neuromas on the distal tongue, intestinal ganglioneuromatosis, thickened lips, and a marfanoid body habitus. Familial MTC is a hereditary syndrome in which only MTC is observed without any of the other components of MEN type IIA. It remains unclear whether familial MTC is a distinct syndrome or a variant of MEN type IIA, in which there is a delayed manifestation of all of the components.

DIAGNOSIS

In patients who present with a thyroid mass, FNA cytology is accurate in establishing the diagnosis of MTC. Rarely, MTC may be diagnosed after thyroidectomy for a thyroid nodule. It is, however, controversial if serum calcitonin levels should be measured in all patients with thyroid nodules. The preoperative serum calcitonin and CEA levels in patients diagnosed with MTC should be measured. Patients who complain of a change in voice, hoarseness, stridor, and dysphagia usually have locally invasive tumors. Genetic screening has largely replaced basal or stimulated calcitonin measurement for screening patients at risk for hereditary MTC. In a family with a known germline mutation, MTC can be safely ruled out if no *RET* mutation is identified in that individual (Figure 3–9). It is recommended that at least two separate blood samples show the same *RET* germline mutation before a

Table 3–1. CLINICOPATHOLOGIC CHARACTERISTICS OF SPORADIC AND HEREDITARY MEDULLARY THYROID CANCER

	Sporadic	Familial	MEN IIA	MEN IIB
MTC	+	+	+	+
Other endocrinopathies	None	None	Hyperparathyroidism Pheochromocytoma	Pheochromocytoma Phenotypic features
Age	3rd to 4th decade	3rd decade	3rd decade	1st or 2nd decade
Tumor multicentricity (usually)	Unilateral	Bilateral	Bilateral	Bilateral
MTC aggressiveness (most to least, 1 to 4)	2	4	3	1
RET point mutations in exons (in decreasing order of frequency)	10, 11, 13, 14, 15	10, 11	11, 10	16, 15
Mode of diagnosis	Thyroid mass	Screening	Screening	Clinically apparent Phenotype ± screening

MEN = multiple endocrine neoplasia; MTC = medullary thyroid cancer.

patient is determined to be a gene carrier. Genetic screening is preferable to biochemical screening because once a patient is found to have no germline mutation in a family with a known *RET* germline mutation, no further follow-up is required. In contrast, biochemical screening (1) requires yearly calcitonin measurements into adulthood before a patient can be assured of not being at risk of developing MTC, (2) can be associated with uncomfortable side effects from provocative stimulation test with pentagastrin or calcium, and (3) is less accurate than genetic testing because of a false-positive or false-negative test result.

Taking a comprehensive history and physical examination is integral to making the diagnosis, as well as determining the familial nature of MTC. Patients should be questioned specifically about

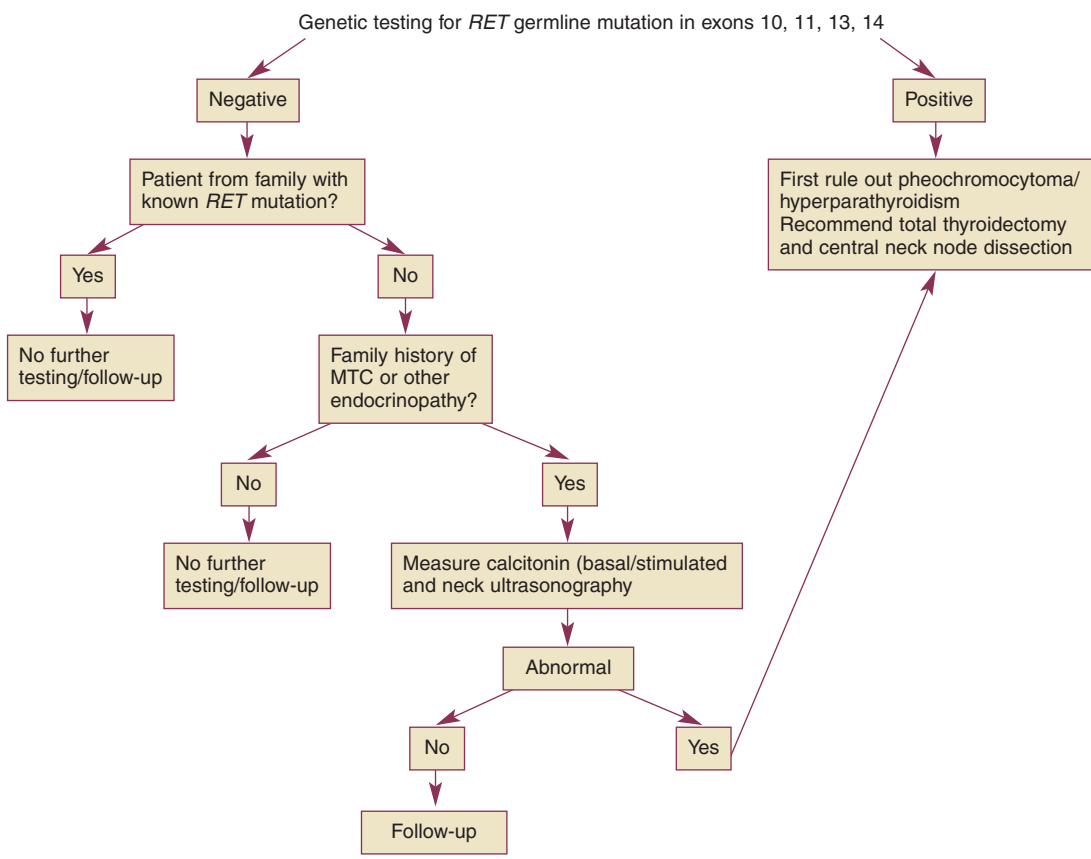


Figure 3–9. Screening, diagnostic, and treatment algorithm for patients suspected of having hereditary medullary thyroid cancer (MTC).

local symptoms and symptoms that can occur from hypercalcitoninemia secondary to widely metastatic disease such as diarrhea and flushing. A thorough family history is important and should include questions regarding a family history of thyroid cancer, pheochromocytoma, hyperparathyroidism, or unexplained sudden death in family members (secondary to an undiagnosed pheochromocytoma). On examination, the extent of the thyroid mass should be carefully determined as well as the presence of lymphadenopathy and any phenotypic features of MEN type IIB. We recommend germline *RET* mutation testing in patients with apparently sporadic MTC as up to 7% of these cases might represent the index case in a kindred with a de novo mutation.[21] This would help determine if other family members would be at risk of developing MTC.

In all patients with hereditary MTC, preoperative urinary catecholamine and metabolite levels should be measured to rule out a pheochromocytoma. Operating on a patient with an undiagnosed pheochromocytoma can be catastrophic. We also recommend preoperative serum calcium levels to rule out hyperparathyroidism. Because the penetrance of hyperparathyroidism and pheochromocytoma in MEN type IIA is variable, some patients may have a pheochromocytoma even if no one in the kindred had a pheochromocytoma or hyperparathyroidism, thus mimicking familial MTC.

PROGNOSIS AND FOLLOW-UP

The survival of patients with MTC is intermediate to that of patients with differentiated thyroid cancer of follicular cell origin and anaplastic thyroid cancer, with an overall 10-year survival rate of 75 to 85%.[1,2,10] There is great variability, however, in the clinical course of patients with MTC. Some patients may survive several decades with persistent disease, whereas some will have rapidly progressive tumors and will die within months of presentation. Only early diagnosis and at least a total thyroidectomy with central neck node clearance give the patient the best chance of disease-free survival. A number of clinical, biochemical, and molecular factors have been reported to predict outcome in patients with MTC (Table 3–2). The most important prognostic factors consistently observed are the age of the patient and the stage of MTC.[10] Some studies, but not all, have also suggested that male gender is associated with a worse prognosis. The presence of diarrhea, cervical node metastasis, large tumor size, extrathyroidal tumor extension, and elevated stimulated serum calcitonin levels (> 10,000 pg/mL) at the time of diagnosis have also been shown to adversely influence survival.[33] Deoxyribonucleic acid (DNA) ploidy (aneuploid tumors), increased N-myc immunoreactivity (messenger ribonucleic acid), weak calcitonin immunostaining (suggesting tumor dedifferentiation), absent amyloid staining, elevated serum CEA levels, absent somatostatin receptor tumor staining, and the absence of thyroiditis have also been implicated as markers of poor prognosis.[33]

TREATMENT OF MTC

Surgery is the primary treatment for MTC. There is a general consensus that those patients who present with clinically evident MTC should have total thyroidectomy with cervical node clearance.[34] Total thyroidectomy is necessary regardless of the size of the tumor because MTC is often bilateral and multifocal. Patients with gross lymphadenopathy should have a

Table 3–2. PROGNOSTIC FACTORS IN MEDULLARY THYROID CANCER

Clinical	Pathologic	Biochemical/Molecular
Age	Stage (TNM)	Elevated serum CT/CEA
Gender	Tumor size	DNA ploidy
Diarrhea*	Nodal metastasis	Amyloid IHC
Bone pain*	Distant metastasis	CT/CRGP IHC
Extrathyroidal invasion	Somatostatin IHC	
Thyroiditis	N-myc expression	

*Usually indicates the presence of distant metastasis.
CEA = carcinoembryonic antigen; CGRP = calcitonin gene–related peptide; CT = calcitonin; DNA = deoxyribonucleic acid; IHC = immunohistochemistry; TNM = tumor, node, metastasis.

bilateral modified radical functional neck dissection, preserving the spinal accessory nerve, internal jugular vein, sternocleidomastoid muscle, and cervical sensory nerves. Even if no gross lymphadenopathy is detected at the time of initial thyroidectomy, at least a central cervical node clearance should be done because up to 75% of these patients with MTC have cervical node metastasis to the central neck compartment. In addition, the presence of MTC lymph node metastasis cannot be determined accurately intraoperatively. Furthermore, the presence of cervical node metastases is associated with an increased risk of recurrence and mortality (especially the presence of > 10 positive nodes, lymph node size > 1 cm, and involvement of more than 2 cervical lymph node compartments).[10,35] Central neck node dissection (level VI) should consist of removal of all lymph nodes and fibrofatty tissue from the hyoid bone (superiorly) to the carotid sheaths (bilaterally) and innominate vessels (inferiorly) (see Figure 3–9). In a functional modified radical neck dissection, all nodal and fibrofatty tissue should be removed from the trapezius muscle (posterolaterally), clavicle, and upper mediastinum (inferiorly) and up to the mandible (superiorly) (see Figure 3–8).

In patients diagnosed by screening to be at risk of developing MTC (asymptomatic MTC), a prophylactic total thyroidectomy is recommended. There is a general consensus that children older than 6 years should have preventive total thyroidectomy.[9,36] Some experts, however, perform prophylactic thyroidectomy in children as young as 1 year old, whereas others follow these patients until they develop basal or stimulated hypercalcitoninemia. The need for prophylactic central neck node dissection has not yet been clearly established; some surgeons recommend prophylactic central neck dissection in children older than 10 years, whereas some routinely perform central neck node dissection at the time of total thyroidectomy.[36] In 139 patients who had prophylactic total thyroidectomy with at least a central neck node dissection for a positive screening test for MTC, 8.6% had regional lymph node metastasis.[9] Central neck node dissection at the time of prophylactic total thyroidectomy is recommended if (1) there is an intrathyroidal lesion at the time of surgery or on preoperative ultrasonography, (2) the basal or stimulated calcitonin level is elevated, or (3) there is obvious lymphadenopathy present.[9]

The need for parathyroidectomy at the time of total thyroidectomy and cervical lymph node clearance is controversial in patients with MTC diagnosed by screening or who are symptomatic. Some experts recommend removal of all parathyroid glands at the time of thyroidectomy and autotransplantation. The rationale for this management strategy is that some surgeons do not believe that an adequate total thyroidectomy and cervical lymph node clearance can be done without devascularizing the parathyroid glands. In our experience, however, the parathyroid glands can usually be left in situ without limiting a complete cervical neck node clearance and minimizing the risk of hypoparathyroidism. In situations in which the viability of a parathyroid gland(s) is questionable, parathyroid autotransplantation to the forearm in patients with MEN type IIA and to the sternocleidomastoid muscle in patients with sporadic MTC, familial MTC, and MEN type IIB is recommended. The remaining parathyroid tissue should be cryopreserved.

PERSISTENT AND RECURRENT MTC

Postoperative serum basal and stimulated calcitonin measurement is a useful and an accurate marker for persistent or recurrent MTC.[37,38] Elevated postoperative CEA also indicates aggressive MTC.[39] Over 50% of patients who present with clinically evident MTC have persistent MTC, manifested by elevated postoperative basal or stimulated calcitonin levels, even after initial "complete" surgical resection.[10] Patients who have an elevated postoperative basal or stimulated calcitonin level can be grouped into two categories: those patients who had "incomplete" initial surgical resection and those patients who had an appropriate initial surgical treatment. Patients who had less than a total thyroidectomy and central neck node clearance (incomplete) usually have residual disease and should undergo cervical re-exploration with removal of all remaining thyroid tissue and bilateral modified radical (functional) neck dissection.

In patients who had apparently complete initial surgical treatment, elevated calcitonin usually indi-

cates occult MTC or an unidentified distant metastasis. The optimal management of patients with hypercalcitoninemia after appropriate initial surgical treatment and without radiographic or clinical evidence of MTC remains unclear. Such patients may enjoy long-term survival without reoperation.[40] Several groups using a "microdissection" surgical approach consisting of cervical and mediastinal fibrofatty and lymph node clearance in patients with persistent MTC have reported up to a 38% biochemical cure rate (normalization of basal or stimulated calcitonin) but with a short follow-up time.[41–43] We found that only 10% of patients ($n = 33$) had normalization of their basal calcitonin using a similar approach, with a longer mean follow-up time of 7.5 years.[38] More importantly, those patients who had more than a 50% decrease in the basal calcitonin after reoperation were less likely to develop distant metastases.[38] Although reoperative cervical and mediastinal lymphadenectomy may provide biochemical cure in only a small subset of patients with subclinical persistent or recurrent MTC, it appears to at least decrease the likelihood of having progressive metastatic MTC. In patients with clinically evident symptomatic persistent or recurrent MTC, reoperation can also result in relief of symptoms.[38,44] We therefore recommend reoperation (consisting of removal of all remaining cervical and mediastinal fibrofatty and nodal tissue) in patients who have (1) increasing calcitonin levels and had inadequate initial operations or (2) postoperative hypercalcitoninemia and a positive localizing study of locoregional residual MTC or (3) for palliation of aggressive locoregional MTC in patients with widely metastatic MTC.

Although persistent MTC usually can be demonstrated by basal or stimulated hypercalcitoninemia, localizing the site of disease remains a challenge.[3] Noninvasive imaging studies may be helpful but are imperfect (Table 3–3). The sensitivity and specificity of computed tomography, magnetic resonance imaging, and radionuclide and ultrasonographic scanning for persistent and recurrent MTC are poor and have been evaluated in only a small group of patients. Selective venous catheterization with calcitonin measurement has been reported to have a high sensitivity in a small study but is not available at most institutions.[45] Positron emission tomography often identifies one or more sites of metastatic disease, but the calcitonin levels usually remain elevated after reoperation, indicating that nonvisualized sites of metastatic MTC are present.[46]

Unfortunately, there is no effective standard chemotherapy regimen for patients with MTC. Most investigators have evaluated agents that had been effective against other neuroendocrine malignancies in patients with widely metastatic MTC.[47–53] Dacarbazine has been used as a single agent or in combination with other agents (5-fluorouracil, epirubicin, cyclophosphamide, vincristine) and resulted in only partial responses in patients with advanced local MTC or metastatic MTC.[3,47–51] Also, the use of interferon alfa-2a and somatostatin analogue treatment (short-term and long-term octreotide) in patients with persistent or metastatic MTC have shown no effective tumor response.[54–56] Some investigators have reported that octreotide reduces the biochemical markers of MTC and relieves symptoms associated with metastatic MTC.[55,56] Tachyphylaxis to long-term octreotide treatment may develop, but the dose can be escalated to relieve symptoms in patients with metastatic MTC. More studies are needed to better define

Table 3–3. LOCALIZING STUDIES IN PATIENTS WITH PERSISTENT OR RECURRENT MEDULLARY THYROID CANCER

Noninvasive	Anatomic Site Detected	Invasive	Anatomic Site Detected
Ultrasonography	Neck	Venous catherization for calcitonin	Local or distant disease
CT scan	Locoregional, lung and liver metastasis	Laparoscopy	Liver metastasis
MRI	Locoregional and distant metastasis to the liver and lung		
Bone scan	Bone metastasis		
Radionuclide*	Neck and mediastinum and distant metastasis to the liver and lung		

* Several radionuclide imaging modalities have been evaluated including thalium, technetium 99m, single-photon emission computed tomography, ^{131}I metaiodobenzylguanidine, radiolabeled anti–carcinoembryonic antigen, and, recently, positron emission tomography.
CT = computed tomography; MRI = magnetic resonance imaging.

the role and agents that would be helpful in patients with unresectable MTC.

Similarly, the role of external beam radiation therapy for patients with MTC remains unclear. In small retrospective studies, several investigators have suggested some benefit in local control associated with the use of perioperative external radiation therapy.[57–63] It appears that patients who benefit from radiotherapy are those with residual microscopic disease, extrathyroidal MTC invasion, or small macroscopic residual locoregional MTC. Some experts have advocated the routine use of radiotherapy in high-risk patients, defined as those with lymph node metastases and extrathyroidal invasion.[64] No studies, however, have demonstrated any benefit in survival, and radiotherapy, at best, only results in partial transient tumor response or disease stabilization in a subgroup of patients. Furthermore, reoperation for locoregional persistent or recurrent MTC would be difficult after radiotherapy, and some patients with persistent or recurrent MTC have long-term survival. Lastly, cervical radiotherapy could be associated with significant side effects.[65] Radiotherapy is recommended in patients who have (1) unresectable locoregional MTC, (2) incomplete tumor resection by an experienced endocrine surgeon, and (3) symptomatic bone metastasis that cannot be resected.

Because radioiodine therapy is not effective for MTC, radiolabeled anti-CEA antibody therapy has been evaluated in phase I and II radioimmunotherapy trials.[66–69] These studies enrolled patients with persistent and metastatic MTC who had tumor that produced CEA. Unfortunately, the antitumor effects were modest, with a decrease in plasma calcitonin and CEA plasma levels and symptom relief reported. Only a few patients had partial transient tumor responses. The toxicity of radiolabeled anti-CEA antibody treatment was mild. As a localizing study, radiolabeled anti-CEA antibody had a sensitivity of 91 to 100% in patients with metastatic MTC and an elevated CEA level.[66–68] Unfortunately, radiolabeled anti-CEA antibody therapy thus far has limited efficacy and can be used only in patients with MTCs that produce CEA. Further studies are needed to determine its utility as a localizing study.

REFERENCES

1. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer 1998;83:2638–48.
2. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. Cancer 1997; 79:564–73.
3. Marsh DJ, Learoyd DL, Robinson BG. Medullary thyroid carcinoma: recent advances and management update. Thyroid 1995;5:407–24.
4. Hazard JB, Hawk WA, Crile GJ. Medullary (solid) carcinoma of the thyroid—a clinicopathologic entity. J Clin Endocrinol Metab 1959;19:152–61.
5. Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum Mol Genet 1993;2:851–6.
6. Mulligan LM, Kwok JB, Healey CS, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature 1993;363:458–60.
7. Lips CJ, Landsvater RM, Hoppener JW, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. N Engl J Med 1994;331:828–34.
8. Wells SA, Chi DD, Toshima K, et al. Predictive DNA testing and prophylactic thyroidectomy in patients at risk of multiple endocrine neoplasia type 2A. Ann Surg 1994; 220:237–50.
9. Kebebew E, Treseler PA, Siperstein AE, et al. Normal thyroid pathology in patients undergoing thyroidectomy for finding a RET gene germline mutation: a report of three cases and review of the literature. Thyroid 1999;9:127–31.
10. Kebebew E, Ituarte PHG, Siperstein AE, et al. Medullary thyroid cancer: clinical characteristics, treatment, prognostic factors and a comparison of staging systems. Cancer 2000;88:1139–48.
11. Cote GJ, Gould JA, Huang SC, Gagel RF. Studies of short-term secretion of peptides produced by alternative RNA processing. Mol Cell Endocrinol 1987;53:211–9.
12. Muszynski M, Birnbaum RS, Roos BA, et al. Phorbol esters increase calcitonin gene transcription and decrease c-myc RNA levels in cultured human medullary thyroid carcinoma. J Biol Chem 1985;260:98–104.
13. Cote GJ, Rogers DG, Huang ES, Gagel RF. The effect of 1,25-dihydroxyvitamin D3 treatment on calcitonin and calcitonin gene-related peptide mRNA levels in cultured human thyroid c-cells. Biochem Biophys Res Commun 1987;149:239–43.
14. Gagel RF, Zeytinoglu FN, Voelkel EF, Tashhian AH Jr. Establishment of a calcitonin producing rat medullary throid carcinoma cell line. II. Secretory studies of the tumor and cells in culture. Endocrinology 1980;107:516–23.
15. Zeytin FN, Rusk SF, Baird A, et al. Induction of c-fos, calcitonin gene expression and acidic fibroblast growth factor production in a multipeptide-secreting neuroendocrine cell line. Endocrinology 1988;122:1114–20.
16. Wells SA Jr, Baylin SB, Linehan WM, et al. Provocative

agents and the diagnosis of medullary carcinoma of the thyroid gland. Ann Surg 1978;188:139–41.
17. Biddinger PW, Brennan MF, Rosen PP. Symptomatic C-cell hyperplasia associated with chronic lymphocytic thyroiditis. Am J Surg Pathol 1991;15:599–604.
18. Albores-Saavedra J, Monforte H, Nadji M, et al. C-cell hyperplasia in thyroid tissue adjacent to follicular cell tumors. Hum Pathol 1988;19:795–9.
19. Guyetant S, Wion-Barbot N, Rousselet MC, et al. C-cell hyperplasia associated with chronic lymphocytic thyroiditis: a retrospective quantitiative study of 112 cases. Hum Pathol 1994;25:514–21.
20. Montesco MC, Pinarello A, Ninfo V. Parafollicular C-cell hyperplasia: report of three cases in primary thyroid lymphomas. Tumori 1988;74:97–100.
21. Eng C. RET proto-oncogene in the development of human cancer. J Clin Oncol 1999;17:380–93.
22. Ponder BAJ. The phenotypes associated with RET mutations in the multiple endocrine neoplasia type 2 syndromes. Cancer Res 1999;59 Suppl:1736–42.
23. Milbrandt J**,** de Sauvage FJ, Fahmer TJ, et al. Persephin, a novel neurotrophic factor related to GDNF and neurturin. Neuron 1998;20:245–53.
24. Jing S, Wen D, Yu Y, et al. GDNF induced activation of the RET protein tyrosine kinase is mediated by GDNFR-α, a novel receptor for GDNF. Cell 1996;85:1113–24.
25. Trupp M, Arenas E, Gainziller M, et al. Functional receptor for glial cell line derived neurotrophic factor encoded by the C RET protooncogene product. Nature 1996;381:785–9.
26. Takahashi M, Nakayama S. The GDNF/neurturin-RET multicomponent receptor system. Neuropathology 1998;18: 139–44.
27. Santoro M, Carlomagno F, Romano A, et al. Activation of RET as a dominant transforming gene by germ-line mutations of MEN 2A and MEN 2B. Science 1995;267:381–3.
28. Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET protooncogene mutations and disease phenotype in multiple endocrine neoplasia type 2: International RET Mutation Consortium analysis. JAMA 1996;276:1575–9.
29. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma. Recommendations for extent of node dissection. Ann Surg 1999;229:880–8.
30. Ponder BA, Ponder MA, Coffey R, et al. Risk estimation and screening in families of patients with medullary thyroid carcinoma. Lancet 1988;i:397–401.
31. Nunziata V, Giannattasio R, di Giovanni G, et al. Hereditary localized pruritus in affected members of a kindred with multiple endocrine neoplasia type 2A (Sipple's syndrome). Clin Endocrinol 1989;30:57–63.
32. Gagel RF, Levy ML, Donovan DT, et al. The association of multiple endocrine neoplasia, type 2a and cutaneous lichen amyloidosis. Ann Intern Med 1990;112:551–2.
33. Treseler PA, Clark OH. Prognostic factors in thyroid carcinoma. Surg Oncol Clin North Am 1997;6:555–98.
34. Dotzenrath C, Goretzki PE, Cupisti K, et al. Is there any consensus in diagnostic and operative strategy with respect to medullary thyroid cancer? A questionnaire answered by 73 endocrine surgical units. Langenbecks Arch Surg 2001;386:47–52.
35. Machens A, Gimm O, Ukkat J, et al. Improved prediction of calcitonin patients by quantitative lymph node analysis. Cancer 2000;88:1909–15.
36. Dralle H, Gimm O, Simon D, et al. Prophylactic thyroidectomy in 75 children and adolescents with hereditary medullary thyroid carcinoma: German and Austrian experience. World J Surg 1998;22:744–51.
37. Moley JF. Surgical management of persistent and recurrent medullary thyroid cancer. Arch Intern Med 1998;243: 521–6.
38. Kebebew E, Kikuchi S, Duh Q-Y, Clark OH. Long-term results of reoperation and localizing studies in patients with persistent or recurrent medullary thyroid cancer. Arch Surg 2000;135:895–901.
39. Busnardo B, Girelli ME, Simioni N, et al. Nonparallel patterns of calcitonin and carcinoembryonic antigen levels in the follow-up of medullary thyroid carcinoma. Cancer 1984;53:278–85.
40. van Heerdan J**,** Grant C, Gharib H, et al. Long-term course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma. Ann Surg 1990;212:395–400.
41. Tissell LE, Hansson G, Jansson S, et al. Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. Surgery 1986;99:60–6.
42. Dralle H, Damm 1, Scheumann GFW, et al. Compartment-oriented microdissection of regional lymph nodes in medullary thyroid carcinoma. Surg Today 1994;24:112–21.
43. Moley JF, Dilley WG, DeBenedetti MK. Improved results of cervical reoperation for medullary thyroid carcinoma. Ann Surg 1997;225:734–43.
44. Chen H, Roberts JR, Ball DW, et al. Effective long-term palliation of symptomatic, incurable metastatic medullary thyroid cancer by operative resection. Ann Surg 1998; 227:887–95.
45. Medina-Franco H, Herrera MF, Lopez G, et al. Persistent hypercalcitoninemia in patients with medullary thyroid cancer: a therapuetic approach based on selective venous sampling for calcitonin. Rev Invest Clin 2001;53:212–7.
46. Diehl M, Risse JH, Brandt-Mainz K, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in medullary thyroid cancer: results of a multicentre study. Eur J Nucl Med 2001;28:1671–6.
47. Petursson SR. Metastatic medullary thyroid carcinoma. Complete response to combination chemotherapy with dacarbazine and 5-fluorouracil. Cancer 1988;62:1899–903.
48. Orlandi F, Caraci P, Berruti A, et al. Chemotherapy with dacarbazine and 5-fluorouracil in advanced medullary thyroid cancer. Ann Oncol 1994;5:763–5.
49. Wu LT, Averbuch SD, Ball DW, et al. Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine, and dacarbazine. Cancer 1994;73:432–6.
50. Di Bartolomeo M, Bajetta E, Bohcicchio AM, et al. A phase II trial of dacarbazine, fluorouracil and epirubicin in patients with neuroendocrine tumours. A study by the Italian Trials in Medical Oncology (I.T.M.O.) Group. Ann Oncol 1995;6:77–9.
51. Schlumberger M, Abdelmoumene N, Delisle MJ, et al. Treatment of advanced medullary thyroid cancer with an

alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. Br J Cancer 1995;71:363–5.
52. Shimaoka K, Schoenfeld DA, DeWys D, et al. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985; 56:2155–60.
53. Sridhar KS, Holland JF, Brown JC, et al. Doxorubicin plus cisplatin in the treatment of apudomas. Cancer 1985;55: 2634–7.
54. Gottlieb JA, Hill CS. Adriamycin (NSC-123127) therapy in thyroid carcinoma. Cancer Chemother Rep 1975;6:283–96.
55. Schlumberger M, Gardet P, De Vathaire F, et al. Chemotherapy in metastatic nonanaplastic thyroid cancer: experience at the Institut Gustave-Roussy. Tumori 1990;76:480–3.
56. Mahler C, Verhelst J, De Longueville M, Harris A. Long-term treatment of metastatic medullary thyroid carcinoma with the somatostatin analogue octreotide. Clin Endocrinol 1990;33:261–9.
57. Modigliani E, Cohen R, Joannidis S, et al. Results of long-term continuous subcutaneous octreotide administration in 14 patients with medullary thyroid carcinoma. Clin Endocrinol 1992;36:183–6.
58. Nguyen TD, Chassard JL, Lagarde P, et al. Results of postoperative radiation therapy in medullary carcinoma of the thyroid: a retrospevtive study by the French Federation of Cancer Institutes—the Radiotherapy Cooperative Group. Radiother Oncol 1992;23:1–5.
59. Rougier P, Parmentier C, Laplanche A, et al. Medullary thyroid carcinoma: prognostic factors and treatment. Int J Radiat Oncol Biol Phys 1983;9:161–9.
60. Samaan NA, Schultz PN, Hickey RC. Medullary thyroid carcinoma. Prognosis of familial versus sporadic disease and the role of radiotherapy. J Clin Endocrinol Metab 1988; 67:801–5.
61. Brierly JD, Tsan RW. External radiation therapy in the treatment of thyroid malignancy. Endocrinol Metab Clin North Am 1996;25:141–57.
62. Simpson WJ, Palmer JA, Rosen IB, Mustard RA. Management of medullary carcinoma of the thyroid. Am J Surg 1982;144:420–2.
63. Mak A, Morrison W, Garden A, et al. The value of postoperative radiotherapy for regional medullary carcinoma of the thyroid. Int J Radiat Oncol Biol Phys 1994;30: 234.
64. Schlumberger M, Gardet P, de Vathaire F, et al. External radiotherapy and chemotherapy in MTC patients. In: Calmettes C, Guliana J, editors. Medullary thyroid carcinoma. Paris: John Libbey; 1991. p. 213–20.
65. Brierley J, Tsan R, Simpson WJ, et al. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. Thyroid 1996; 6:305–10.
66. Harmer C, Bidmead M, Shepherd S, et al. Radiotherapy planning techniques for thyroid cancer. Br J Radiol 1998; 71:1069–75.
67. Kraeber-Bodere F, Bardet S, Hoefnagel CA, et al. Radioimmunotherapy in medullary thyroid cancer using bispecific antibody and iodine 131-labeled bivalent hapten: preliminary results of a phase I/II clinical trial. Clin Cancer Res 1999;5 Suppl:3190–8.
68. Juweid M, Sharkey RM, Behr T, et al. Targeting and initial radioimmunotherapy of medullary thyroid carcinoma with ^{131}I-labeled monoclonal antibodies to carcinoembryonic antigen. Cancer Res 1995;55 Suppl:5946–51.
69. Behr TM, Sharkey RM, Jueweid ME, et al. Phase I/II clinical radioimmunotherapy with an iodine-131-labeled anti-carcinoembryonic antigen murine monoclonal antibody IgG. J Nucl Med 1997;38:858–70.

4

Anaplastic Thyroid Carcinoma

THIERRY M. JAHAN, MD
JENNIFER BRAEMAR OGILVIE, MD

Anaplastic thyroid carcinoma (ATC) is, fortunately, a rare entity. It is one of the most aggressive neoplasms with which we have to deal. The treatment options are limited, and the sensitivity of the disease to intervention is minimal, making it a rather daunting process. Recent molecular advances have afforded us more insight in this extraordinary disease. Hopefully, these same basic scientific advances will lead to earlier diagnoses and better therapeutic options.

EPIDEMIOLOGY

The American Cancer Society estimates that there were 20,700 new cases of thyroid cancer and 1,300 deaths owing to thyroid cancer in 2002.[1] ATC accounts for less than 4% of all thyroid cancer, but with its nearly 100% fatality ratio, it accounts for more than half of all deaths attributable to thyroid cancer.

Like most thyroid neoplasms, ATC is more common in women. However, the female-to-male ratio is only 1.5 to 1, whereas it tends to be higher in other thyroid neoplasms.[2] ATC patients are older, typically presenting in their sixth and seventh decade. Over 90% of ATC patients are over the age of 50.[3] The risk factors for ATC are not as clearly established as they have been for other thyroid neoplasms. Nonetheless, up to 80% of patients who develop ATC can have an antecedent history of long-standing thyroid goiter.[4] ATC also seems to develop from well-differentiated thyroid cancer (WDTC). It is not uncommon to see WDTC transform into ATC as a natural evolution of the disease. The majority (80 to 90%) of ATC cases have been found to have coexisting areas of WDTC on histology.[5,6] The relationship between the two forms of cancer makes adequate management of WDTC all the more important as a way to prevent the eventual progression to ATC. Given that WDTC may evolve into ATC and that WDTC is frequently treated with radioactive iodine therapy, there may be a role played by exposure to radioactivity in the transformation sequence from WDTC to ATC. The role of thyroid/neck radiation exposure in the etiology of ATC is not clear.[7,8] Family history does not seem to play a role in the development of ATC.

DIAGNOSIS AND STAGING

ATC presents as a rapidly enlarging neck mass (Figure 4–1). The rate of growth is one of the fastest of all neoplasms; it is not unusual to see the masses double in size in a matter of days. The lesions are typically firm and large. Over 80% of ATC masses are larger than 5 cm on initial presentation.[9] As the tumor grows rapidly, it can outgrow its blood supply, and the resulting necrotic areas can feel fluctuant in an otherwise firm background. The tumor cells may infiltrate the skin and cause overlying necrosis. More than 40% of patients present with associated adenopathy in other areas of the neck.[3,5,9] The tumor has a tendency to invade the vital structures of the neck and to not respect tissue planes (Figure 4–2). Up to 30% of patients can present with hoarseness owing to vocal cord paralysis following tumor involvement of the recurrent laryngeal nerve.[3,5,9] They can also present with dyspnea owing to airway

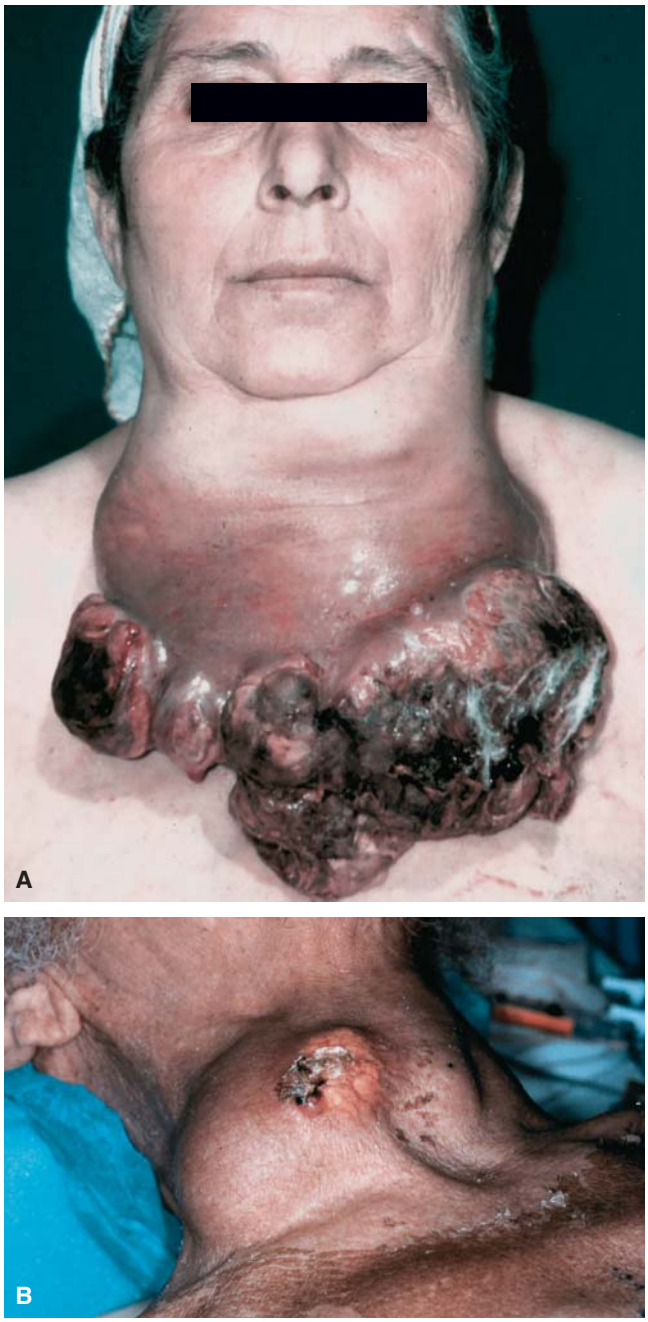


Figure 4–1. *A*, Rapidly enlarging neck mass in a patient with anaplastic thyroid carcinoma (ATC). *B*, Rapidly enlarging neck mass in a patient with ATC.

compromise following tracheal or laryngeal invasion. ATC invasion of the superior vena cava (SVC) can result in obstruction of the SVC (Figure 4–3). Patients with SVC syndrome present with upper body, face, and neck plethora. They also show signs of neck, chest, and upper extremity vascular congestion causing edema and prominent superficial venous engorgement. If the tumor mass invades the

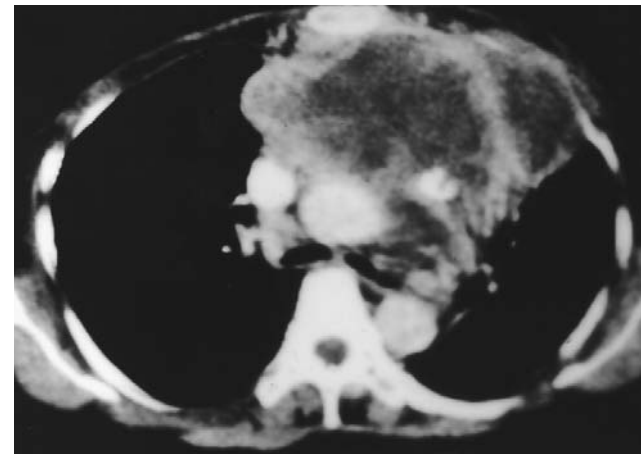


Figure 4–2. Computed tomographic scan illustrating invasion of mass with loss of tissue planes.

esophagus, patients can experience dysphagia. The rapid growth rate can result in significant pain owing to invasion into nerves or muscles. Occasionally, ATC masses can present with leukocytosis that results from independent production of granulocyte colony-stimulating factor.

ATC is diagnosed with a tissue biopsy. Fine-needle aspirations tend to yield an accurate diagnosis; there can be false-negative or nondiagnostic results if the sample is obtained from an area of inflammatory or fibrotic reaction or from an area of hemorrhage. Several passes or the use of larger-core needles may be necessary. Rarely, one may need to carry out an incisional biopsy to obtain enough tissue for accurate classification. Unlike WDTC, there is usually no role for radioactive iodine scanning in

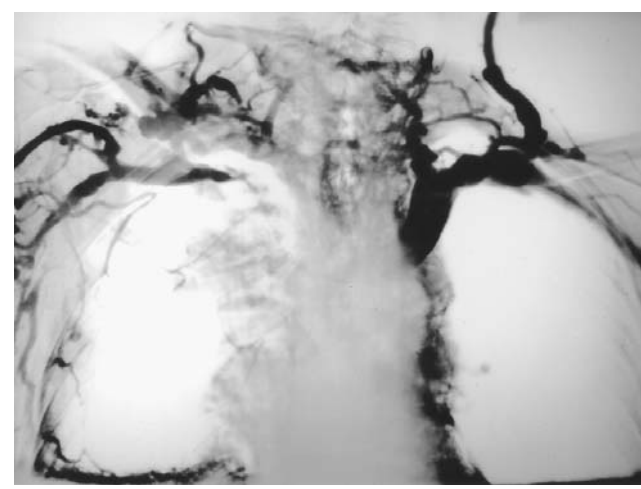


Figure 4–3. Angiogram illustrating interruption of superior vena cava flow.

ATC. The use of serum markers is also of limited value because ATC cells do not secrete thryoglobulin, calcitonin, or carcinoembryonic antigen (CEA). In fact, the presence of an elevated CEA level and an elevated calcitonin level would suggest that the tumor is more likely to be a poorly differentiated medullary carcinoma of the thyroid. The presence of an elevated CEA without elevated calcitonin may be seen in a metastatic neoplasm involving the thyroid. Both of these entities may have a better prognosis than ATC so that accuracy in diagnosis is quite important. In younger patients, it is crucial to exclude tumors with much better prognosis. Young patients who present with poorly differentiated tumors should have their serum checked for the presence of α-fetoprotein and human chorionic gonadotropin (βhCG), which would suggest that one is dealing with a poorly differentiated germ cell tumor, quite curable, rather than with an incurable ATC.

Imaging studies are helpful in assessing the extent of disease. Magnetic resonance imaging (MRI) is particularly helpful in the neck (Figure 4–4) and brain. Computed tomography provides more information for the lungs and mediastinum (Figure 4–5). The scans can help assess the extent of disease to help define anatomic planes in anticipation of surgery or radiation. ATC is a systemic disease, with 50% of patients presenting with distant metastases. At least 80% of these patients will present with clinically evident pulmonary metastases, 15% of patients can present with bone metastases, and 13% with brain metastases.[10] Distant metastases to the adrenals are seen in 33% and to intra-abdominal lymph nodes in 17%.[2,10] Autopsy studies have shown that metastases are microscopically present in many patients, even when the imaging tests have been negative. One autopsy series showed pulmonary metastases in 100%, bone metastases in 80%, invasion of adjacent cervical soft tissues in 60%, and tracheal invasion in 27%.[11] MRI of the brain can detect the presence of occult brain metastases and should be performed as part of the initial staging procedure. Bone scans are also valuable to confirm the presence of metastases in vulnerable weight-bearing areas, whether or not patients have actual symptoms. Positron emission tomography is gaining acceptance as a staging modality; its true value remains to be fully established. Staging procedures help determine the extent of disease, which, in turn, leads to early intervention. Although not curative, radiation to the brain or to bones affected with metastases can help preserve function and quality of life while avoiding seizures or catastrophic fractures.

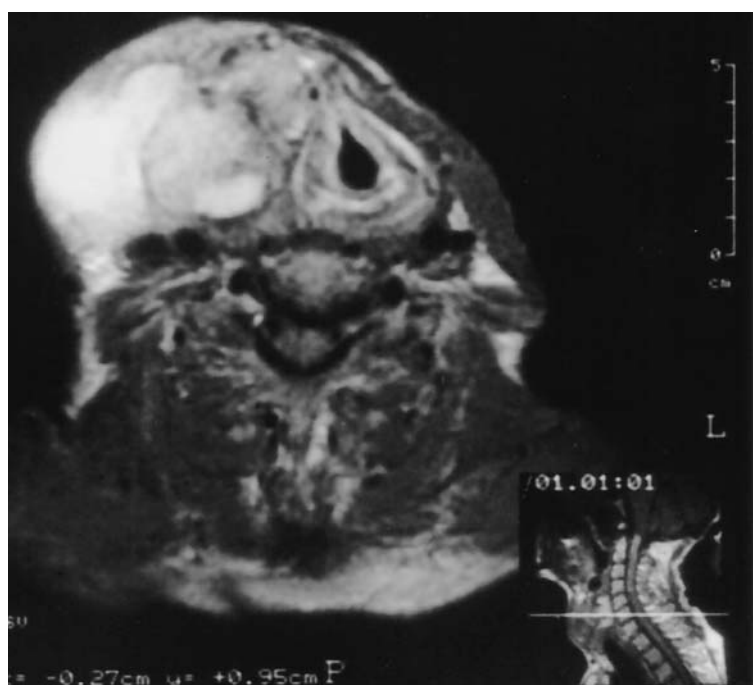


Figure 4–4. Magnetic resonance image of neck mass showing tracheal deviation and anatomic relationships.

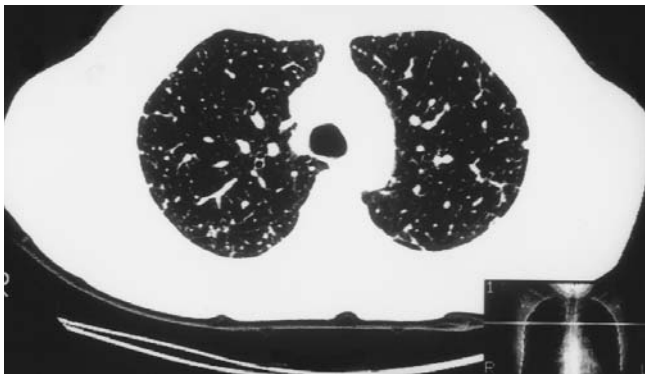


Figure 4–5. Computed tomographic scan of chest with multiple pulmonary metastases.

The staging system in ATC is quite simple. The American Joint Committee on Cancer (AJCC) automatically classifies all patients with a histologic diagnosis of ATC as stage IV.[12] All ATC tumors are considered T4. They are further divided into T4a (confined to the thyroid, surgically resectable) and T4b (extending beyond the thyroid, surgically unresectable). Stage grouping is listed in Table 4–1.

PATHOLOGY

Three histologic variants of anaplastic carcinoma include giant cell, spindle cell, and squamoid. Studies have clearly demonstrated that ATC labeled "small cell" in the past was, in fact, thyroid lymphoma (TL) or medullary thyroid carcinoma (MTC).[9,13–15] TL represents an extranodal variant of non-Hodgkin's lymphoma. It is typically seen in patients with a prior history of Hashimoto's thyroiditis. It is less aggressive than true ATC, with an overall 5-year survival of 50% and a median survival of 2 years. Although most anaplastic tumors exhibit mixed morphology, the most common histologic pattern is the giant cell variant, with abundant eosinophilic, granular cytoplasm, multiple hyperchromatic nuclei, and occasional acidophilic intracytoplasmic hyaline globules. The spindle cell variant has spindle-shaped cells with a fascicular architecture that can mimic fibrosarcoma, occasional inflammatory infiltrates resembling malignant fibrous histiocytoma, and pronounced vascularization suggesting hemangioendothelioma. The squamoid variant is characterized by nests of large pleomorphic cells that occasionally form keratin pearls.[16]

Pathologic features of ATC include bizarre cells with polymorphic nuclei of varying size (see Figure 4–5). The cells exhibit a high mitotic rate.[4] There is frequently extensive necrosis occurring because the tumor outgrew its blood supply, with acute inflammatory infiltrates and osteoclast-like giant cells of monocytic/histiocytic lineage.[17] One can see areas of invasion into the muscular wall of small and medium-sized arteries with thrombosis. There is usually invasion into adjacent perithyroidal tissues. One can also see residual areas of follicular or papillary differentiation. Immunohistochemistry is helpful to exclude tumors with a more favorable prognosis. TL cells will stain positive with stains directed at the leukocyte common antigen. MTC cells will stain positive with stains directed at calcitonin, calcitonin gene–related peptide, neuron-specific enolase, chromogranin, or CEA. Thyroid leiomyosarcomas will stain positive with stains directed at vimentin, smooth muscle actin, or muscle-specific actin. Angiosarcomas and hemangioendotheliomas are positive for factor VIII–associated antigen. Only about 50% of ATC will stain with thyroglobulin (TG). The staining occurs only in the areas with coexistent well-differentiated remnants. The dedifferentiated areas have lost the ability to synthesize TG and therefore will not label with TG-directed stains, although synthesized TG has been shown to diffuse into tumor cells and demonstrate weak positive staining.[18] ATC may stain positive for cytokeratins, high-molecular-weight keratins, and epithelial membrane antigen, reflecting its epithelial cell origin.[19] About half of ATCs stain positive with stains directed at α_1-antichymotrypsin. The squamoid variant of ATC may stain positive for

Table 4–1. TNM STAGING ADOPTED BY THE AMERICAN JOINT COMMITTEE ON CANCER (2002 REVISIONS INCORPORATED) FOR ANAPLASTIC THYROID CANCER

	T	N	M
IVa	T4a	Any N	M0
IVb	T4b	Any N	M0
IVc	Any T	Any N	M1

M = metastasis; N = nodes; T = tumor.
Adapted from Greene FL, Balch CM, Page DL, et al, editors. American Joint Committee on Cancer (AJCC) cancer staging manual. 6th ed. New York: Spring-Verlag; 2002. p. 77–87.

CEA.[20] At least 30% of ATCs will not stain with any of the above markers.

Molecular studies of ATC cells reveal the presence of multiple abnormalities. Several mutations in key oncogenes have been described (*CMYC*,[21] *HRAS*,[22] *NM23*[23]). The contribution of each of these mutations to the malignant transformation process for ATC remains unclear. *P53* mutations are also frequently noted.[24] They seem to be a late mutational event and are rarely seen in either follicular or papillary cells. In ATC tumors that have foci of WDTC cells, *P53* mutations are noted in the ATC cells but not in the WDTC, suggesting that the *P53* mutation may be an important event in the evolution from WDTC to ATC.[25,26] The fact that *P53* mutations appear to be a consistent event in the ATC cells may be exploited as a therapeutic target in the future.

Intermediate in prognosis and morphology between ATC and differentiated thyroid carcinomas is insular carcinoma, representing 4 to 7% of thyroid cancers.[27] This tumor of follicular cell origin has "insular" nests of small uniform tumor cells, rare mitotic figures, and single-cell necrosis on histology. The cells have intranuclear inclusion, grooves, and folds typical of papillary cancer, with scant cytoplasm. Insular carcinomas often take up iodide and respond to radioiodine treatment and may represent a transition from differentiated to undifferentiated thyroid carcinomas.[28]

Another unusual variant of ATC is the paucicellular variant, with rare atypical spindle cells, extensive fibrosis, and foci of calcification or infarction. Cells stain positive for cytokeratin, actin, and CEA. Like ATC, this variant presents with rapid tumor growth and compressive symptoms.

PROGNOSIS

The natural history of ATC is not encouraging. The disease is quite relentless, with mean survivals, untreated, ranging between 2.5 and 7.4 months.[10,20,29,30] In some series, 82 to 90% of patients have died within the first 6 months.[20,30] Only 10 to 20% are alive longer than 1 year.[31] The aggressiveness of the disease varies somewhat with the presentation. Patients who present with localized disease tend to have median survivals on the order of 8 months, whereas patients who present with overtly disseminated disease will have median survivals on the order of 3 months or so.[10] As in WDTC, a younger age at presentation with more focal disease portends a better prognosis. Patients who are able to tolerate more aggressive multimodal treatment, including complete resection, external irradiation, and chemotherapy, also tend to have a better chance at longer survival.[10,30–32] In an attempt to predict which patients benefit from aggressive multimodal therapy, Sugitani and colleagues studied 47 patients with ATC and identified four prognostic factors that were independent risk factors for death from ATC: acute symptoms, tumor size > 5 cm, distant metastases, and white blood cell count > 10,000/mm^3.[33] Patients with one prognostic factor had an increased survival of 62% at 6 months, whereas all patients with three or more factors died within 6 months and all patients with four factors died within 3 months.

TREATMENT

Treatment for ATC remains limited in its effectiveness. The mainstay of therapy will involve one or more of the three conventional anticancer treatment modalities: surgery, radiation therapy, and chemotherapy.

The role of aggressive surgery has not been clearly defined. ATC is a systemic disease, so surgery alone cannot be curative. Aggressive surgery can help protect vital neck structures from invasion by ATC and therefore help preserve function. There have been several reports of series showing that patients treated with complete or near-complete resections tended to have a better outcome than patients treated without resection.[32,34–37] Haigh and colleagues found that potentially curative resection was the only significant survival benefit by multivariate analysis in 33 patients with ATC. Survival benefit was not correlated with age, gender, prior goiter, or WDTC or tumor size.[32] Although encouraging, these results could also be explained by a selection of patients, who, by virtue of their improved resectability, are more likely to have a more favorable outcome. Consequently, these studies must be interpreted cautiously in the absence of randomized clinical trials. Surgery does play an important role in the adequate protection of neck struc-

tures. It should be considered even in the presence of widespread systemic metastasis, unless the patient is overwhelmed physiologically by the metastatic disease. Prophylactic tracheostomy for unresected disease may cause wound complications that delay or prevent radiation treatment and does not appear to lengthen survival.[38]

Radiotherapy is another modality best suited for local control. Because the majority of patients are not completely resectable, radiotherapy can be used to help treat unresectable areas or positive surgical margins to optimize local control. The preferred method of treatment delivery has not been established. Once again, there have not been randomized clinical trials to help firmly define the optimal radiotherapy dose and fractionation schemas. On the basis of existing single-institution experiences, it would appear that fractionation schema including hyperfractionation with doses of 1.5 to 1.6 Gy administered at least 4 hours apart twice daily for a total dose of at least 30 Gy seem to be relatively effective as an adjuvant to surgery.[39–41] The advantage of hyperfractionated radiation is the ability to deliver a larger dose in a smaller amount of time. The disadvantages include moderately more intense tracheoesophagitis, skin toxicity, and radiation myelopathy. When combined with radiosensitizing doses of chemotherapy (most often with doxorubicin), the local toxicity is also more apparent.

The largest experience with this approach comes from the Swedish Anaplastic Thyroid Cancer Group at the Karolinska Hospital.[41] Dr. Tennvall and associates treated 33 patients with hyperfractionated doses of 1 Gy twice a day (16 patients) or 1.3 Gy (17 patients) with concurrent weekly low-dose intravenous doxorubicin to a radiotherapy dose of 30 Gy preoperatively followed by 16 Gy postoperatively. They allowed their patients a 4-week interval between the completion of the first radiation course and the start of the second radiation course, during which surgery took place. Most of the patients continued to receive doxorubicin to an average cumulative dose of 810 mg following the completion of radiation therapy. The authors reported a high rate of complete resectability (58%) and a high rate of local control (48%). Median survival remained low (3.5 and 4.5 months, respectively, for the two groups), with most patients succumbing to progressive distant metastases. Nonetheless, three patients in each group achieved survival that lasted over 1 year, and four patients (12%) achieved long-term survival and were considered "cured."

Results such as those reported by the Scandinavian group illustrate the fact that ATC is primarily a systemic illness. Aggressive local measures have led to some improvements in the outcome of patients with ATC. However, further improvements can continue to take place only with the development of better systemic therapy. Doxorubicin (Adriamycin) has remained the established standard, despite the fact that it has been shown to have only a 4 to 23% response rate as a single agent.[42,43] There has not been another single drug that can claim a better result than doxorubicin

Combinations of older chemotherapy drugs have been poorly studied. Most of the results emanate from small studies; there are no large studies to help answer the question of their efficacy. The most promising studies used combinations of cisplatin, vincristine and mitoxantrone or bleomycin, cyclophosphamide, and 5-fluorouracil with modest response rates and prolongation of survival.[44,45]

New drugs with a broad spectrum of activity have recently become available. One of these, paclitaxel (Taxol), has shown promise in the laboratory.[46] Paclitaxel is an inhibitor of microtubule depolymerization and also a potent radiosensitizer and has been combined effectively with radiation to treat other types of cancer. The combination of paclitaxel-based chemotherapy with radiation is currently being explored for the treatment of ATC. A recent phase 2 trial of paclitaxel alone following radiation and surgical therapy showed a 53% total response rate (47% partial response) with mild to moderate toxicity.[47] Studies of the cellular mechanisms responsible for chemotherapy resistance, such as the expression of P-glycoprotein, multidrug resistance–associated protein (MRP), LRP (major vault protein), and deoxyribonucleic acid (DNA) topoisomerase II-α mutations, have shown that all ATC lines examined express MRP, a drug-resistance protein that is less able to transport paclitaxel out of the cancer cell.[48–50] These drug-resistance proteins or their parent genes could serve as targets for inactivation to restore cytotoxic

response to older chemotherapeutic agents. Other promising new cytotoxic agents, such as docetaxel (Taxotere), vinorelbine (Navelbine), gemcitabine (Gemzar), irinotecan (Camptosar), and topotecan (Hycamtin), should provide us with new systemic therapeutic possibilities that warrant further investigations, either on their own or combined in some fashion with radiation therapy.

Cytotoxic therapy will always be limited by its narrow therapeutic index. The overall toxicity of the treatment is usually too severe for most patients. In 20 patients with ATC treated with doxorubicin and cisplatin or mitoxantrone plus radiation therapy, all patients had severe tracheitis and pharyngoesophagitis.[51] Therefore, different approaches need to be explored. A new class of drugs, the angiogenesis inhibitors, has been receiving a great deal of attention. These drugs were developed because of their ability to block the growth of blood vessels in experimental models. It has been recognized that the growth of tumors beyond 1 to 2 mm in size requires that the tumor secure an adequate blood supply. Tumors that can acquire the ability to establish their own blood supply or that can co-opt the host organism's blood supply to sustain their own growth develop a clear survival advantage. The mechanisms of angiogenesis are currently being elucidated, yet there are a number of agents that target known steps of these mechanisms. Certain thyroid cancer cell lines have been shown to overexpress receptors for the vascular endothelial growth factor (VEGF). The VEGF receptor is the target of an anti-VEGF monoclonal antibody that is currently being tested for efficacy in non–small cell lung cancer, prostate cancer, and colorectal cancer. The anti-VEGF monoclonal antibody has been documented to be effective in reducing the growth of transplanted human thyroid cancer cells in nude mice.

There are other agents in clinical development that target other aspects of angiogenesis pathways. Among these, there are inhibitors of the enzymes that degrade the tissue matrix through which growing blood vessels must pass in order to reach their destination. ATC cells in culture produce growth-stimulating factors such as insulin-like growth factor 1 somatostatin receptor subtypes 1, 3, and 5; CD97; and platelet-derived growth factor (PDGF) receptor B type.[51–55] The role of these proteins and their potential use as antineoplastic targets will need to be evaluated in the management of patients with ATC. Somatostatin receptor agonists have been shown to inhibit cellular proliferation, suggesting a possible role for specific receptor subtype somatostatin analogues to target ATC cells.[56]

ATC cells are poorly differentiated. They have reached a molecular developmental block or maturational arrest. If this block can be overcome, the cancer cells might lose some of the characteristics that make them cancerous and might return to a more benign state. A number of agents are currently being studied in the laboratory that show clear promise. Phenylacetate and *cis*-retinoic acid are two such compounds that have shown excellent capacity to cause poorly differentiated cells to overcome their maturational arrest and to demonstrate signs of differentiation into more normal thyroid tissue, possibly through the inhibition of VEGF secretion.[57,58] The toxicity of these compounds appears minimal. Human clinical trials will need to be undertaken to verify the laboratory results.

The treatment of ATC is extremely limited by the tumor's resistance to radioiodine therapy. Two animal trials of ATC cells implanted into nude mice treated with the α-emitting halogen isotope astatine 211 demonstrated a 2.6- to 12.5-fold increase in astatine 211 concentration over iodine 125, with uptake increased by propylthiouracil and thiouracil, suggesting a role for alternative radiation therapy in ATC using this α-emitter, although the radiotoxicity has not been defined.[59–60]

Another experimental strategy to sensitize ATC cells to radioiodine therapy is to increase the expression of the sodium iodide symporter (NIS). Treatment of ATC cell lines with the histone deacetylase inhibitor depsipeptide (FR901228) led to the increased expression of thyroglobulin and NIS in the ATC cells, with resultant iodine 125 accumulation.[61] Another study showed that the histone deacetylase inhibitors sodium butyrate and trichostatin A induced apoptosis and differential cell-cycle arrest in ATC cell lines.[62,63]

Finally, it would appear that mutations to the *P53* gene are a late and important event in the transformation of WDTC to ATC. Tumor suppressor *P53*

mutations have been observed in 70 to 85% of ATC versus 0 to 9% in differentiated thyroid carcinomas.[24,64,65] Replacing the missing *P53* gene in ATC cells with a normal copy of the gene could help restore these cells to a more normal phenotype or allow them to be more sensitive to the effects of conventional therapeutic modalities such as chemotherapy and radiation. Nagayama and colleagues showed that the administration of a replication-defective recombinant adenovirus vector expressing wild-type *P53* to nude mice with established ATCs led to inhibition of tumor cell growth and regression of tumor when combined with doxorubicin.[66]

ATC remains an extremely difficult disease to control. It appears that there are new research opportunities that may make a significant impact in the future. Coordination of efforts at the national and international levels should result in significant advances over a shorter period and allow us to master this dreadful illness.

REFERENCES

1. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer 1998;83:2638–48.
2. Tan RK, Finley RK, III, Driscoll D, et al. Anaplastic carcinoma of the thyroid: a 24 year experience. Head Neck 1995;17:41–7.
3. Hadar T, Mor C, Shvero J, et al. Anaplastic carcinoma of the thyroid. Eur J Surg Oncol 1993;19:511–6.
4. LiVolsi VA. Surgical pathology of the thyroid. Philadelphia: WB Saunders; 1990.
5. Aldinger KA, Samaan NA, Ibanez M, Hill CS Jr. Anaplastic carcinoma of the thyroid: a review of 84 cases of spindle and giant cell carcinoma of the thyroid. Cancer 1978;41: 2267–75.
6. Nishiyama RH, Dunn EL, Thompson NW. Anaplastic spindle-cell and giant-cell tumors of the thyroid gland. Cancer 1972;30:113–27.
7. Yoshida A, Kamma H, Asaga T, et al. Proliferative activity in thyroid tumors. Cancer 1992;69:2548–52.
8. Kapp DS, LiVolsi VA, Sanders MM. Anaplastic carcinoma following well-differentiated thyroid cancer: etiological considerations. Yale J Biol Med 1982;5:521–8.
9. Nel CJ, van Heerden JA, Goellner JR, et al. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 82 cases. Mayo Clin Proc 1985;60:51–8.
10. Venkatesh YS, Ordonez NG, Schultz PN, et al. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 121 cases. Cancer 1990;66:321–30
11. Thomas CG Jr, Buckwalter JA. Poorly differentiated neoplasms of the thyroid gland. Ann Surg 1973;177:632–42.
12. Fleming ID, et al, editors. American Joint Committee on Cancer manual for staging of cancer. 5th ed. Philadelphia: Lippincott-Raven; 1997.
13. Rosai J, Saxen EA, Woolner L. Undifferentiated and poorly differentiated carcinoma. Semin Diagn Pathol 1985;2: 123–36.
14. Wolf BC, Sheahan K, DeCoste D, et al. Immunohistochemical analysis of small cell tumors of the thyroid gland: an Eastern Cooperative Oncology Group study. Hum Pathol 1992;23:1252–61.
15. Holting T, Moller P, Tschahargane C, et al. Immunohistochemical reclassification of anaplastic carcinoma reveals small and giant cell lymphoma. World J Surg 1990;14: 291–4.
16. Asa SL, Bedard YC. Fine-needle aspiration cytology and histopathology. In: Clark OH, Noguchi S, editors. Thyroid cancer diagnosis and treatment. St. Louis: Quality Medical Publishing; 2000. p. 39–104.
17. Gaffey MJ, Lack EE, Christ ML, Weiss LM. Anaplastic thyroid carcinoma with osteoclast-like giant cells. A clinicopathologic, immunohistochemical, and ultrastructural study. Am J Surg Pathol 1991;15:160–8.
18. Rosai J. Tumors of the thyroid gland. In: Atlas of tumor pathology. 3rd series, fascicle 5. Washington (DC): Armed Forces Institute of Pathology; 1992.
19. Ordonez NG, El-Naggar AK, Hickey RC, Samaan NA. Anaplastic thyroid carcinoma. Immunocytochemical study of 32 cases. Am J Clin Pathol 1991;96:15–24.
20. Carcangiu ML, Steeper T, Zampi G, Rosai J. Anaplastic thyroid carcinoma: a study of 70 cases. Am J Clin Pathol 1985;83:135–58.
21. Hoang-Vu C, Dralle H, Scheumann G, et al. Gene expression of differentiation and dedifferentiation markers in normal and malignant human thyroid tissues. Exp Clin Endocrinol 1992;100:51–6.
22. Stringer BM, Rowson JM, Parkar MH, et al. Detection of the H-RAS oncogene in human thyroid anaplastic carcinoma. Experientia 1989;45:372–6.
23. Zou M, Shi Y, al-Sedairy S, Farid NR. High levels of Nm23 gene expression in advanced stage of thyroid carcinomas. Br J Cancer 1993;68:385–8.
24. Fagin JA, Matsuo K, Karmakar A, et al. High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. J Clin Invest 1993;91:179–84.
25. Matias-Guiu X, Villanueva A, Cuatrecasas M, et al. p53 in a thyroid follicular carcinoma with foci of poorly differentiated and anaplastic carcinoma. Pathol Res Pract 1996; 192:1242–9.
26. Dobashi Y, Sugimura H, Sakamoto A, et al. Stepwise participation of p53 gene mutation during dedifferentiation of human thyroid carcinomas. Diagn Mol Pathol 1994;3: 9–14.
27. Pietribiasi F, Sapino A, Papotti M, Bussolati G. Cytologic features of poorly differentiated 'insular'carcinoma of the thyroid, as revealed by fine-needle aspiration biopsy. Am J Clin Pathol 1990;94:687–92.
28. Van der Laan F. The association of well-differentiated thyroid carcinoma with insular or anaplastic thyroid carcinoma: evidence for dedifferentiation in tumor progression. Endocr Pathol 1993;4:215.
29. Lampertico P. Anaplastic (sarcomatoid) carcinoma of the thyroid gland. Semin Diagn Pathol 1993;10:159–68.

30. Jereb B, Stjernsward J, Lowhagen T. Anaplastic giant-cell carcinoma of the thyroid: a study of treatment and prognosis. Cancer 1975;35:1293–5.
31. Nilsson O, Lindeberg J, Zedenius J, et al. Anaplastic giant cell carcinoma of the thyroid gland: treatment and survival over a 25-year period. World J Surg 1998;22:725–30.
32. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. Cancer 2001;91:2335–42.
33. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid. World J Surg 2001;25:617–22.
34. Tennvall J, Tallroth E, el Hassan A, et al. Anaplastic thyroid carcinoma: doxorubicin, hyperfractionated radiotherapy and surgery. Acta Oncol 1990;29:1025–8.
35. Tan RK, Finley RK III, Driscoll D, et al. Anaplastic carcinoma of the thyroid: a 24-year experience. Head Neck 1995;17:47–8.
36. Kobayashi T, Asakawa H, Umeshita K, et al. Treatment of 37 patients with anaplastic carcinoma of the thyroid. Head Neck 1996;18:36–41.
37. Junor EJ, Paul J, Reed NS. Anaplastic thyroid carcinoma: 91 patients treated with surgery and radiotherapy. Eur J Surg Oncol 1992;18:83–8.
38. Ain KB. Anaplastic thyroid carcinoma: behavior, biology, and therapeutic approaches. Thyroid 1998;8:715–26.
39. Kim JH, Leeper RD. Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy. Cancer 1987;60:2372–5.
40. Wong CS, Van Dyk J, Simpson WJ. Myelopathy following hyperfractionated accelerated radiotherapy for anaplastic thyroid carcinoma. Radiother Oncol 1991;20:3–9.
41. Tennvall J, Lundell G, Hallquist A, et al. Combined doxorubicin, hyperfractionated radiotherapy and surgery in anaplastic thyroid carcinoma. Cancer 1994;74:1348–54.
42. Shimaoka K, Schoenfeld DA, DeWys WD, et al. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985;56:2155–60.
43. Shimaoka S. Adjunctive management of thyroid cancer: chemotherapy. J Surg Oncol 1980;15:283–6.
44. Kober F, Heiss A, Keminger K, Depisch D. Chemotherapie hochmalinger schilddrusentumore. Wien Klin Wochenschr 1990;102:274–6.
45. Ekman ET, Lundell G, Tennvall J, Wallin G. Chemotherapy and multimodality treatment in thyroid carcinoma. Otolaryngol Clin North Am 1990;23:523–7.
46. Ain KB, Tofiq S, Taylor KD. Antineoplastic activity of Taxol against human anaplastic thyroid carcinoma cell lines in vitro and in vivo. J Clin Endocrinol Metab 1996;81:3650–3.
47. Ain KB, Egorin MJ, DeSimone PA. Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Thyroid 2000;10:587–94.
48. Satake S, Sugawara I, Watanabe M, Takami H. Lack of a point mutation of human DNA topoisomerase II in multidrug resistant anaplastic thyroid carcinoma cell lines. Cancer Lett 1997;116:33–9.
49. Loe DW, Deeley RG, Cole SP. Biology of the multidrug resistance-associated protein, MRP. Eur J Cancer 1996;32A: 945–57.
50. Venkataraman GM. MDR1 and MRP1 mRNA expression in primary thyroid cancers and cell lines. Presented at the 79th Annual Meeting of the Endocrine Society, Minneapolis, MN, 1997. p. 248.
51. Schlumberger M, Parmentier C, Delisle MJ, et al. Combination therapy for anaplastic giant cell carcinoma. Cancer 1991;67:564–6.
52. Tanaka Y, Kubota K, Sasaki N, et al. Growth stimulating activity secreted by human anaplastic thyroid carcinoma cells. Endocrinol Jpn 1991;38:413–20.
53. Ain KB, Taylor KD, Tofiq S, Venkataraman G. Somatostatin receptor subtype expression in human thyroid and thyroid carcinoma cell lines. Cancer Res 1997; J Clin Endocrinol Metab 82:1857–62.
54. Aust G, Eichler W, Laue S, et al. CD97: a differentiation marker in human thyroid carcinoma. Cancer Res 1997; 57:1798–806.
55. Heldin NE, Gustavsson B, Claesson-Welsh L, et al. Aberrant expression of receptors for platelet derived growth factor in an anaplastic thyroid carcinoma cell line. Proc Natl Acad Sci U S A 1988;85:9302–6.
56. Ain KB, Taylor KD. Somatostatin analogues affect proliferation of human thyroid carcinoma cell lines in vitro. J Clin Endocrinol Metab 1994;78:1097–102.
57. Kebebew E, Wong MG, Siperstein AE, et al. Phenylacetate inhibits growth and vascular endothelial growth factor secretion in human thyroid carcinoma cells and modulates their differentiated function. J Clin Endocrinol Metab 1999;84:2840–7.
58. Van Herle AJ, Agatep ML, Padua DN 3rd, et al. Effects of 13-*cis*-retinoic acid on growth and differentiation of human follicular carcinoma cells in vitro. J Clin Endocrinol Metab 1990;71:755–63.
59. Brown I, Carpenter RN. Endogenous ^{211}At a-particle radiotherapy for undifferentiated thyroid cancer. Acta Radiol Suppl 1991;376:174–5.
60. Cobb LM, Harrison A, Dudley NE, et al. Relative concentration of astatine-211 and iodine-125 by human fetal thyroid and carcinoma of the thyroid in nude mice. Radiother Oncol 1989;13:203–9.
61. Kitazono M, Robey R, Zhan Z, et al. Low concentrations of the histone deacetylase inhibitor, depsipeptide (FR901228) increase expression of the Na+/I- symporter and iodine accumulation in poorly differentiated thyroid carcinoma cells. J Clin Endocrinol Metab 2001;86:3430–5.
62. Greenberg VL, Williams JM, Cogswell JP, et al. Histone deacetylase inhibitors promote apoptosis and differential cell cycle arrest in anaplastic thyroid cancer cells. Thyroid 2001;11:315–25.
63. Greenberg VL, Williams JM, Boghaert E, et al. Butyrate alters the expression and activity of cell cycle components in anaplastic thyroid carcinoma cells. Thyroid 2001;11:21–9.
64. Donghi R, Longoni A, Pilotti S, et al. Gene p53 mutations are restricted to poorly differentiated and undifferentiated carcinomas of the thyroid gland. J Clin Invest 1993;91: 1753–60.
65. Ito T, Seyama T, Mizuno T, et al. Unique association of p53 mutations with undifferentiated but not with differentiated carcinomas of the thyroid. Cancer Res 1992;52:1369–71.
66. Nagayama Y, Yokoi H, Takeda K, et al. Adenovirus-mediated tumor suppressor p53 gene therapy for anaplastic thyroid carcinoma in vitro and in vivo. J Clin Endocrinol Metab 2000;85:4081–6.

5

Benign Primary Tumors: Primary Hyperparathyroidism

M. SEAN BOGER, PharmD
NANCY D. PERRIER, MD

Primary hyperparathyroidism (PHPT) is a common disorder, occurring in at least 1 in every 500 women over 40 years of age and 1 in every 2,000 men.[1] It is estimated that 100,000 patients develop PHPT each year in the United States.[2] PHPT occurs in patients with multiple endocrine neoplasia (MEN) types I, IIA, and, rarely, IIB and as a distinct familial entity without other associated endocrinopathies.[3,4] PHPT also occurs in patients with hereditary hyperparathyroidism–fibrous jaw tumor syndrome.[5] Neonatal hyperparathyroidism occurs in members of families with benign familial hypocalciuric hypercalcemia (BFHH) who have a homozygous mutation (Table 5–1).[6] PHPT is the most common endocrinopathy in MEN type I (90%) and occurs in about 20% of patients with MEN type IIA and 1% of patients with MEN type IIB. PHPT is more common in patients previously exposed to low-dose therapeutic radiation.[7]

ANATOMY

There are usually four parathyroid glands: a superior and an inferior gland on either side of the neck. The two superior glands descend symmetrically from the fourth brachial pouch, and the two inferior glands originate with the thymus from the third brachial pouch. The normal position of a superior gland is on the posterior surface of the thyroid gland, near where the recurrent laryngeal nerve (RLN) enters the larynx posterior to the cricothyroid muscle. The normal position of the inferior glands is more ventral and near the thyrothymic ligament. Eighty-five percent of all glands are within 1 cm of where the RLN crosses the inferior thyroidal artery. Normal parathyroid glands are ovoid and "peanut butter" or light yellow-brown in color. Parathyroid glands are often confused with small lobules of fat, accessory nodules of thyroid tissue, or lymph nodes. When patients have mature or brown fat, identification of normal parathyroid glands is more difficult because the color is similar. In general, parathyroid glands are softer in consistency than the adjacent thyroid or lymph nodes, the latter being more glassy in appearance. Fat lobules are paler and do not have a network of surface blood vessels. Lymph nodes are, in general, more rounded, occur in groups, and are more often adherent to surrounding tissues. Thyroid nodules are harder, more reddish, and less homogeneous than parathyroid glands. Abnormal parathyroid glands move from adjacent tissues when gentle pressure is applied. This has often been referred to as "the floating sign." A normal-size gland

Table 5–1. CHROMOSOME AND GENE ABNORMALITIES IN PATIENTS WITH SPECIFIC HYPERPARATHYROIDISM SYNDROMES

Diagnosis	Chromosome	Gene
Familial PHPT[7]	11q, 1q21–31	
MEN type I[8]	11q	*Menin*
MEN type II[9,10]	10q	*RET*
PHPT-jaw tumor syndrome[5]	1q21–31*	*HRPT2*
Neonatal PHPT[6]	3q	*Ca-R*

PHPT = primary hyperparathyroidism.
*Analogous to RET proto-oncogene responsible for multiple endocrine neoplasia (MEN) type II.

measures 5 to 7 mm × 3 to 4 mm × 0.5 to 2 mm. A normal weight is 40 mg. The percentage of individuals with supramammary glands varies from 2.5 to 22%. The most common site of supernumerary glands is in the thymus.

The arterial supply to both parathyroid glands arises primarily from the inferior thyroidal artery, a branch of the thyrocervical trunk, but can also arise from the superior thyroidal arteries. A rich anastomosis is present with vessels from the superior thyroidal (the first branch off the external carotid), thyroidal ima, and vessels that supply the larynx, trachea, and esophagus. The venous drainage is via the superior, middle, and inferior thyroidal veins, which ultimately empty into the internal jugular veins.

PATHOLOGY

The normal parenchymal content of adult parathyroid tissue is half stroma and fat and half chief cells (Figure 5–1). In children, the parenchyma is almost entirely composed of chief cells. The size of parathyroid adenomas tends to correlate with the severity of hypercalcemia. These adenomas are hypercellular and usually devoid of stromal fat (Figure 5–2). A thin compressed rim of normal tissue may be identified. Oncocytic and water clear cells may also be present. Parenchymal cells are arranged in solid sheets, cords, tubular structures, or microcytic formations, and the admixture of stromal and adipose elements varies with age and function. The parenchyma-to-stroma ratio is used as an indicator for a normocellular or hypercellular gland. The median ratio is about 50%. In abnormal glands, stromal fat is scant. Molecular studies have established that parathyroid adenomas are clonal proliferations. The cells are larger than normal, and the nuclei show hyperchromasia and atypia and have an increased deoxyribonucleic acid (DNA) content.[8]

Primary parathyroid hyperplasia results from an increase in chief cells, oncocytic cells, transitional oncocytic cell mixtures, and stromal elements in the absence of a known stimulus. Grossly and microscopically, parathyroid hyperplasia does not differ from adenomatous disease, although adenomas are more likely to have a compressed rim of normal parathyroid tissue. The surgeon can usually determine whether a parathyroid gland is normal or hyperplastic because hyperplastic or adenomatous glands are darker, firmer, and larger.

PHPT can be caused by three different pathologic lesions: adenoma, hyperplasia, or carcinoma. An adenoma is a benign neoplasm composed of chief cells, transitional oncocytic cells, or a mixture of these cell types. Adenomas, macroscopically enlarged glands, are responsible for approximately 80% of cases of PHPT and usually affect a single gland (Figure 5–3). By definition, the other glands are normal or atrophic. PHPT is associated with the dominantly inherited MEN types I and II.

For distinction between parathyroid hyperplasia and a parathyroid adenoma, the gross appearance

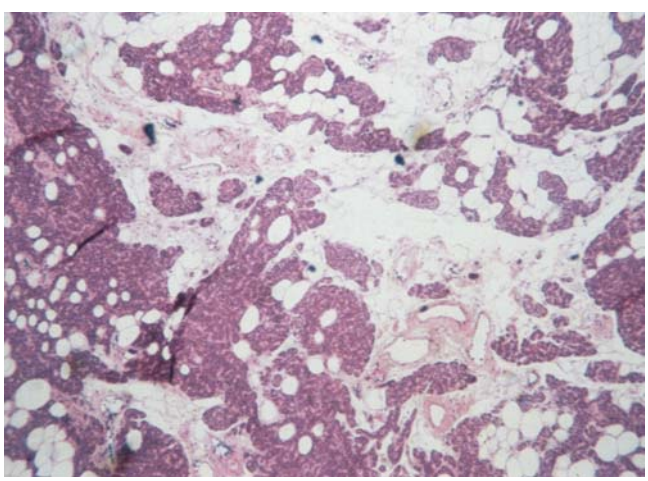


Figure 5–1. Normal parathyroid parenchyma is half stroma and half chief cells (hematoxylin and eosin; ×25 original magnification).

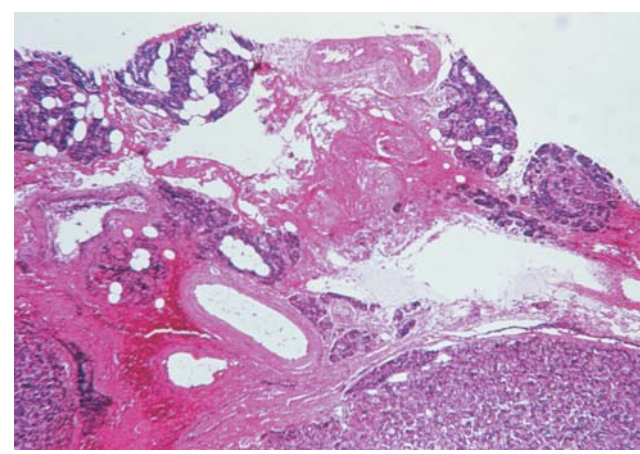


Figure 5–2. Parathyroid adenoma is usually devoid of stromal fat. A rim of compressed normal tissue can be identified (hematoxylin and eosin; ×25 original magnification).

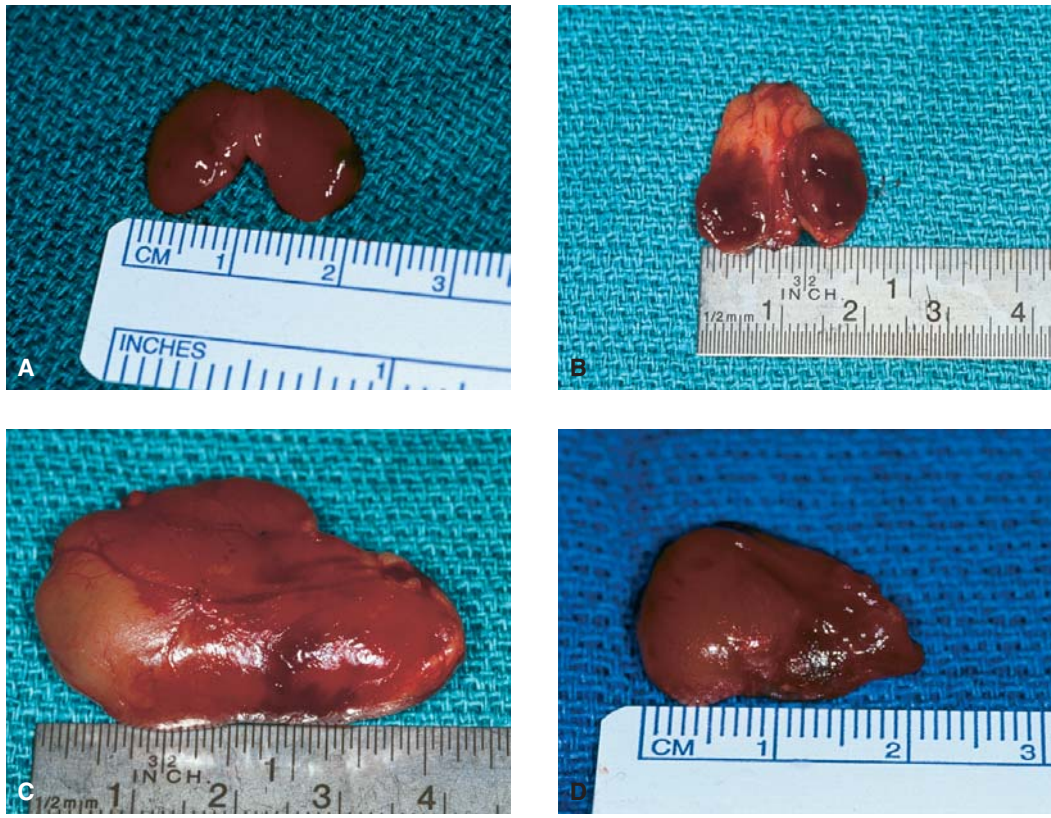


Figure 5–3. Classic variations in the shape of parathyroid adenomas.

of the glands at the time of surgery is of utmost importance. Hyperplasia, by definition, involves all of the parathyroid glands. Most adenomas involve a single gland, whereas some patients may have enlargement of two or three parathyroid glands with one normal gland (double and triple adenomas). The diagnosis is based on the combination of gross features and histologic parameters but mostly on the finding of one or more normal parathyroid glands. Because it is impossible to distinguish between a hyperplastic or adenomatous gland histologically, some experts use the term multiple abnormal parathyroid glands rather than hyperplasia. The surgeon should know that when there is more than one abnormal parathyroid gland, all glands should be considered abnormal unless proven otherwise.

Parathyroid carcinoma is responsible for 1% of cases of PHPT. It is usually a slow-growing neoplasm of parenchymal cells. It will be discussed in further chapters. Other rare parathyroid tumors include lipoadenomas and carcinosarcomas.

PATHOPHYSIOLOGY

Whole-body calcium homeostasis occurs as a flux of calcium across bone. In healthy subjects, this 300 to 500 mg/day flux is largely balanced, and there is little daily loss of calcium from bone. The kidneys filter up to 10,000 mg of calcium each day, but this load is 98% reabsorbed. The excreted calcium in urine largely reflects the net absorption from the gut.

Parathyroid hormone (PTH) regulates the serum ionized calcium level by controlling the rate of bone resorption and the renal tubular handling of calcium and phosphorus. Calcium sensor receptors are expressed in parathyroid and renal tissue. These sensors allow the parathyroid gland to detect the ionized calcium concentration in the extracellular fluid. This ionized calcium accounts for 50% of the circulating calcium and is mostly bound to albumin. Normal function of the calcium sensor is critical to calcium conservation by the kidney and is also influenced by vitamin D and phosphorus levels. Vitamin D is primarily responsible for calcium absorption from the

gastrointestinal tract. Inactivation of the calcium sensor leads to failure of PTH to be suppressed as it normally is in response to elevated serum calcium. This leads to an inappropriate conservation of calcium by the kidney in the face of hypercalcemia.

SYMPTOMS

The symptoms and physical findings consistent with hyperparathyroidism are illustrated in Figure 5–4. The physical examination is aimed at determining the etiology of hypercalcemia once the diagnosis is confirmed by the laboratory. In chronic, slowly progressive hypercalcemia, serious symptoms are usually absent or mild until the calcium level is very high (> 13.0 mg/dL).[9] Symptoms and clinical manifestations in patients with PHPT do not correlate with blood calcium results, except in patients with profound hypercalcemia in which nausea, vomiting, pancreatitis, and coma are very common.

MAKING THE DIAGNOSIS

The development of first carboxyl and midterminal PTH assays and, subsequently, intact or two-site PTH assays has made it considerably easier to diagnose patients with PHPT (Figure 5–5).[10] PHPT is the most common cause of hypercalcemia in outpatients, whereas malignancy is the most common cause of hypercalcemia in hospitalized patients. These two conditions account for more than 90% of all patients with hypercalcemia. The differential diagnosis of hypercalcemia includes granulomatous diseases, most commonly sarcoidosis; increased consumption of calcium, vitamin D, vitamin A, and alkali; and other endocrinopathies such as hyperthyroidism, hypothyroidism, vasoactive intestinal peptide-secreting tumor (VIPoma), Addison's disease, and pheochromocytoma (Table 5–2). Other causes are immobilization in patients with high turnover bone disease such as Paget's disease and BFHH. Very rarely, a nonparathyroid malignant tumor secretes pure PTH.[11,12]

Patients with documented hypercalcemia for more than 6 months do not have malignancy-associated hypercalcemia because patients with malignancy, unfortunately, do not live this long. Patients with hypercalcemia, hypercalciuria, and an elevated or inappropriately high PTH virtually all have PHPT. It is, therefore, no longer necessary to do excessive testing to rule out other causes of hypercalcemia to

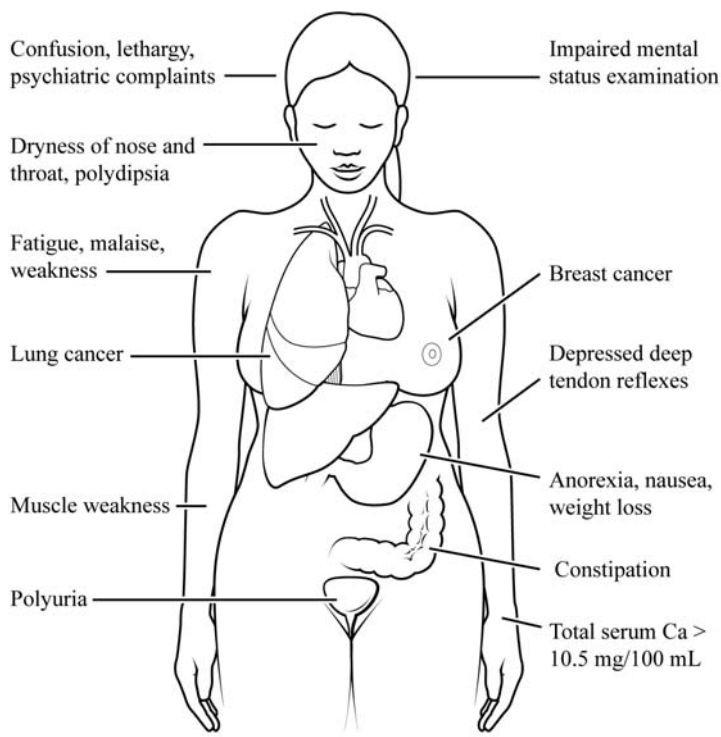


Figure 5–4. Symptoms and physical findings of hyperparathyroidism.

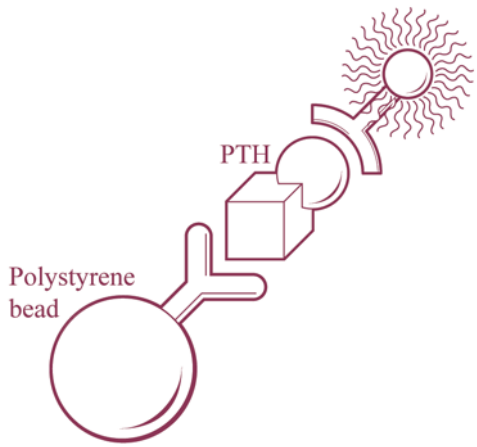


Figure 5–5. Two-site antibody assay targeting the parathyroid hormone (PTH). An anti-PTH antibody is tagged to an acridium ester. Then an antibody-coated bead is added to the sample, creating a sandwich and activating the ester, which emits chemiluminescence and can be measured.

make an accurate diagnosis in hypercalcemic patients. Assessment of renal function, serum phosphorus and chloride, alkaline phosphatase, and uric acid levels, however, is helpful and can document mild renal tubular acidosis, renal dysfunction, high turnover bone disease with possible osteitis fibrosa cystica (Figure 5–6), and a predisposition to gout (Table 5–3). An elevated bone alkaline phosphatase will predict the need for calcium replacement owing to "bone hunger" in the postoperative period. Industrial-grade hand films can clarify the diagnosis in patients with an elevated alkaline phosphatase and often expedite therapy in patients with hypercalcemic crisis. Evidence of subperiosteal resorption in a hypercalcemic patient is diagnostic of hyperparathyroidism so that one does not have to wait until the PTH level is available.

Table 5–2. DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA

Cancer (especially breast), squamous cell lung, and multiple myeloma and lymphoma
Endocrinopathies
Hyperparathyroidism
Hyperthyroidism
Hypothyroidism
VIPoma
Addison's disease
Pheochromocytoma
Granulomatous disease (especially sarcoidosis)
Increased consumption of calcium, vitamin D, vitamin A, alkali, and thiazides
Immobilization
High turnover bone disease (Paget's)
Acute renal failure
Benign familial hypocalciuric hypercalcemia

VIPoma = vasoactive intestinal peptide-secreting tumor.

INDICATIONS FOR SURGERY

Because of better diagnostic tests and routine blood calcium determination, PHPT is diagnosed sooner and few patients have severe symptoms or dramatic associated metabolic problems. This, however, does not alter the need for treatment to prevent metabolic complications such as decreased bone density with osteopenia and osteoporosis, decreased creatinine clearance, and hypercalciuria. One reason why fewer patients present with severe metabolic problems is that most patients are easily treated.[13] Currently, parathyroidectomy is the only definitive treatment for patients with PHPT. (The National Institutes of Health [NIH] consensus meeting in 2002 recommended parathyroidectomy for patients with evidence of the symptoms seen in Table 5–4. At previous consensus conferences, the need for a prospective randomized trial to define the disease's multisystem effects and to assess the long-term incidence and progression of complications in asymptomatic PHPT patients over 50 years was recognized.[14])

An NIH-sponsored consensus conference was held in April 2002 to re-evaluate these guidelines, and a new consensus statement is forthcoming at the time of this publication. Many surgeons feel that the original guidelines need to be broadened to include nonspecific manifestations of the disease,

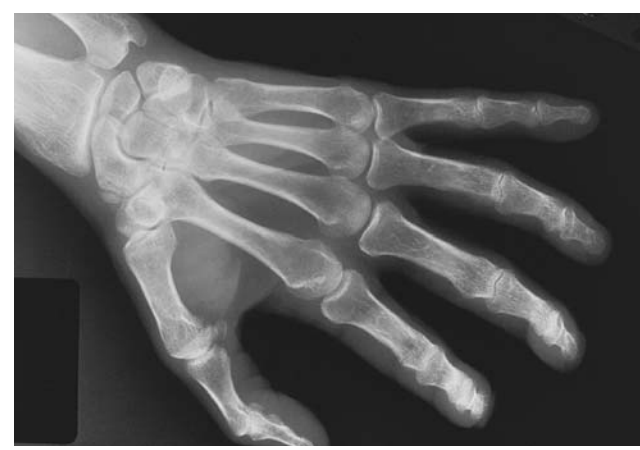


Figure 5–6. Subperiosteal resorption in a patient with hyperparathyroidism.

Table 5–3. BIOCHEMICAL TESTING IN PRIMARY HYPERPARATHYROIDISM

↓ Phosphorus level (50% of patients)
Chloride-to-phosphorus level ≥ 33 (99%)
↑ Uric acid levels (25%)
↑ Alkaline phosphatase owing to increased bone turnover (25%)
↑ Alkaline phosphatase and subperiosteal resorption (75% of patients presenting with "hypercalcemic crisis")
Renal dysfunction and anemia (rare)

given that parathyroidectomy in primary hyperparathyroidism significantly improves vague, nonspecific symptoms. Since the 1990 consensus conference, it has been demonstrated that PHPT is associated with increased mortality and, if untreated, may reduce a patient's survival by approximately 10%. The new guidelines for asymptomatic PHPT management should bring new insight into our current treatment strategies.[15]

Although many patients with PHPT have mild clinical manifestations and a few are completely asymptomatic, both asymptomatic and symptomatic patients appear to benefit from parathyroidectomy symptomatically,[16–18] metabolically,[19–21] and with improved survival.[22–25] In a classic study at the Mayo Clinic of 147 patients with mild hyperparathyroidism (serum calcium < 11.0 mg/dL) followed nonoperatively for 10 years, 1 patient developed hypercalcemic crisis and 38 patients (26%) required parathyroidectomy. By the end of 10 years, half of the patients who were available to be followed up developed some symptoms or complications that warranted parathyroidectomy. Thirty-five of the patients died.[26,27]

Table 5–4. ASYMPTOMATIC HYPERPARATHYROIDISM CRITERIA FOR PARATHYROIDECTOMY; NIH CONSENSUS 1990

Virtually all patients < 50 yr of age
Symptomatic patients*
Serum calcium level ≥ 11.5 mg/dL
Significant symptoms of metabolic complications
Renal insufficiency (↓ CrCl by more than 30% for age in absence of another cause)
Hypercalcemic crisis
Urinary calcium ≥ 400 mg/24 h
↓ Bone density > 2 SD compared with controls

CrCl = creatinine clearance.
*Fatigue, lethargy, musculoskeletal aches and pains, polydipsia, polyuria, nocturia, dyspepsia, and constipation not included.

Parathyroidectomy appears to decrease the risk of subsequent complications such as osteoporosis, renal dysfunction, nephrolithiasis and, perhaps, hypertension. Although some metabolic problems can be partially reversed after successful parathyroidectomy (osteoporosis, renal impairment, nephrolithiasis, and gout), others, such as hypertension, usually do not improve. Asymptomatic patients also appear to receive the same metabolic benefits on bone, renal dysfunction, and other systems as symptomatic patients.[27–31] They also return more quickly to a normal life expectancy after successful parathyroidectomy.[22–24] Parathyroidectomy prevents the subsequent development of hypercalcemic crises, eliminating the need to manage hypercalcemia when patients are hospitalized for other serious, unrelated medical problems.

PREOPERATIVE LOCALIZATION STUDIES

Preoperative localization studies are not considered by many to be cost effective prior to initial bilateral, standard parathyroid operations.[32] In these cases, the experienced surgeon can identify all glands and remove those that are abnormal. Preoperative imaging, including sestamibi scanning or ultrasonography, is indicated in patients with PHPT if a unilateral or a limited, minimally invasive procedure is planned (Figures 5–7 and 5–8).[33,34] Noninvasive localization studies are about 85% accurate in patients with solitary parathyroid adenomas but are only about 33% accurate in patients with multiple abnormal parathyroid glands or parathyroid hyperplasia.[35] These studies are particularly useful given

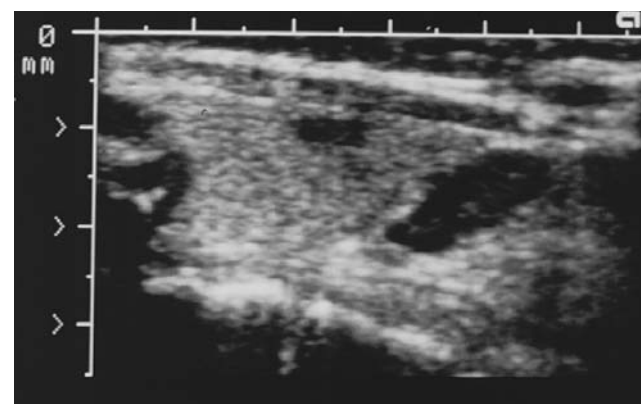


Figure 5–7. Preoperative sonogram suggestive of a right-sided parathyroid adenoma.

the limited predictive value of PTH for estimating the size of parathyroid adenomas.[36]

The results of both of these imaging studies are highly dependent on the expertise of the technician. The limitations of sestamibi are false-positive results from increased uptake of thyroid nodules, failure to accurately identify multiple abnormal glands, and poor visualization of hyperplastic glands.[37] The limitations of ultrasonography include the inability to detect adenomas at ectopic sites, including mediastinal tumors and often those situated deep in the neck or the paraesophageal or retroesophageal area.[38] It is highly operator dependent and has a successful identification rate of nearly 75%.[37] If used, both of these studies should be accompanied by intraoperative PTH monitoring to allow a limited exploration with an excellent outcome.[38–40] The Mayo Clinic was one of the first institutions to develop the intraoperative PTH (IOPTH) assay.[41] Magnetic resonance imaging and computed tomography are helpful prior to reexplorations but are not cost effective in patients prior to initial parathyroid explorations.[37] Highly selective venous catheterization for PTH assay is useful in patients with recurrent or persistent hyperparathyroidism when noninvasive studies are negative or equivocal or suggest different sites for elusive parathyroid tumors.

Perrier and colleagues compared the accuracy of preoperative sestamibi scans, intraoperative gamma probe examinations, and IOPTH monitoring in a prospective cohort study.[42] Adenoma localization by sestamibi scanning was correct in 95% of solitary adenomas but in only 25% of multiple adenomas. It was incorrect in 64% of cases of secondary and tertiary disease. The gamma probe was not useful in locating other glands after single gland removal. It failed to identify remaining abnormal tissue in all cases of non-

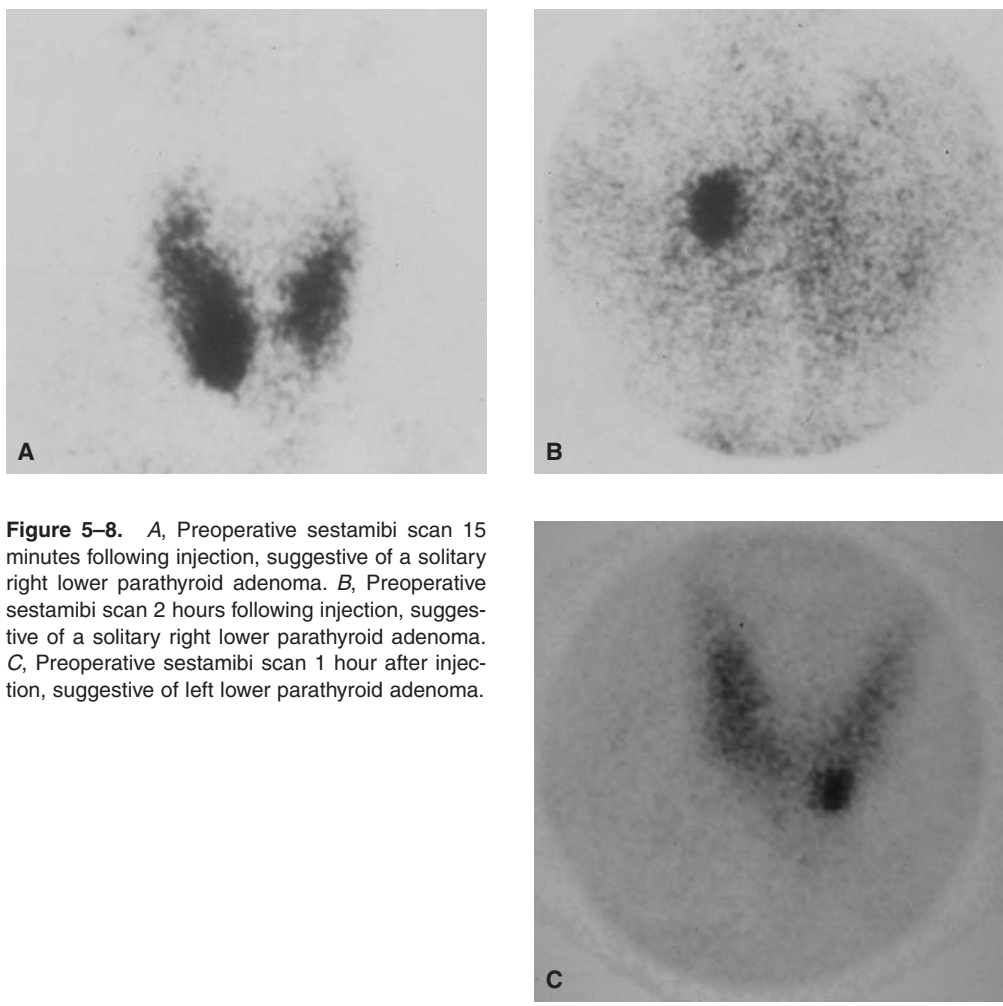


Figure 5–8. *A*, Preoperative sestamibi scan 15 minutes following injection, suggestive of a solitary right lower parathyroid adenoma. *B*, Preoperative sestamibi scan 2 hours following injection, suggestive of a solitary right lower parathyroid adenoma. *C*, Preoperative sestamibi scan 1 hour after injection, suggestive of left lower parathyroid adenoma.

primary disease. IOPTH was accurate in 78% of cases of primary disease and in only 45% of cases of secondary disease. For this reason, only patients with a positive single hot area on sestamibi scan should be considered candidates for a minimal approach.

Use of radioguidance via the gamma probe makes use of the fact that cells in a parathyroid adenoma contain a proportionately higher number of mitochondria compared with those in normal parathyroids and surrounding tissues. Thus, these mitochondria take up and retain Tc 99m sestamibi to a greater degree, and the increased radioactivity can be assessed with a gamma probe.[43] Proponents of this technique feel that it minimizes incision length, permits local anesthesia, and directs the dissection. The use of the gamma probe for intraoperative radioguidance was recently evaluated.[44] Prior to surgery, a sestamibi scan was used to visualize the solitary adenoma and a gamma probe was used to guide surgical dissection. In 48% of cases, the gamma probe provided confusing or inaccurate information and only detected increased radioactivity when placed directly over the exposed adenoma, and there was significant equipment failure and logistical problems with radioisotope administration. Another study found false-positive results owing to sestamibi retention from thyroid nodules. The gamma probe failed to locate a second adenoma in 75% of cases.[45] It appears to add little benefit, especially with experienced endocrine surgeons. This seems especially true given the well-established efficacy of parathyroidectomy without radioguidance. It nearly tripled operating time in one study,[46] and there was a 2-hour delay after intravenous injection until the probe could be used.[42] It is certainly no substitute for sound surgical technique. Another study found that preoperative Tc 99m sestamibi imaging is far more accurate than intraoperative gamma probe detection in localizing abnormal parathyroids.[47] The sensitivity of sestamibi was 100% for hyperplasia and 81% for adenoma compared with 0% and 50% for the gamma probe, respectively.

SURGICAL TREATMENT

The success of experienced surgeons in patients with PHPT using a bilateral approach is better than 95%, and complications such as hypoparathyroidism or injury to the RLNs occur in less than 1% of patients.[16,28] It is the only curative therapy.[9] When parathyroid operations are done by less experienced surgeons, defined as fewer than 10 parathyroid operations per year, the success rate is only about 70%, and hypoparathyroidism is more common.[48] We have never had a patient with postoperative hypoparathyroidism in over 1,500 patients having had initial operations for PHPT.

The standard approach to patients with sporadic disease is bilateral exploration with identification of four parathyroid glands and removal of the adenoma, with or without biopsy of one normal parathyroid gland. Normal parathyroid glands should definitely not be removed. The newer, minimally invasive approach is now occasionally recommended in a select group of patients. The results of limited explorations are improved with intraoperative parathyroid hormone monitoring and when nuclear medicine physicians perform preoperative localization tests. The former is used to recognize patients with double adenomas or asymmetric hyperplasia. In these cases, patient selection is of utmost importance. Potential patients are those with preoperative studies that are highly suggestive of a solitary adenoma (see Figure 5–8). Limited procedures are not recommended in patients who have a high likelihood of multiple abnormal parathyroid glands, such as patients with secondary, tertiary, or familial hyperparathyroidism. In these patients, localization studies are only about 35% accurate and could lead to an appreciable failure rate.[35]

Patients with suspected sporadic, nonfamilial hyperparathyroidism should undergo a preoperative localization study when a focal approach is considered. Sestamibi scanning is currently the most accurate and cost effective. If a solitary hot spot is identified, a 2 cm incision can be made over the corresponding portion of the neck. Use of a gamma probe has been suggested for guiding this approach,[39] but we and others have not found it to be more helpful than the preoperative sestamibi scan in localizing the suspected parathyroid tumor. The gland is approached lateral to the strap muscles and medial to the sternocleidomastoid muscle. Once the parathyroid adenoma is identified, it is removed (Figures 5–9 and 5–10). Pre-excision and 10-minute

postexcision blood samples are obtained from the ipsilateral internal jugular vein or arm vein and are analyzed for PTH levels. During this time, the neck tissue and other presumably normal parathyroid glands should not be manipulated. The results are available within 15 minutes. When the postoperative PTH level falls by 50% or more, the operation is concluded (Figure 5–11). If the percent decrease is less than 50%, a repeat PTH sample should be obtained or a standard bilateral exploration should be performed.

In patients with sporadic hyperplasia, biopsy or subtotal resection of the most normal-appearing hyperplastic glands is recommended first. The parathyroid tissue remnant should be the size of a normal parathyroid gland, approximately 60 mg. Histology or chemiluminescence is used to confirm that the tissue is of parathyroid origin via PTH-level analysis of tumor aspirate. Subsequently, the other abnormal parathyroid glands and upper thymus are removed. Parathyroid tissue should be cryopreserved as insurance against possible hypoparathyroidism in all patients having parathyroid reoperations and in all patients having subtotal parathyroidectomy or total parathyroidectomy with parathyroid autotransplantation as insurance against permanent postoperative hypoparathyroidism.

Patients with familial hyperparathyroidism present a more difficult surgical problem. In contrast to patients with sporadic disease, in whom solitary adenomas occur in about 80% of cases, more than 80% of patients with familial disease have multiple abnormal parathyroid glands. Supernumerary glands (more than four parathyroid glands) are also more common.[49–51]

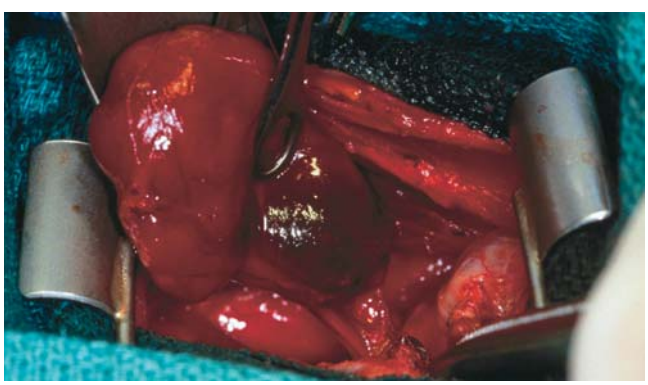


Figure 5–9. Parathyroid adenoma excised through a 2 cm lateral incision.

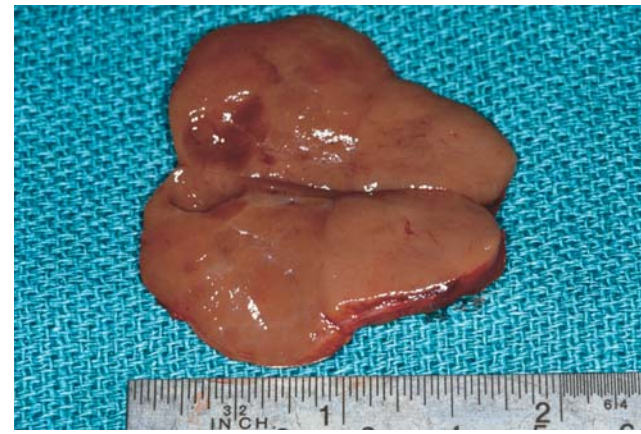


Figure 5–10. Bisected ex vivo parathyroid adenoma.

Parathyroid carcinoma and parathyroidosis are also more frequent in patients with familial PHPT with and without other endocrinopathies.[52] The approach to patients with familial PHPT differs from that in patients with sporadic disease because the former are more likely to have inadequate removal of hyperfunctioning tissue (persistent disease) or redevelopment of hyperfunctioning tissue after 6 months (recurrent disease).[49–51] When a solitary parathyroid tumor is found, occurring in only 20% of cases, the normal-appearing parathyroid glands ipsilateral to the tumor are also removed, and any remaining normal-appearing parathyroid glands are biopsied and marked with a stitch or a clip. This is recommended in case the patient develops recurrent hyperparathyroidism as only one side of the neck would usually require reexploration. The thymus should be removed bilaterally as it is a common location for ectopic parathyroid glands; in patients with MEN type I disease, it can be the site of malignant carcinoid tumors.[53,54]

Some surgeons recommend total parathyroidectomy with immediate autotransplantation in patients with familial hyperparathyroidism as disease in patients with MEN type I and familial PHT without other endocrinopathies is highly likely to recur. Cryopreservation should be performed in these situations for insurance against possible permanent hypoparathyroidism. Unfortunately, cryopreservation is effective only in approximately 60% of patients.[55] Immediately autotransplanted parathyroid tissue appears to function in about 95% of patients. If a total parathyroidectomy is performed, the surgeon should look out for early and late hypoparathyroidism, which

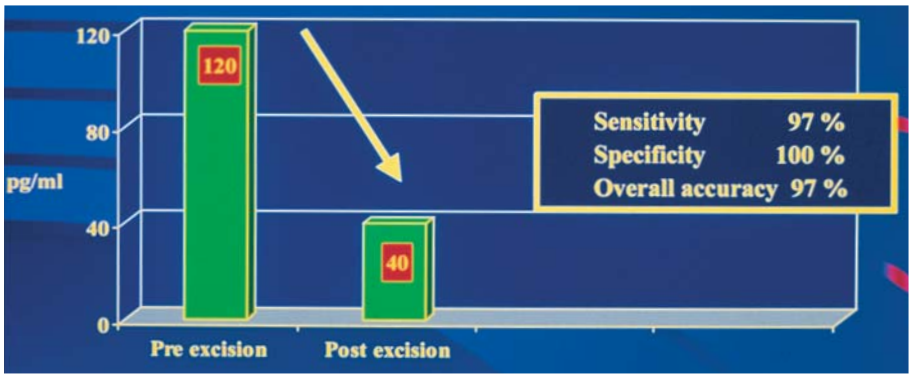


Figure 5–11. Example of intraoperative parathyroid assay measurements (pg/mL) obtained pre- and postexcision of adenoma. A 50% decline in the absolute values suggests cure. Reproduced with permission from Boggs JE et al.[38]

has been reported after parathyroid autotransplantation.[56] Autotransplantation is performed by mincing parathyroid tissue into 1 mm slices (Figure 5–12) and reimplanting into 15 to 20 individual pockets of the forearm via one skin incision. The forearm is used as it is easier to document whether the transplant is functional by documenting a twofold increase in the basilic vein PTH level compared with the contralateral side.

Patients with persistent or recurrent disease despite subtotal parathyroidectomy should usually undergo either subtotal resection of the remaining abnormal parathyroid gland or it should be removed, autotransplanted, and cryopreserved. If there is any question about the viability of the parathyroid remnant that is to remain, it should be removed and autotransplanted or another hyperplastic gland, when present, should be biopsied and marked before removing the other hyperplastic glands. Again, tissue should be cryopreserved.

Patients with MEN type IIA should be selectively managed as they require total thyroidectomy with removal of central neck lymph nodes. This makes them more prone to hypoparathyroidism. These patients should have only the abnormal parathyroid glands removed to avoid this risk, although some surgeons recommend total parathyroid autotransplantation. This is also discussed further in other chapters.

Ethanol ablation is a new procedure under development at the Mayo Clinic. Candidates are patients who have undergone a subtotal parathyroidectomy for multigland disease with subsequent recurrence owing to the remnant. Hypoparathyroidism and RLN damage are rarely seen with this procedure. However, cure rates are much lower than with surgery, and alcohol injection can complicate future surgical attempts. Thus, using this modality should be a joint decision between the endocrine surgeon, endocrinologist, and radiologist.[9]

Because the majority of cases of PHPT are caused by a single parathyroid adenoma, there is much evolving interest and excitement about using minimally invasive parathyroidectomy (MIP), which is depicted in Figure 5–13. Minimally invasive approaches include (1) unilateral open approaches, (2) the open minimally invasive procedure, and (3) endoscopic parathyroidectomy. The first method uses the conventional Kocher cervical incision followed by unilateral neck exploration (UNE). The second involves small, selective incisions under local or regional anesthesia.[37] This procedure is not performed with MEN, isolated familial HPT, or secondary HPT as bilateral exploration is necessary, as discussed in Chapter 6. It involves the use of sestamibi scans for preoperative localization, surgeon-administered cervical block anesthesia, directed exploration, and rapid IOPTH assay.

Limited parathyroid surgery is safe, cost effective, and efficacious in the management of PHPT.

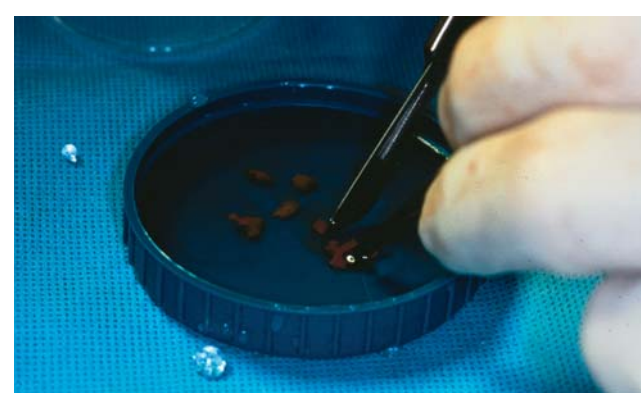


Figure 5–12. Mincing of parathyroid tissue to be autotransplanted.

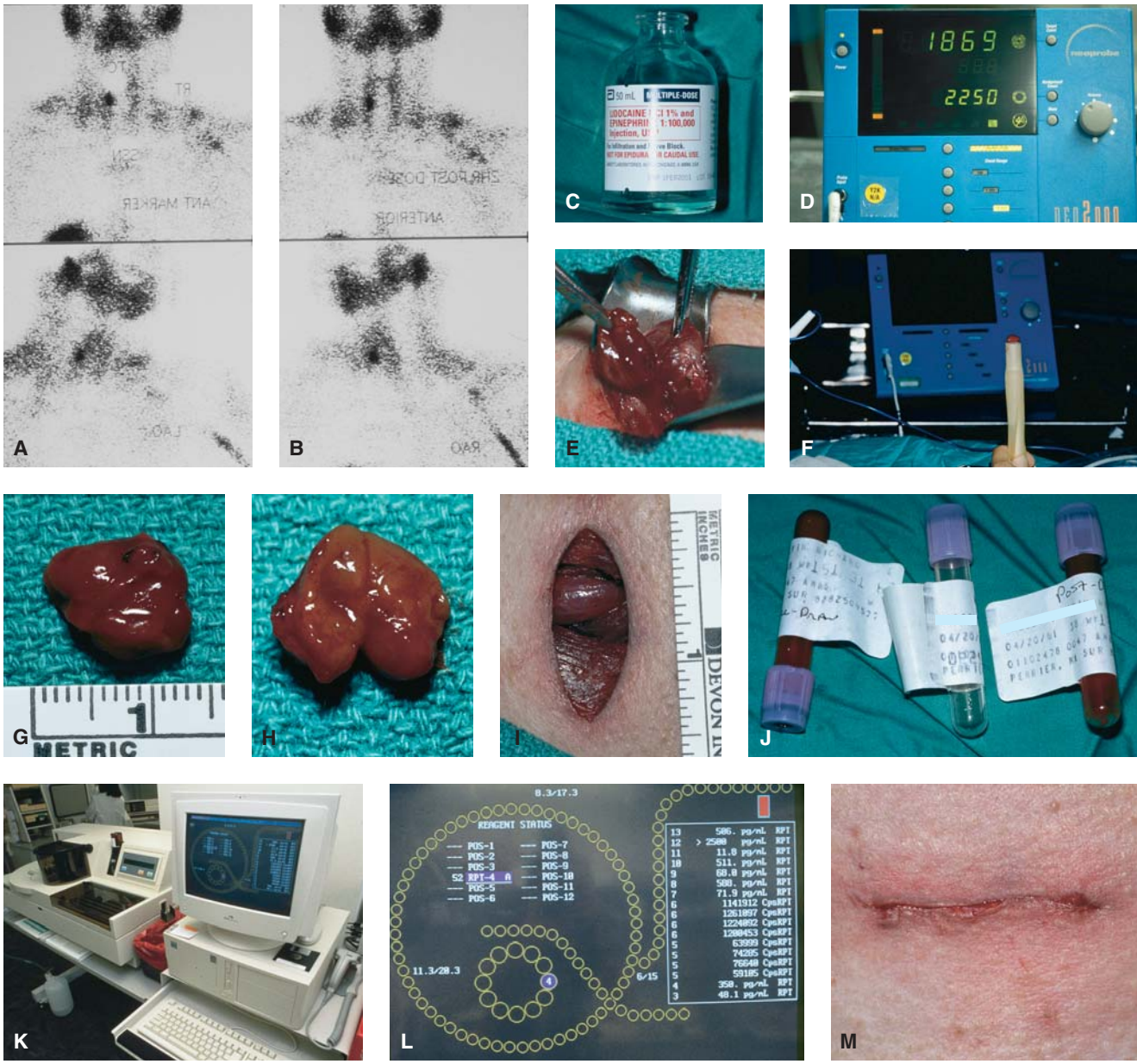


Figure 5–13. Scenario of minimally invasive parathyroidectomy. *A*, This is a preoperative sestamibi scan with increased uptake in the left neck on posterior orientation, suggesting a left upper gland. *B*, An oblique view of a sestamibi scan at 20 minutes. Close scrutiny suggests increased uptake near the left lower lobe of the thyroid. *C*, Lidocaine is used as a local anesthetic for skin incisions in addition to intravenous sedation. *D*, A Geiger counter gamma probe machine. Auditory counts are used to localize adenoma as a "hot spot." *E*, Parathyroid adenoma being removed through a small incision. The thyroid lobe is being retracted medially. *F*, The gland is excised and probed. Ex vivo counts are measured. *G*, A 1.3 cm parathyroid adenoma is measured ex vivo. *H*, Parathyroid adenoma is bivalved. The parenchyma has a classic brownish-yellow appearance. *I*, After excision, the 3 cm incision is noted. An interrupted absorbable suture is used to reapproximate the anterior fascia. *J*, Three tubes are immediately sent to the chemistry laboratory. The tube on the left has 3 mL of blood drawn before adenoma excision and is labeled "pre." The tube in the middle has 3 mL of normal saline and aspirated cells from the adenoma. The tube on the right has 3 mL of blood drawn 10 minutes after parathyroid tumor excision and is labeled "post." *K*, The automated machine is in the chemistry laboratory. The three samples are processed and the results are available in 10 minutes. *L*, The screen of the automated machine shows the parathyroid hormone levels from each sample after each has been spun and processed. The pre-excision value of 511 pg/mL and postexcision value of 11.0 pg/mL are observed. The aspiration confirms parathyroid tissue as the values > 2,500 pg/mL. *M*, The patient's small incision is closed in the operating room while the blood samples are being processed. When a 50% drop is noted, the patient is taken to the recovery room.

Compared with BNE, UNE leads to reduced cost from lower operating room charges, less general anesthesia, and earlier discharge (23- to 24-hour inpatient observation versus discharge 2 to 3 hours after surgery, respectively). There is a higher risk of permanent RLN injury with BNE versus UNE.

MIP produces favorable cosmetic results for the patient and allows more favorable technical conditions should reoperation be necessary. Udelsman compared the outcomes of conventional versus MIP performed by a single surgeon on 656 patients.[57] Sixty-one percent of procedures were performed using the standard technique of bilateral cervical exploration under general anesthesia and 39% underwent MIP. The success rate for all procedures combined was 98% without significant difference between the two techniques. The complication rates for standard surgery versus MIP were 3.0% and 1.2%, respectively. MIP was associated with nearly a 50% reduction in operating time, a sevenfold reduction in length of hospital stay, and nearly a 50% reduction in total hospital charges.

POSTOPERATIVE MANAGEMENT

A successful parathyroidectomy results in normalization of the calcium level. This level usually reaches its nadir 36 to 48 hours after the operation. Postoperative hypocalcemia is common in patients with severe skeletal calcium depletion, commonly referred to as "bone hunger." This can be predicted preoperatively as such patients have an elevated preoperative alkaline phosphatase level with otherwise normal liver function tests. Clinical manifestations of hypercalcemia are perioral numbness, tingling of the fingers, muscle cramps, anxiety, trembling of the masseter muscle, contraction with facial nerve stimulation anterior to the ear (Chvostek's sign), carpopedal spasm (Trousseau's sign), convulsions, and opisthotonus. If mild symptoms appear, calcium supplementation should be given orally with calcium carbonate (500 to 1,000 mg three times daily). If symptoms are moderate, the calcium dose can be increased, and calcitriol (0.25 to 1.0 mg orally twice daily 1,25-dihydroxyvitamin D [Rocaltrol]) is additionally provided. The vitamin D facilitates gastrointestinal calcium absorption and calcium mobilization from the skeleton.

If symptoms are severe, one ampule of 10% calcium gluconate (90 mg elemental calcium) dissolved in 100 cc of normal saline should be administered intravenously over 15 minutes, followed by a constant infusion of calcium (10 ampules in 10% calcium gluconate in 1,000 cc of normal saline) at 20 to 100 cc/hour, if needed. It is essential to avoid extravasation of intravenous calcium because skin necrosis may result. Hyperventilation and vomiting should be addressed because alkalosis aggravates symptoms. Serum calcium and magnesium levels should be checked if symptoms occur. Hypomagnesemia can cause symptoms similar to hypocalcemia. Patients should be educated about the warning signs and instructions given for appropriate action, if necessary. For limited, focused, unilateral operations, same-day discharge has been recommended, whereas 23- or 24-hour observation remains the standard for bilateral explorations. The latter is mainly recommended because, rarely, a bleeding complication may result in respiratory distress, warranting immediate evacuation.

COMPLICATIONS

Prolonged symptomatic hypocalcemia (hypoparathyroidism), hematoma formation, RLN injury, and keloid formation are uncommon but possible complications. Other problems include nausea, vomiting, and urinary retention. Treatment is outlined in Table 5–5. Persistently elevated serum PTH levels after parathyroidectomy appear to be associated with development of cardiovascular disease,[58] with a significantly higher frequency of ischemic heart disease and hypertension. After successful operation, left ventricular hypertrophy from elevated PTH is reversible. However, it does not appear reversible in the setting of persistently high PTH with normocalcemia. Lundgren and colleagues found a 1.72 hazard ratio for hypercalcemia as an independent cause of cardiovascular mortality. Therefore, monitoring and medical intervention, if necessary, are essential.[59]

OUTCOME

Ninety-five percent of hyperparathyroid patients can be cured when treated by an experienced endocrine

Table 5–5. POSSIBLE COMPLICATIONS AND TREATMENTS FOLLOWING PARATHYROID SURGERY

Complication	Circumstances	Treatment
Hypocalcemia	Hungry bone syndrome Aparathyroid Hypoparathyroid	Acute: 1–2 g Ca carbonate q4h PO or 10% Ca gluconate in 100 cc NS IV or Rocaltrol (vitamin D) 0.25–1.0 µg q12h PO Chronic: 1–2 g Ca carbonate PO with meals or aluminum hydroxide to bind phosphorus in the gastrointestinal tract
Hematoma	More frequent when combined with thyroid operations	Emergency airway—open wound at bedside or operating room and evacuate blood
Recurrent laryngeal nerve injury	Unilateral injury Bilateral injury	Weak voice, adequate airway Normal voice but inadequate airway; may require emergent tracheostomy

Ca = calcium; PO = orally; NS = normal saline; IV = intravenous.

surgeon. BNE remains the standard approach because it is safe and avoids missing a second adenoma or other abnormal glands in patients with asymmetric or adenomatous hyperplasia. It also does not require intraoperative PTH assays and gamma probe localization. A unilateral, focused approach is acceptable when the prevalence of double adenoma and hyperplasia is low, a preoperative imaging study strongly suggests a solitary adenoma, thyroid disease warranting removal is absent, and intraoperative PTH assays are available. Most noninvasive studies are about 80% sensitive for single adenomas and less so for double adenomas or hyperplasia. However, the addition of IOPTH can improve the success of surgery to 93%.

The most common causes for persistent hyperparathyroidism are an ectopic parathyroid tumor and multiple abnormal parathyroid glands. Inexperienced surgeons are often unfamiliar with the aberrant location of these glands. The inferior parathyroid glands develop with the thymus from the third brachial pouch and descend to the lower thyroid area (Figure 5–14). The most common position of the inferior glands is anterior-inferior to the junction of the inferior thyroid artery and RLN (Figure 5–15). Ectopic glands are frequently found adjacent to or within the thymus or perithymic fat or in the anterior mediastinum (Figure 5–16).

The superior parathyroid glands develop from the fourth brachial pouch and migrate a short distance, therefore having less variation in position. They are most commonly located superior-posterior to the junction of the inferior thyroid artery and RLN at the level of the cricoid cartilage (see Figure 5–15). Ectopic locations include (1) the tracheoesophageal groove posteriorly, (2) along the esophagus in the posterior mediastinum, (3) intrathyroidal, (4) within the carotid sheath, and (5) other locations.

Use of IOPTH should help in patients with multiple abnormal parathyroid glands because the PTH level should not fall > 50% at 10 minutes when abnormal parathyroid tissue remains (see Figure 5–13). Reasons for persistent or recurrent hyperparathyroidism after a subtotal parathyroidectomy include (1) failure to remove a fifth supernumerary or hyperplastic gland, (2) leaving too large a remnant after subtotal resection, (3) regrowth, (4) spilling tumor (parathyroidosis), and (5) parathyroid cancer. About 15% of patients have more than four parathyroid glands.

Primary hyperparathyroidism causes significant morbidity, including depression, constipation, renal

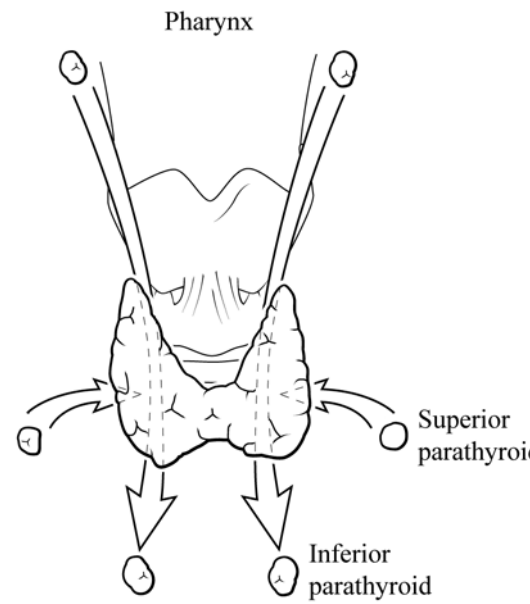


Figure 5–14. Normal embryologic descent of superior and inferior parathyroid glands from the third and fourth pharyngeal pouches.

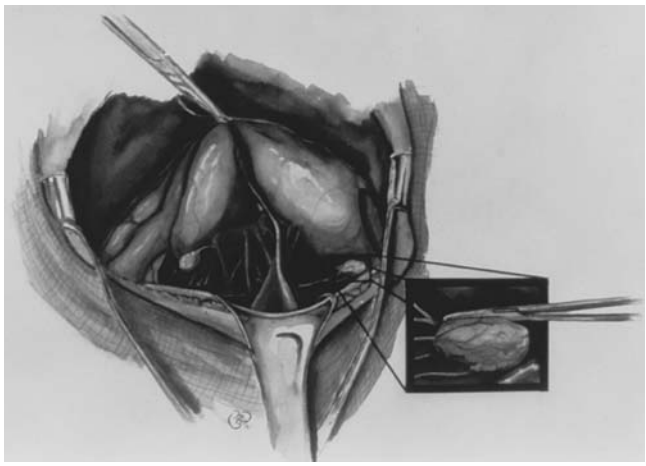


Figure 5–15. Normal location of superior and inferior parathyroid glands.

calculi, weight loss, and joint pain. Patients often seek care from multiple medical providers and acquire extensive treatment regimens. Thus, the cost savings of surgery are significant. Surgery has striking benefits on quality of life in patients with primary hyperparathyroidism, even with mild disease. A survey with the 28-item version of the General Health Organization revealed a clinically and statistically significant reduction in psychological distress at 3 months after surgery.[60]

The NIH 1990 consensus statement recognized the need for a randomized clinical trial to address the role of surgery in asymptomatic patients with PHPT with minimal hypercalcemia.[14] In one trial, 53 patients with asymptomatic hyperparathyroidism underwent parathyroidectomy or observation, completing the Short-Form SF-36 Health Survey to assess wellness every 6 months for 2 years.[61]

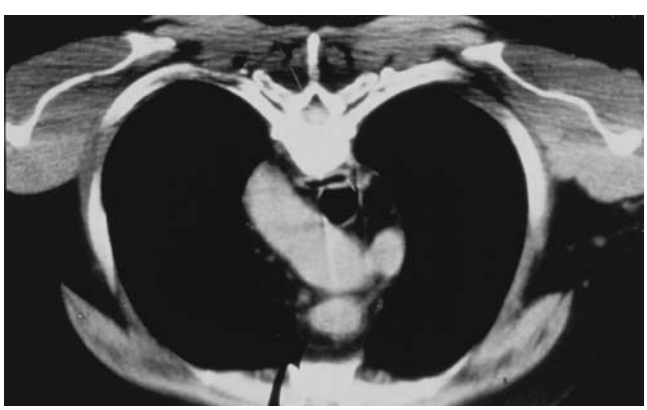


Figure 5–16. Computed tomographic scan of a parathyroid adenoma in the anterior mediastinum.

The scores on two of nine domains, social functioning and emotional role functioning, were significantly different, favoring the intervention group. This trial supports intervention by an experienced endocrine surgeon for mild PHPT at the time of diagnosis as many patients have reversible nonclassic symptoms of disease. The best outcomes are achieved by initially referring patients to an experienced endocrine surgeon because repeated surgery, even by experienced surgeons, may result in compromised outcome.[9]

SUMMARY

Patients with primary hypoparathyroidism can be accurately diagnosed. Clinical manifestations, including symptoms and metabolic conditions, improve in most patients (75%) after successful surgery. Preoperative localization testing is helpful but not essential when a bilateral approach is performed but is essential if a unilateral or focal operation is performed. Approximately 65% of patients would qualify for a focal approach (positive localized test, sporadic disease, and no significant thyroid nodules). An approximate 95% success rate of parathyroidectomy is expected when an experienced surgeon performs the operation. Patients with familial primary hyperparathyroidism need to be treated more aggressively than patients with sporadic disease because they are more prone to both persistent and/or recurrent disease. Most current literature suggests that patients with PHPT benefit symptomatically, metabolically, and in longevity after a successful parathyroidectomy.

ACKNOWLEDGMENT

We owe many thanks to the following individuals, without whom preparation of this chapter would not have been possible: Orlo H. Clark, MD, Professor of Surgery and Vice-Chair, Department of Surgery, UCSF, San Francisco, California, for generously providing prize photographs, pathology images, and radiographs of the manifestations of primary hyperparathyroidism; and Phyllis Easter, Secretarial Assistant, Department of Surgery, Wake Forest University School of Medicine, for her endless devotion in assisting the preparation of this chapter.

REFERENCES

1. Consensus development conference statement. J Bone Miner Res 1991;6 Suppl 2:S9–13.
2. Akerstrom G, Ljunhall S, Lundgren E. Natural history of untreated primary hyperparathyroidism. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1993. p. 303–10.
3. Kraimps JL, Duh QY, Demeure M, et al. Hyperparathyroidism in multiple endocrine neoplasmia syndrome. Surgery 1992;112:1080–6.
4. Mallette LE. Management of hyperparathyroidism in the multiple endocrine neoplasia syndromes and other familial endocrinopathies. Endocrinol Metab Clin North Am 1994;23:19–36.
5. Jackson CE, Norum RA, Boyd SB, et al. Hereditary hyperparathyroidism and multiple ossifying jaw fibromas: a clinically and genetically distinct syndrome. Surgery 1990;108:1006–12.
6. Heath H III. Familial benign hypercalcemia—from clinical descriptions to molecular genetics. West J Med 1994; 160:554–61.
7. Cutler RE, Reiss E, Ackerman LV. Familial hyperparathyroidism: a kindred involving eleven cases with a discussion of primary chief-cell hyperplasia. N Engl J Med 1964;270:859–65.
8. Reisa A, Hecht W, Groger R, et al. Cloning and sequence analysis of the human parathyroid hormone gene region. Hum Genet 1990;84:119–24.
9. Kearns AE, Thompson GB. Medical and surgical management of hyperparathyroidism. Mayo Clin Proc 2002;77:87–91.
10. Nussbaum SR, Zahradnik RJ, Lavigne JR, et al. Highly sensitive two-site immunoradiometric assay of parathyroid hormone and its clinical utility in evaluating patients with hypercalcemia. Clin Chem 1987;33:1364–7.
11. Strewler GJ, Budayr AA, Clark OH, Nissenson RA. Production of parathyroid hormone by a malignant nonparathyroid tumor in a hypercalcemic patient. J Clin Endocrinol Metab 1993;76:1373–5.
12. Yoshimoto K, Yamasaki R, Sakai H, et al. Ectopic production of parathyroid hormone by small cell lung cancer in a patient with hypercalcemia. J Clin Endocrinol Metab 1989;68:976–81.
13. Levin K, Galante M, Clark OH. Parathyroid carcinoma versus parathyroid adenoma in patients with profound hypercalcemia. Surgery 1987;101:649–60.
14. National Institutes of Health Conference. Diagnosis and management of asymptomatic primary hyperparathyroidism. Consensus development conference statement. Ann Intern Med 1991;114:593.
15. McHenry CR. What's new in general surgery: endocrine surgery. J Am Coll Surg 2002;195:364–71.
16. Clark OH. "Asymptomatic" primary hyperparathyroidism: is parathyroidectomy indicated? Surgery 1994;116:947–53.
17. Chan AK, Duh QY, Katz MH, et al. Clinical manipulations of primary hyperparathyroidism before and after parathyroidectomy: a case control study. Ann Surg 1995;222: 402–12.
18. Burney RE, Jones KR, Coon JW, et al. Assessment of patient outcomes after operation for primary hyperparathyroidism. Surgery 1996;120:1013–8.
19. Silverberg SJ, Locker FG, Bilezikian JP. Vertebral osteopenia: a new indication for surgery in primary hyperparathyroidism. J Clin Endocrinol Metab 1996;81:4007–12.
20. Chou FF, Sheen-Chen SM, Leong CP. Neuromuscular recovery after parathyroidectomy in primary hyperparathyroidism. Surgery 1995;117:18–25.
21. Abela C, Neiderle B. Metabolic complications of primary hyperparathyroidism. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 311–20.
22. Palmer M, Adami HO, Bergstrom R, et al. Survival and renal function in untreated hypercalcemia. Population-based cohort study with 14 years follow up. Lancet 1987;i:59–62.
23. Hedback G, Oden A, Tisell LE. The influence of surgery on the risk of death in patients with primary hyperparathyroidism. World J Surg 1991;15:399–403.
24. Hedback G, Tisell LE, Bengtsson BA, et al. Premature death in patients operated on for primary hyperparathyroidism. World J Surg 1990;14:829–35.
25. Tisell LE, Hansson G. Natural history of treated primary hyperparathyroidism. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 321–6.
26. Purnell DC, Smith LH, Scholz DA, et al. Primary hyperparathyroidism: a prospective clinical study. Am J Med 1971;50:670–8.
27. Scholz DA, Purcell DC. Asymptomatic primary hyperparathyroidism. Mayo Clin Proc 1981;56:473–8.
28. Clark OH, Wilkes W, Siperstein AE, et al. Diagnosis and management of asymptomatic hyperparathyroidism. Safety, efficacy, and deficiency in our knowledge. J Bone Miner Res 1991;6 Suppl 2:S135–42.
29. Clark OH. Surgical treatment of primary hyperparathyroidism. Adv Endocrinol Metab 1995;6:1–16.
30. Uden P, Chan A, Duh QY, et al. Primary hyperparathyroidism in younger and older patients: symptoms and outcome of surgery. World J Surg 1992;16:791–7.
31. Kaplan RA, Snyder WH, Steward A. Metabolic effects of parathyroidectomy in asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab 1976;4:415.
32. Doppman JL, Miller DL. Localization of parathyroid tumors in patients with asymptomatic hyperparathyroidism and no previous surgery. J Bone Miner Res 1991;6 Suppl 2: S153–8.
33. Tibblin S, Bizard JP, Bondeson AG, et al. Primary hyperparathyroidism due to solitary adenoma: a comparative multicenter study of early and long-term results of different surgical regimens. Eur J Surg 1991;157:511–5.
34. Duh QY, Uden P, Clark OH. Unilateral neck exploration for primary hyperparathyroidism: analysis of a controversy using a mathematical model. World J Surg 1992;16:654–61.
35. Shen W, Sabanci U, Morita, et al. Sestamibi scanning is inadequate for directing unilateral neck exploration for first-time parathyroidectomy. Arch Surg 1997;132:969–76.
36. Mozes G, Curlee KJ, Rowland CM, et al. The predictive value of laboratory findings in patients with primary hyperparathyroidism. J Am Coll Surg 2002;194:126–30.
37. Roman S, Udelsman R. Minimally invasive parathyroid surgery. Minerva Chir 2002;57:105–10.
38. Boggs JE, Irvin GL, Molinari AS, Deriso GT. Intraoperative parathyroid hormone monitoring as an adjunct to parathy-

roidectomy. Surgery 1996;120:954–8.
39. Norman J, Chheda H. Minimally invasive parathyroidectomy facilitated by intraoperative nuclear mapping. Surgery 1997;122:998–1004.
40. Carty SE, Worsey MJ, Virji MA, et al. Concise parathyroidectomy: the impact of preoperative SPECT 99^{m} Tc sestamibi scanning and intraoperative quick parathormone assay. Surgery 1997;122:1107–16.
41. Kao PC, van Heerden JA, Farley DR, et al. Intraoperative monitoring of parathyroid hormone with a rapid automated assay that is commercially available. Ann Clin Lab Sci 2002;32:244–51.
42. Perrier ND, Ituarte PH, Morita E, et al. Parathyroid surgery: separating promise from reality. J Clin Endocrinol Metab 2002;87:1024–9.
43. Hetrakul N, Civelek AC, Stagg CA, Udelsman R. In vitro accumulation of technetium-99m sestamibi in human parathyroid mitochondria. Surgery 2001;130:1011–8.
44. Inabnet WB, Kim C, Haber R, Lopchinsky R. Radioguidance is not necessary during parathyroidectomy. Arch Surg 2002;137:967–70.
45. Jaskowiak NT, Sugg SL, Helke J, et al. Pitfalls of intraoperative quick parathyroid hormone monitoring and gamma probe localization in surgery for primary hyperparathyroidism. Arch Surg 2002;137:659–69.
46. Inabnet WB, Dakin GF, Haber RS, et al. Targeted parathyroidectomy in the era of intraoperative parathormone monitoring. World J Surg 2002;26:921–5.
47. Saaristo RA, Salmi JJ, Koobi T, et al. Intraoperative localization of parathyroid glands with gamma counter probe in primary hyperparathyroidism: a prospective study. J Am Coll Surg 2002;195:19–22.
48. Malmaeus J, Granberg P, Halvorsen J, et al. Parathyroid surgery in Scandinavia. Acta Chir Scand 1988;154:409–13.
49. Huang GM, Duh QY, Shaver J, et al. Familial hyperparathyroidism without multiple endocrine neoplasia. World J Surg 1997;21:22–9.
50. Barry MK, van Heerden JA, Grant CS, et al. Is familial hyperparathyroidism a unique disease? Surgery 1997; 122:1028–33.
51. Kraimps JL, Barbier J. Familial hyperparathyroidism in multiple endocrine neoplasia syndromes. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1994. p. 381–4.
52. Dinnen JS, Greenwood RH, Jones JH, et al. Parathyroid carcinomas in familial hyperparathyroidism. J Clin Pathol 1977;30:966–75.
53. Duh QY, Hybarger CP, Geist R, et al. Carcinoids associated with multiple endocrine neoplasia syndromes. Am J Surg 1987;154:142–8.
54. Teh BT, McArdle J, Chan SP, et al Clinicopathologic studies of thymic carcincoids in multiple endocrine neoplasia type 1. Medicine 1997;76:21–9.
55. Saxe A, Gibson G. Cryopreservation of parathyroid tissue. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 421–5.
56. Wells SA Jr, Farndon JR, Dale JK, et al. Long term evaluation of patients with primary parathyroid hyperplasia managed by total parathyroidectomy and heterotopic autotransplantation. Ann Surg 1980;192:451–8.
57. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 2002;235: 665–72.
58. Vestergaard H, Kristensen LO. Normocalcemia and persistent elevated serum concentrations of 1-84 parathyroid hormone after operation for sporadic parathyroid adenoma: evidence of increased morbidity from cardiovascular disease. World J Surg 2002;26:657–60.
59. Lundgren E, Lind L, Palmer M, et al. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. Surgery 2001;130:978–85.
60. Okamoto T, Kamo T, Obara T. Outcome study of psychological distress and nonspecific symptoms in patients with mild primary hyperparathyroidism. Arch Surg 2002;137: 779–83.
61. Talpos GB, Bone HG, Kleerekoper M, et al. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. Surgery 2000;128:1013–21.

Benign Secondary Tumors: Secondary Hyperparathyroidism

NANCY D. PERRIER, MD
FATMA TATAR, MD
M. SEAN BOGER, PharmD
ORLO H. CLARK, MD

An association between parathyroid hyperplasia and uremia has been known since the early 1930s.[1] Secondary hyperparathyroidism (HPT) is a common problem of patients receiving chronic dialysis and is the most frequently encountered endocrine abnormality in patients with chronic renal failure.[2] Such patients develop high turnover bone disease, osteitis fibrosa cystica. This disease is associated with excess parathyroid hormone (PTH) secretion and deficiency of 1,25-dihydroxyvitamin D. The pathogenesis of secondary HPT in patients with chronic renal failure is not completely known, but new information about the pathophysiology is becoming available. Today, therapeutic modalities have been developed to correct the abnormal calcium, phosphorus, and vitamin D metabolism. As a consequence, most patients with renal failure will not develop clinically significant secondary HPT and renal osteodystrophy.[3]

PATHOPHYSIOLOGY

Role of Calcium

The major factor involved in the regulation of PTH secretion is the ionized calcium concentration in the extracellular fluid (Table 6–1). Low calcium levels stimulate increased PTH secretion, whereas high levels suppress PTH secretion. Even high blood levels of calcium, however, fail to completely suppress PTH secretion. The blood calcium level appears to have an initial direct effect on parathyroid cell membrane potential. Calcium may also affect PTH secretion by regulating the amount of hormone available for secretion as a result of calcium-dependent regulation of hormone degradation within the parathyroid glands. After a prolonged decrease in extracellular ionized calcium, newly synthesized PTH is available for secretion. Subsequently, hypocalcemia stimulates increased PTH secretion over days and is associated with an increase in parathyroid cell growth and number.[4]

Role of Phosphorus

Hyperphosphatemia occurs as a result of impaired renal excretion of phosphate. Several investigators have demonstrated that phosphorus retention plays an important role in the pathogenesis of secondary HPT. The mechanisms considered are as follows:

1. A phosphorus-induced decrease in 1,25-dihydroxyvitamin D_3 (calcitriol) that is independent of changes in ionized calcium and calcitriol. This results from decreased activity of the renal enzyme 1 α-hydroxylase, with consequent diminished 1,25-dihydroxyvitamin D secretion and decreased intestinal calcium absorption.
2. Phosphorus-induced hypocalcemia and hyperphosphatemia lead to a reciprocal fall in the serum calcium-phosphate product. A decrease in

Table 6–1. PATHOPHYSIOLOGY OF SECONDARY HYPERPARATHYROIDISM

Initiating Factors	Results	Treatment
Hypocalcemia		
↓ GI absorption	↑ PTH secretion	Calcium supplementation
↓ Dietary consumption	↑ Parathyroid cell growth	Low-phosphorus diet
		Phosphate binders
Hyperphosphatemia		
↑ α1-Hydroxylase activity		1,25-Dihydroxyvitamin D supplementation
↓ 1,25-Dihydroxyvitamin D		Calcitriol PO
Metabolic acidosis		
Parathyroid resistance to 1,25-Dihydroxyvitamin D		Calcitriol IV or IP

GI = gastrointestinal; PTH = parathyroid hormone; PO = orally; IV = intravenous; IP = intraperitoneal.

the synthesis of calcitriol possibly affects phosphorus retention. In patients with moderate renal insufficiency, phosphate restriction increases plasma calcitriol with a concomitant normalization of plasma PTH. In severe chronic renal failure, phosphorus appears to regulate PTH secretion by a mechanism independent of calcitriol. When phosphate binders are given and dietary phosphorus is reduced, serum PTH levels decrease substantially, although the values remain higher than normal.

Some investigators have also observed that phosphate restriction prevents parathyroid cell growth in uremic rats.[5] In vitro studies have demonstrated that phosphorus increases PTH synthesis and secretion by an unknown mechanism. In the presence of hyperphosphatemia, the parathyroid glands are resistant to the action of calcitriol.[6]

Role of Vitamin D

Vitamin D is hydroxylated at the 25 position in the liver and then requires activation by a second hydroxylation at the number one position in the kidney to become active. As renal function worsens and renal mass decreases, renal hydroxylation of vitamin D_3 decreases because of decreased 1 α-hydroxylase activity.[7] Deficiency of calcitriol, the most active form of vitamin D, causes defective synthesis of calcium binding protein in the intestine and decreased gastrointestinal absorption of calcium. A decreased serum concentration of calcitriol directly stimulates PTH secretion and synthesis.[1,3] Because larger doses of calcitriol can induce the regression of parathyroid hyperplasia, calcitriol may not only suppress parathyroid cell proliferation but may play a role in defining the overall cellular turnover rate in the parathyroid gland.[8]

The parathyroid glands in chronic dialysis patients with secondary HPT appear to be somewhat resistant to the physiologic concentration of calcitriol but are not as resistant to the pharmacologic concentrations of calcitriol.[3,9] Resistance of parathyroid cells to calcitriol may serve as another stimulus for PTH secretion in patients with chronic renal failure.[3] In vitro studies have shown that calcitriol inhibits serum-stimulated proliferation of parathyroid cells.[9] Vitamin D deficiency results in parathyroid hyperplasia, but this situation is in part owing to concomitant hypocalcemia. Undoubtedly, the reduced number of vitamin D and calcium-sensing receptors in hyperplastic and adenomatous parathyroid disease also plays an important role in the development of secondary HPT.[4]

The reduction of calcitriol receptor density in parathyroid glands has been considered the central mechanism of the resistance of parathyroid cells to calcitriol. It has been shown that larger hyperplastic parathyroid glands are more resistant to calcitriol pulse therapy than are smaller hyperplastic glands.[9] Calcitriol receptor density is inversely correlated with the weight of enlarged gland.[3] Parathyroid hyperplasia is divided into two types: nodular hyperplasia and diffuse hyperplasia (Figure 6–1). The calcitriol receptor density is less in nodular hyperplasia than in diffuse hyperplasia even in the same patient. Nodular hyperplasia, a more severe type of parathyroid hyperplasia, is usually seen in larger glands (90% of glands are heavier than 500 mg).

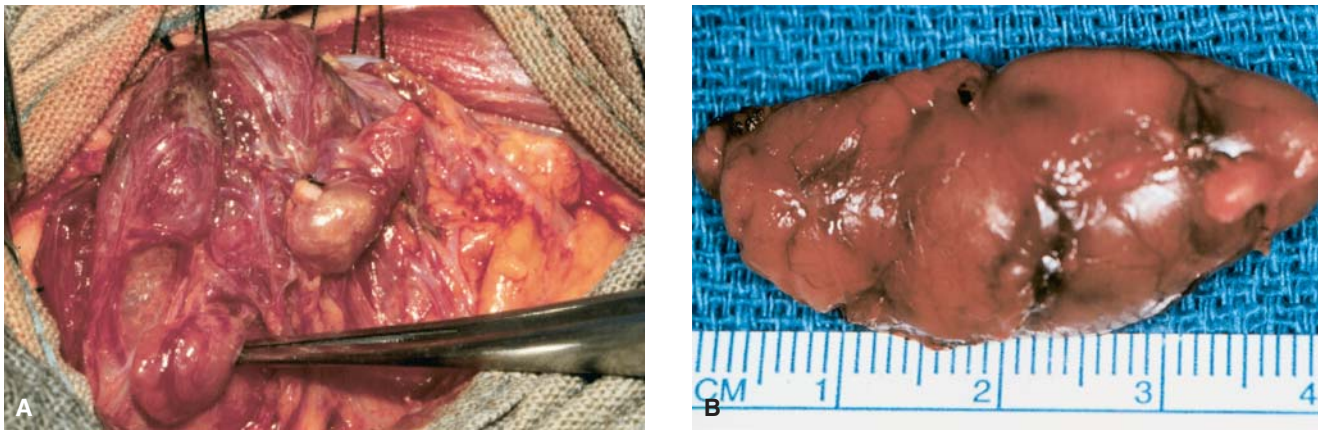


Figure 6–1. Nodular parathyroid hyperplasia: intraoperatively (*A*) and ex vivo (*B*).

CLINICAL MANIFESTATIONS OF SECONDARY HPT

The major subjective and objective findings and associated manifestations of secondary HPT are summarized in Table 6–2. Many clinical conditions may mimic secondary HPT, as demonstrated in Table 6–3. Increased PTH and decreased calcitriol levels lead to excessive bone resorption and poor bone mineralization. Renal osteodystrophy develops, which often causes bone pain and occasionally results in deformity or pathologic fractures. Systemic acidosis may also contribute to bone resorption. Elevated alkaline phosphatase levels have been correlated with increased bone resorption and are associated with a good probability of ameliorating bone pain after parathyroidectomy in symptomatic patients with secondary HPT. Subperiosteal resorption may be observed in the phalanges, pelvis, distal clavicles, ribs, femur, mandible, or skull. Skeletal deformities including kyphosis, scoliosis, and long bone bowing may occur. Progressive bone demineralization leads to thinning and weakening of the bones, manifesting as lytic lesions involving the skull (salt and pepper skull) or subperiosteal resorption of the hand, usually best seen on the radial side of the index finger. Pathologic fractures involving the spine, ribs, or long bones may occur. Soft tissue calcifications such as tumoral calcinosis may compress adjacent structures and may cause pain, organ dysfunction, and cosmetic deformities.[8] Systemic calcifications may involve blood vessels, kidneys, lungs, heart, and skin and result in calciphylaxis. The exact mechanism has not been elucidated (Figures 6–2 to 6–5).[10]

Easy fatigability, weakness, headache, weight loss, and irritable eyes owing to conjunctival and corneal calcifications and band keratopathy are clinical manifestations of secondary HPT. Other symp-

Table 6–2. CLINICAL MANIFESTATIONS OF SECONDARY HYPERPARATHYROIDISM

Symptoms	Objective Findings	Complications or Associated Conditions
Bone pain Pruritus Irritable eyes: conjunctival and corneal calcifications and keratopathy) Headache Weight loss Easy fatigability Weakness Proximal myopathy Fatigue Memory loss Depression	Renal osteodystrophy Osteomalacia Bone resorption, poor mineralization: phalanges, pelvis, distal clavicle, ribs, femur, mandible, skull	Skeletal deformities: scoliosis, kyphosis, long bone bowing Soft tissue calcifications Cutaneous ulcerations Gangrene Tendon rupture Extremity ischemia Decreased myocardial contractility Peptic ulcer

Table 6–3. DIFFERENTIAL DIAGNOSIS OF SECONDARY HYPERPARATHYROIDISM

Diagnosis	Secondary HPT	HPT with Comorbid CRF	Vitamin D Intoxication	Metastatic Cancer	Multiple Myeloma	Granulomatous Diseases	BFHH	Milk-Alkali Syndrome	Paget's Disease
Serum calcium	↓	↑	↑	↑	↑	↑	↑	↑	↔ or ↑
Serum phosphate	↑	↓	↑	↔	↔	↔ or ↑	↔ or ↑	↔ or ↑ in RF	↔
Serum alkaline phosphatase	↔ or ↑	↔ or ↑	↓	↔ or ↑	↔	↔ or ↑	↔	↔	↑
Urine calcium	↓	↑	↑	↑	↔ or ↑	↑	↓	↔ or ↓	↑
Urine phosphate	↓	↑	↑	↔	↔ or ↑	↑	↔ or ↑	↔ or ↓	↔
Special tests		PTH	Ectopic calcifications on radiographs	Metastases on radiographs	Radiograph lesions; Bence Jones protein		FMH	History of intake	Bone changes on radiographs

BFHH = benign familial hypocalciuric hypercalcemia; CRF = chronic renal failure; FMH = family medical history; HPT = hyperparathyroidism; PTH = parathyroid hormone; RF = renal failure.

toms include proximal myopathy, cutaneous ulcerations, gangrene, tendon ruptures, pseudogout, aseptic necrosis of the femoral heads, and decreased myocardial contractility. Pruritus is observed in up to 35% of patients with secondary HPT and has been attributed to increased deposition of calcium in the skin, resulting in increased reactivity of the mast cells. Psychoneurologic disorders and peptic ulcer disease also occur more often in patients with secondary HPT.

MEDICAL TREATMENT OF SECONDARY HPT

The factors responsible for the development of secondary HPT, including hypocalcemia, hyperphosphatemia, and vitamin D deficiency, should be corrected.[11] Early treatment is of value to prevent bone disease. Overall, only about 5% of patients with chronic renal failure on dialysis require parathyroidectomy. A diet low in phosphorus and high in phosphorus binders should be prescribed to keep serum phosphate levels normal. Phosphate binders containing aluminum hydroxide should be avoided or used intermittently to avoid aluminum bone disease. This diagnosis should be kept in mind in the differential diagnosis of patients with bone pain and renal osteodystrophy. The diagnosis can be made with bone biopsy, and most patients with aluminum bone disease do not have markedly increased PTH levels or alkaline phosphatase levels.[12] Hypophosphatemia, although uncommon, should also be avoided in patients with chronic renal failure as it may cause hypophosphatemic osteomalacia. A normal or low blood phosphate level, however, lessens the risk of soft tissue calcification.

Calcium supplementation is required since intestinal absorption of calcium is diminished in renal failure patients with reduced 1,25-dihydroxyvitamin D levels. Diets low in phosphate are usually also low in calcium. Calcitriol supplementation is mandatory and should be started even before the patient is dialysis dependent. During treatment with calcitriol, care should be taken to avoid hypercalcemia because it worsens renal function and causes metastatic calcifications, especially in individuals with high blood phosphate levels. The rare patient without an elevated PTH level does not require vitamin D supplementation (Figure 6–6).

PTH levels and parathyroid gland size should be evaluated when the selection of therapy is being considered. Patients with markedly increased PTH levels and parathyroid glands greater than 1 cm by ultrasonographic examination (Figure 6–7) or 0.5 g are almost never adequately controlled on medical therapy. Cessation of treatment always results in disease relapse. Parathyroid glands larger than 1 cm are also more resistant to calcitriol therapy.[8] In such cases, medical therapy with pulse calcitriol loses its effectiveness and may also be dangerous because of increased hypercalcemia.

PTH should also not be overly suppressed in order to avoid adynamic bone disease. The metabolic acidosis in dialysis patients should be corrected. Charcoal hemoperfusion has been reported

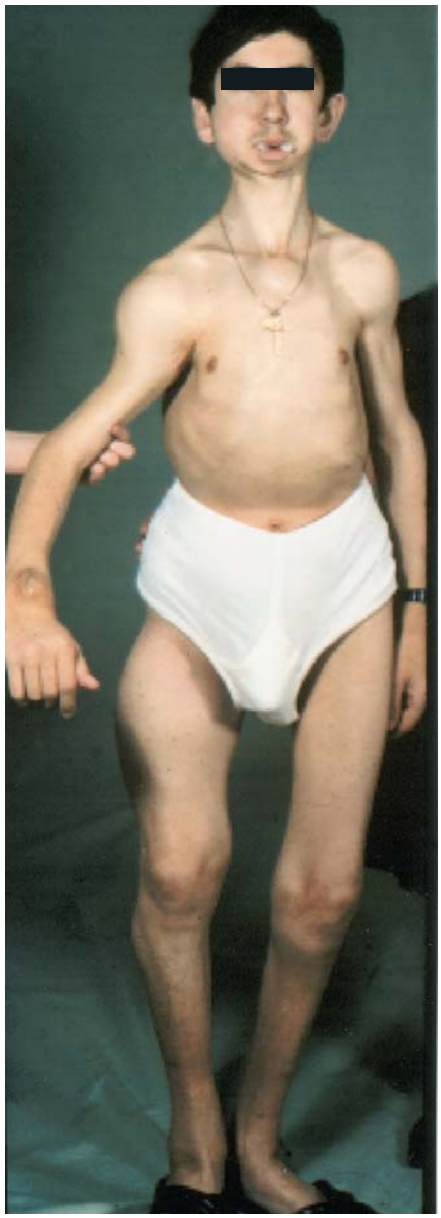


Figure 6–2. Skeletal deformities such as kyphosis, scoliosis, and long bone bowing in a patient with secondary hyperparathyroidism.

to be effective for treatment of pruritus, but patients with severe pruritus and bone pain with secondary HPT benefit from parathyroidectomy. Bisphosphonates, synthetic analogues of pyrophosphate, have recently been used to reduce bone resorption.

SURGICAL MANAGEMENT OF SECONDARY HPT

Nearly all patients with chronic renal failure develop some degree of parathyroid hyperplasia, although, as mentioned previously, only about 5% need to be treated surgically.[5] Secondary HPT has been documented to be present in about 67% of patients with renal failure by bone biopsy. Successful renal transplantation usually leads to resolution of HPT within 6 to 12 months. PTH levels often remain elevated for 1 or 2 years, suggesting a gradual involution of hyperplastic parathyroid glands. Some patients with more severe secondary HPT with extensive renal osteodystrophy and soft tissue calcifications have persistent hypercalcemia after renal transplantation (tertiary HPT) and benefit from subtotal or total parathyroidectomy with parathyroid autotransplantation.[13] Operative intervention for tertiary HPT is recommended for an asymptomatic increase in scrum calcium to greater than 12 mg/dL persisting for more than 1 year after renal transplantation, acute hypercalcemia (serum calcium greater than 1.5 ml [dL] in the immediate postoperative period, and symptomatic hypercalcemia.[14]

Parathyroidectomy is recommended for patients with chronic renal failure and secondary HPT who have severe pruritus, extensive soft tissue calcification, bone pain, spontaneous bone fractures, psychoneurologic disorders, calcium-phosphate product greater than 70, serum calcium greater than

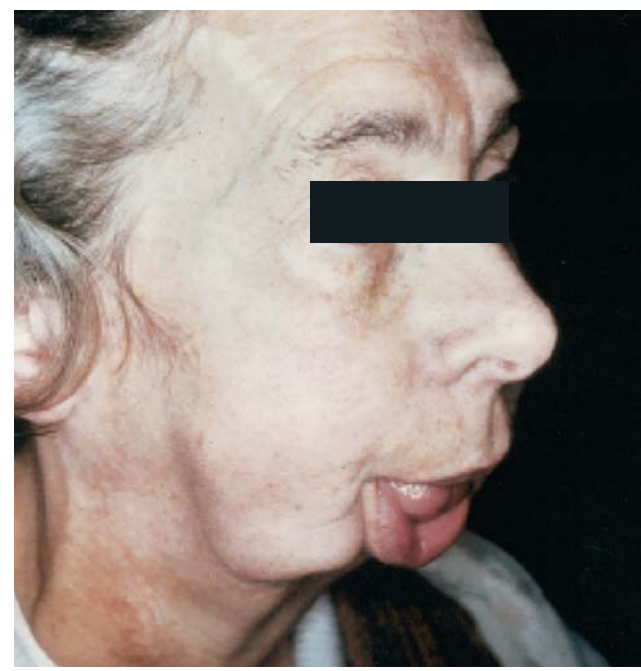


Figure 6–3. Skeletal deformity of the mandible in secondary hyperparathyroidism.

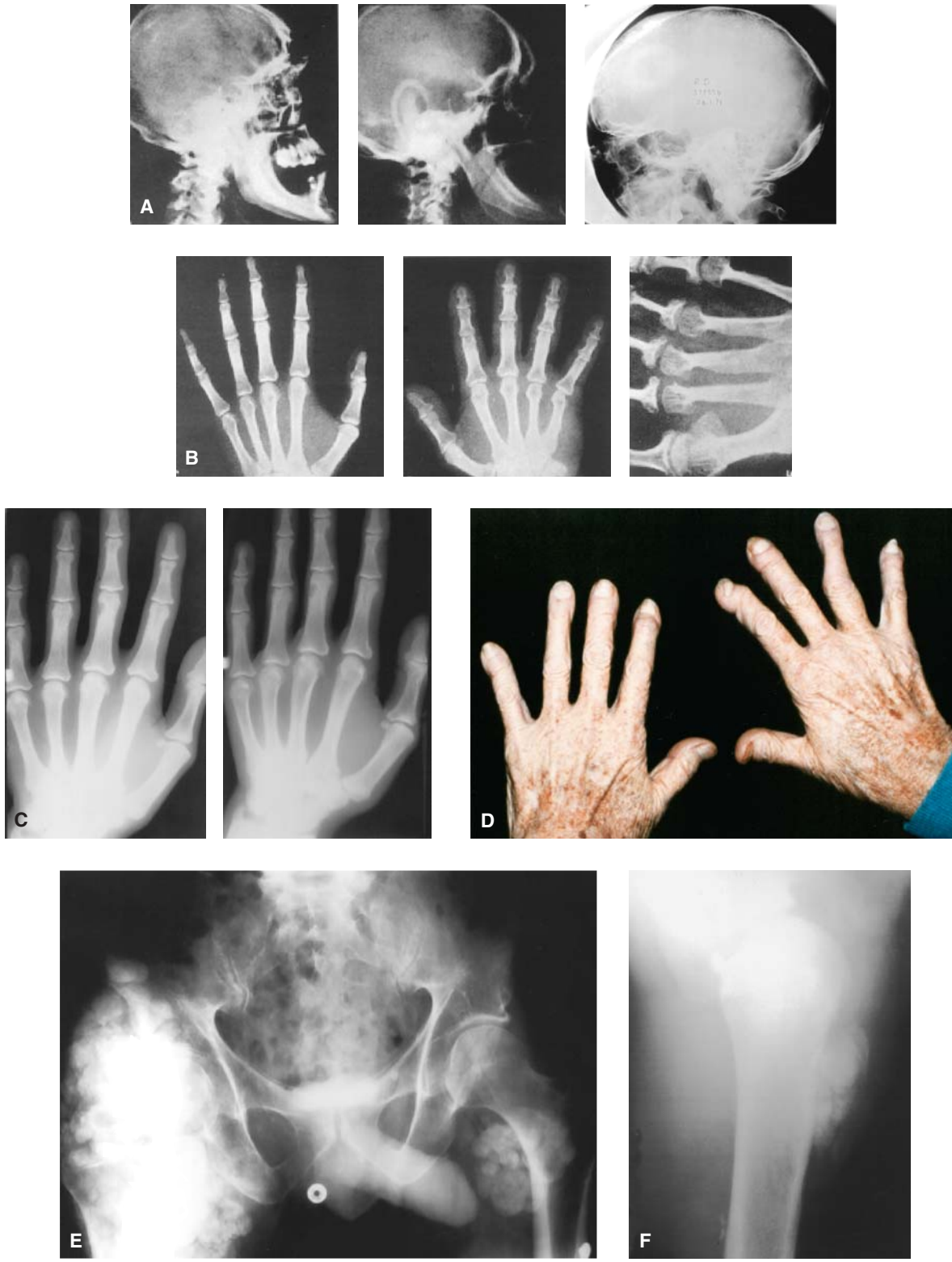


Figure 6–4. *A*, Lytic lesions in the skull. *B*, Radiographic evidence of subperiosteal resorption of phalanges. *C*, Radiographic evidence of subperiosteal resorption best seen on the radial side of the index finger. *D*, Clinical evidence of subperiosteal resorption of the hand. *E*, Fatty brown tumors of long bones. *F*, Fatty brown tumors of long bones.

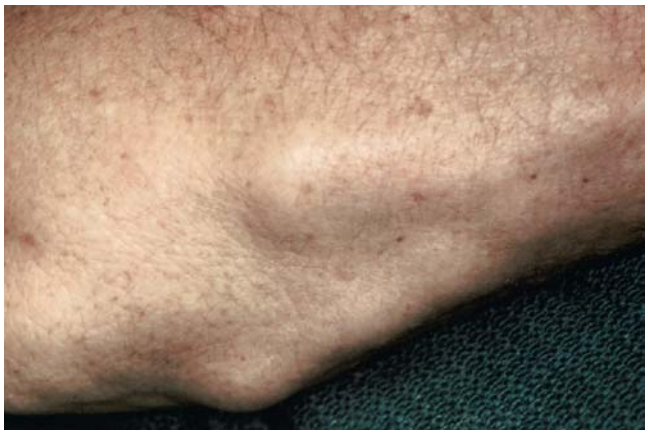


Figure 6–5. Tumoral calcinosis resulting from soft tissue calcifications.

11 mg/dL, or parathyroid gland size > 1 cm in diameter by ultrasonographic examination (Table 6–4).[15,16] Criteria for resistance to medical treatment are hypercalcemia, uncontrollable hypertension, progressive ectopic calcification, severe symptoms, severe skeletal deformity, progressive bone loss, calciphylaxis, and anemia resistant to erythropoietin. Because skeletal deformity, vessel calcification, and the remarkable reduction of bone content in severely advanced renal HPT are irreversible, it is essential to perform surgery early. Surgery is also recommended if parathyroid hyperplasia progresses to nodular hyperplasia; set points for PTH release in the latter are shifted toward significantly higher calcium levels.[17] Preoperative tumor localization studies are not cost effective in patients with secondary HPT because of a significant number of both false-positive and false-negative results and because virtually all patients have multiple gland disease.[18]

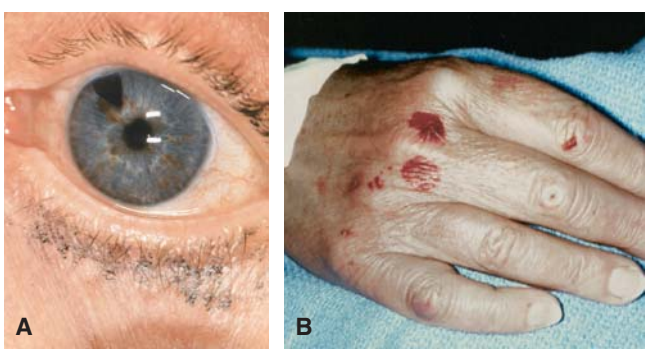


Figure 6–6. *A*, Band keratopathy seen in the eye of a patient with secondary hyperparathyroidism. *B*, Cutaneous ulceration owing to hypercalcemia.

Subtotal parathyroidectomy and total parathyroidectomy with autotransplantation of parathyroid tissue into the forearm are the procedures of choice for patients with secondary HPT (Figure 6–8). We prefer subtotal parathyroidectomy, leaving 50 mg of parathyroid tissue for compliant patients who will take vitamin D (calcitriol [Rocaltrol]), phosphate binders, and calcium. During exploration, all four hyperplastic glands should be identified, and about 20% of patients may have a fifth parathyroid gland. In both procedures, a transcervical thymectomy should also be performed to remove any supernumerary parathyroid glands or embryogenic nest of parathyroid tissue.

While performing a subtotal parathyroidectomy, $3^1/_2$ of the 4 glands are resected. Approximately 50 mg of the most normal of the hyperplastic parathyroid glands that is not situated on the recurrent laryngeal nerve is left in place with its vascular pedicle intact and marked with a clip or stitch. The viability of the remnant gland should be ensured prior to removing the hyperplastic glands. We also recommend cryopreservation of parathyroid tissue for all patients who have a subtotal parathyroidectomy resection or a total parathyroidectomy with autotransplantation. Care is taken to avoid transplanting tissue from macroscopically visible nodules.[2] One should

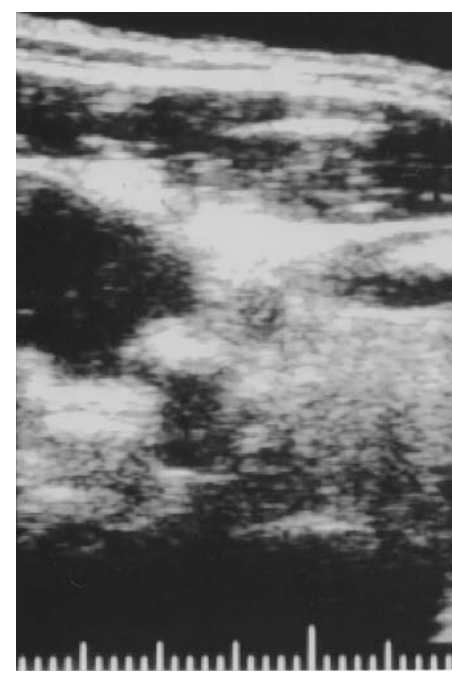


Figure 6–7. Parathyroid gland greater than 1 cm seen on sonogram.

Table 6–4. INDICATIONS FOR SURGICAL TREATMENT*

Clinical	Laboratory
Bone pain, spontaneous bone fractures	$Ca \times PO_4$ product > 70
Severe pruritus	Ca > 11 mg/dL
Extensive soft tissue calcifications (tumoral calcinosis)	Alkaline phosphatase > twofold increased
Calciphylaxis	
Parathyroid gland > 1 cm	
General weakness	

*Also symptoms and complications listed above.
Ca = calcium; PO_4 = phosphorous.

also avoid fracturing parathyroid glands to decrease the risk of parathyroid hyperplasia. If renal transplantation is anticipated, the remnant should be larger (40 to 60 mg) to avoid post-transplant hypoparathyroidism. The major advantage of subtotal parathyroidectomy is knowing the location of the remaining parathyroid gland. Postoperative hypoparathyroidectomy is less common. The disadvantage of subtotal resection is that a second neck exploration is needed in the event of persistent or recurrent HPT.[5]

Total parathyroidectomy and parathyroid gland autotransplantation to the forearm are preferred by some surgeons. They decrease the need for a second neck exploration, although some patients have persistent or recurrent secondary HPT owing to failure to remove a supernumerary parathyroid gland in the neck or superior mediastinum. During transplantation, the autograft is left in iced physiologic saline at 4°C for 30 minutes and sliced into 1 × 1 mm pieces. Twelve to 20 of these slices are then transplanted into the brachioradial muscle bed through a single incision in the nondominant forearm. Each implant is located in a separate small pocket and secured with a permanent suture mark. Some parathyroid tissue should also be cryopreserved (Figures 6–8).

There is much debate regarding routine bilateral neck exploration in multiple endocrine neoplasia (MEN) or secondary HPT. A recent study by Chou and colleagues assessed intraoperative PTH monitoring during surgery for secondary HPT.[19] They anticipated that because total or subtotal parathyroidectomy is needed for successful treatment of secondary HPT or MEN, the 50% decline in PTH levels used in estimating an appropriate treatment response in primary HPT may be inadequate. They found that complete surgical removal can be ensured if levels are less than 60% that of baseline at 10 minutes.

Postoperative calcium and 1,25-dihydroxyvitamin D replacement is important as the PTH secretion from the autografted parathyroid tissue is insufficient for at least 3 weeks. For all patients with secondary HPT, treatment with vitamin D_3, calcium, and phosphate binders is necessary to prevent recurrent hyperplastic and secondary HPT.[20] In the case of recurrent or persistent HPT, determination must be made whether the condition is attributable to a missed gland in the neck or a hyperfunctioning forearm graft. To ascertain this, venous sampling from both arms should be obtained. If the level is high in only one arm (ie, a twofold increase versus the nontransplanted arm), one may surmise that a hyperfunctioning graft is the cause (see Figure 6–8).[5]

Patients with symptomatic secondary HPT and osteoporosis should have early parathyroidectomy

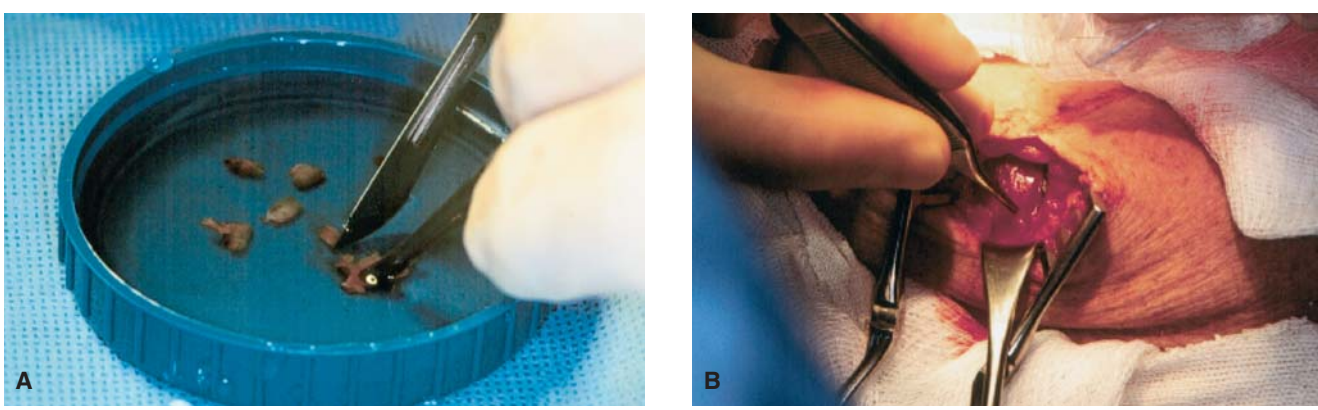


Figure 6–8. Autotransplantation of parathyroid tissue. *A*, Autograft parathyroid tissue sliced into 1 × 1 mm pieces, and *B*, transplanted into the nondominant forearm.

to prevent the morbidity of bone fracture. Parathyroidectomy and autotransplantation can improve the bone mineral density of symptomatic secondary HPT at both the lumbar spine and femoral neck.[21] Sexual dysfunction is common in chronic renal failure, with nearly half of uremic men complaining of erectile dysfunction. It is hypothesized that an excess of PTH in uremic patients may contribute to hormonal disturbances and the impotence of uremia. Parathyroidectomy with autotransplantation improved sexual function, frequency of attempted intercourse, satisfaction of attempted intercourse, and enjoyment of intercourse in men with previously symptomatic secondary HPT.[22] It was postulated that the improved sexual function was related to reduced prolactin in association with decreased calcium, phosphorus, and PTH.

Calciphylaxis is a rare, life-threatening condition in secondary HPT, characterized by vascular calcification in the tunica media of blood vessel walls. Such calcifications create painful violaceous mottled skin lesions of the upper and lower extremities, which may progress to ischemic necrosis. Gangrene of the digits often requires amputation, leading to poor wound healing and possibly sepsis and death.[23,24] Associations have been seen with high serum calcium phosphate product and severe secondary HPT, but it may occur in patients with normal or mildly elevated serum phosphate of PTH levels.[25] The only potential curative therapy in this situation is prompt parathyroidectomy. Palliative interventions include focal wound care, antimicrobials, phosphate binders, and avoidance of vitamin D load.[23,24] A recent study of patients with calciphylaxis revealed that there was resolution of pain and healing of cutaneous wounds in all patients treated with surgery. However, five of seven patients treated with medical therapy alone died of complications from calciphylaxis, including gangrene and sepsis. Patients with surgery had a significantly longer median survival than those who did not—36 months versus 3 months, respectively.[24]

SUMMARY

Patients with secondary HPT are more likely to have severe skeletal manifestations and persistent or recurrent disease than those with primary HPT, making management more challenging. Surgery in secondary HPT significantly improves osteoporosis, anemia and platelet counts, and nutritional status; increases serum erythropoietin levels; and improves sexual dysfunction.[22,26,27] It can also prevent life-threatening complications of the disorder. The experienced endocrine surgeon can, therefore, substantially impact the quality of life of patients with secondary HPT who fail medical management or who have severe disease.

ACKNOWLEDGMENT

Drs. Perrier, Tatar and Boger would like to thank the following individuals, without whom preparation of this chapter would not have been possible: Orlo H. Clark, MD, Professor of Surgery and Vice-Chair, Department of Surgery, UCSF, San Francisco, California, for kindly providing photographs, pathology images, and radiographs of the manifestations of secondary hyperparathyroidism; and Phyllis Easter, Secretarial Assistant, Department of Surgery, Wake Forest University School of Medicine, for her endless devotion in assisting the preparation of this chapter.

REFERENCES

1. Tominaga Y, Johansson H, Johansson H, Takagi H. Secondary hyperparathyroidism: pathophysiology, histopathology, and medical and surgical management. Surg Today 1997; 27:787–92.
2. Tsukamato Y. Pathophysiology and treatment of secondary hyperparathyroidism in patients with chronic renal failure. Nephrol Dial Transplant 1995;10:22–4.
3. Fukagawa M, Kurokawa K. Pathogenesis and medical treatment of secondary hyperparathyroidism. Semin Surg Oncol 1997;13:73–7.
4. Slatopolsky E. The role of calcium, phosphorus, and vitamin D metabolism in the development of secondary hyperparathyroidism. Nephrol Dial Transplant 1998;13:3–8.
5. Packman K, Demeure MJ. Indications for parathyroidectomy and extent of treatment for patients with secondary hyperparathyroidism. Surg Clin North Am 1995;75:465–82.
6. Llach F. Secondary hyperparathyroidism in renal failure: the trade off hypothesis revisited. Am J Kidney Dis 1995; 25:663–79.
7. Slatopolsky E, Delmez J. Pathogenesis of secondary hyperparathyroidism. Nephrol Dial Transplant 1996;11:130–5.
8. Tezelman S, Siperstein A, Duh Q, Clark O. Tumoral calcinosis: controversies in the etiologies and alternatives in the treatment. Arch Surg 1993;128:737–45.

9. Fukagawa M, Kurokawa K. Pathogenesis and medical treatment of secondary hyperparathyroidism. Semin Surg Oncol 1997;13:73–7.
10. Duh Q, Lim R, Clark O. Calciphylaxis in secondary hyperparathyroidism: diagnosis and parathyroidectomy. Arch Surg 1991;126:1213–9.
11. Clark O. Current management of patients with hyperparathyroidism. Adv Surg 1996;30:179–87.
12. Sitgos-Serra A, Caralps-Riera A. Hyperparathyroidism asociated with renal disease. Pathogenesis, natural history and surgical treatment. Surg Clin North Am 1987;67:359–77.
13. Kilgo MS, Pirson JD, Warner TF. Tertiary hyperparathyroidism after renal transplantation surgical strategy. Surgery 1998;124:677–83.
14. Kerby JD, Rue W, Blair H. Operative treatment of tertiary hyperparathyroidism: a single center experience. Ann Surg 1998;227:878–86.
15. Fukagawa M, Fukuda N, Kurokawa K. Resistance of parathyroid cell to calcitriol as a cause of parathyroid hyperfunction in chronic renal failure. Nephrol Dial Transplant 1995;10:316–9.
16. Chou FF, Lee Ch, Chen JB. General weakness as an indication for parathyroid surgery in patients with secondary hyperparathyroidism. Arch Surg 1999;134:1108–11.
17. Tominaga Y. Surgical management of secondary hyperparathyroidism in uremia. Am J Med Sci 1999;317:390–8.
18. Edis A. Hyperparathyroidism: what does surgery have to offer? Med J Aust 1998;168:148–9.
19. Chou FF, Lee CH, Chen JB, et al. Intraoperative parathyroid hormone measurement in patients with secondary hyperparathyroidism. Arch Surg 2002;137:341–4.
20. Indvadason OS, Quarles LD. Hyperphosphatemia in end stage renal disease. Adv Ren Replac Ther 2002;9:188–92.
21. Chou FF, Chen JB, Lee CH, et al. Parathyroidectomy can improve bone mineral density in patients with symptomatic secondary hyperparathyroidism. Arch Surg 2001;136:1064–8.
22. Chou FF, Lee CH, Shu K, et al. Improvement of sexual function in male patients after parathyroidectomy for secondary hyperparathyroidism. J Am Coll Surg 2001;193:486–92.
23. Duh QY, Lim RC, Clark OH. Calciphylaxis in secondary hyperparathyroidism: diagnosis and parathyroidectomy. Arch Surg 1991;126:1213–18.
24. Girotto JA, Harmon JW, Ratner LE, et al. Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism. Surgery 2001;130:645–50.
25. Monier-Faugere MC, Malluche HH. Renal osteodystrophy. In: Goldman L, Bennett JC, editors. Cecil textbook of medicine. 21st ed. Philadelphia: WB Saunders Company; 2000. p. 1409–14.
26. McHenry CR, Wilhelm SM, Ricanati E. Refractory renal hyperparathyroidism: clinical features and outcome of surgical therapy. Am Surg 2001;67:310–7.
27. Yasunaga C, Matsuo K, Yanagida T, et al. Early effects of parathyroidectomy on erythropoietin production in secondary hyperparathyroidism. Am J Surg 2002;183: 199–204.

7

Parathyroid Carcinoma

THIERRY M. JAHAN, MD
JENNIFER BRAEMAR OGILVIE, MD

EPIDEMIOLOGY

Parathyroid carcinoma is one of the less likely causes of what is a common endocrinologic problem: primary hyperparathyroidism. The majority of cases present with symptomatic hypercalcemia. The incidence of parathyroid carcinoma has been the subject of some debate, with several studies out of Japan and Italy claiming that it accounts for up to 5% of all cases of primary hyperparathyroidism.[1–3] These data may be influenced by lower screening rates for asymptomatic hypercalcemia. Most surveys in the United States show that parathyroid carcinoma accounts for less than 1% of all cases of primary hyperparathyroidism.[4–6] A recent analysis of the National Cancer Database revealed that there were only 286 cases of parathyroid carcinoma recorded in the United States during the period of 1985 to 1995, or approximately 30 cases per year.[7] This number is far less than earlier estimates of 1 to 5% of all causes of primary hyperparathyroidism, which has an incidence of 1 per 2,000 to 5,000.

CLINICAL MANIFESTATIONS

The initial manifestations of parathyroid carcinoma are quite similar to those of the two leading causes of primary hyperparathyroidism: nonmalignant parathyroid hyperplasia and parathyroid adenoma. The intensity of the symptoms and manifestations tends to be greater for parathyroid carcinoma than benign lesions, as is the rapidity of onset. Patients with parathyroid carcinoma present more commonly with hypercalcemic crisis and significantly higher levels of hypercalcemia than patients with nonmalignant causes of hyperparathyroidism. The levels of circulating parathyroid hormone are also significantly higher in parathyroid carcinoma. The signs and symptoms of parathyroid carcinoma are therefore an exaggeration of those of primary hyperparathyroidism owing to benign disease. They are well summarized by the mnemonic "stones, bones, groans, psychic moans and fatigue overtones," referring to the effect of hyperparathyroidism-induced hypercalcemia on target organs.

Stones refer to hypercalcemia-induced nephrolithiasis, seen in 30 to 60% of cases of primary hyperparathyroidism. In parathyroid carcinoma, it is not uncommon to see both nephrolithiasis (kidney stones) and nephrocalcinosis (precipitation of calcium phosphate in the renal tubules). Untreated and unmanaged, both complications may lead to irreversible azotemia and renal failure. One recent study revealed a prevalence of renal insufficiency of 84% in parathyroid carcinoma.[8] In addition, hypercalcemia leads to an obligatory calciuria with large-volume polyuria that can result in significant intravascular volume depletion, further contributing to the underlying azotemia.

Bones refer to the skeletal manifestations of hypercalcemia, which range from myalgias and arthralgias to osteopenia and severe osteoporosis, seen in 40 to 70% of cases of persistent hyperparathyroidism. The radiographic manifestations of prolonged hyperparathyroidism, subperiosteal bone resorption (Figure 7–1), "salt and pepper" skull, dif-

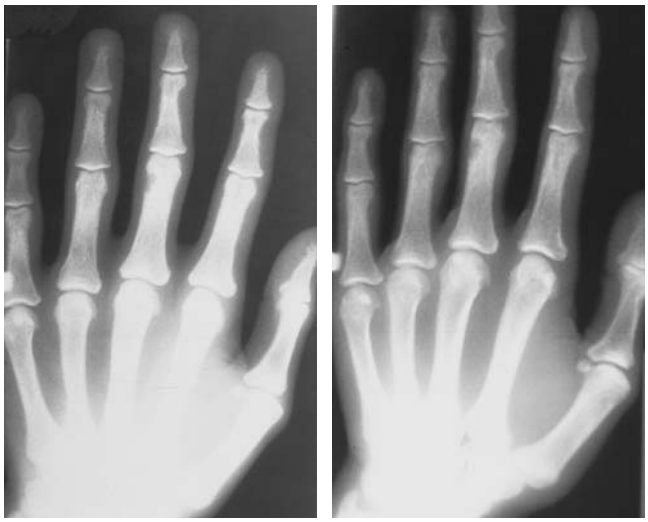


Figure 7–1. Example of subperiosteal bone resorption seen in patients with hyperparathyroidism.

fuse spinal osteopenia, or osteitis fibrosis cystica (abnormal calcium deposits in soft tissue or muscles), are seen in 41 to 91% of patients with parathyroid carcinoma, compared with 5% of benign hyperparathyroidism.[9–11] The concurrent development of skeletal and renal manifestations of hypercalcemia is also seen much more commonly in the presentation of parathyroid carcinoma than in benign hyperparathyroidism. It is a distinguishing feature of the higher level of hypercalcemia and hyperparathyroidism associated with parathyroid carcinoma.

Groans refer to the gastrointestinal manifestations of hypercalcemia, seen in 15% of primary hyperparathyroidism. Patients can present with anorexia, constipation, weight loss, nausea and vomiting, and, peptic ulcer disease. Up to 10% of patients with parathyroid carcinoma can present with acute pancreatitis or recurrent severe pancreatitis. Unfortunately, the degree of anorexia, decreased fluid intake, and vomiting seen with untreated parathyroid carcinoma only aggravates the underlying intravascular depletion caused by hyperparathyroid-induced hypercalcemia.

Finally, psychic moans and fatigue overtones refer to the psychological and general systemic manifestations of uncontrolled hypercalcemia, seen commonly in primary hyperparathyroidism. These symptoms range from depression and fatigue to mild confusion, muscle weakness, and profound coma. The severity of the confusion or coma correlates with the degree and duration of hypercalcemia. Rapid treatment and correction of the hypercalcemia, which will reverse the alteration in sensorium associated with hypercalcemia, should be initiated rapidly. The first step is to replenish the depleted intravascular volume with aggressive intravenous normal saline, typically at rates of 300 cc/hour for 24 or more hours. Only when intravascular volume is restored can the use of calciuric diuretics, such as furosemide (at a starting dose of 20 to 40 mg intravenously or orally), begin in earnest. If attempts at diuresis are initiated prior to replenishing intravascular volume, one runs the risk of exacerbating the renal dysfunction and underlying azotemia present in hypercalcemia.

Approximately 50% of patients with parathyroid carcinoma present with a palpable neck mass, in contrast to patients with primary hyperparathyroidism in whom the parathyroid tumor is palpable in 4%.[12] The parathyroid cancers tend to be firm and may be fixed to the underlying structures; they are usually painless. In a few patients with direct invasion of underlying structures, there can be pain; there can also be hoarseness owing to invasion of the recurrent laryngeal nerve. Most patients with parathyroid carcinoma will have a neck mass of 3 cm. At surgery, the mass will often appear as a gray-white firm mass (Figure 7–2). In contrast, adenomas and hyperplastic parathyroid glands tend to be reddish brown or chestnut (Figure 7–3).

The laboratory abnormalities in patients with parathyroid carcinoma are those of primary hyperparathyroidism. The level of hypercalcemia tends to be higher than for other nonmalignant causes of primary hyperparathyroidism, on the order of 14 to 15 mg/dL. The level of parathyroid hormone is usually also much more elevated in patients with parathyroid carcinoma than in patients with hyperplasia or adenoma (Table 7–1), usually 3 to 10 times the upper limit of normal. Alkaline phosphatase and α and β subunits of human chorionic gonadotropin may also be elevated in parathyroid carcinoma.

ETIOLOGY

The etiology of parathyroid carcinoma remains unclear. The incidence of parathyroid carcinoma is equal between males and females, with a peak age of onset in the fifth decade, approximately 10 years

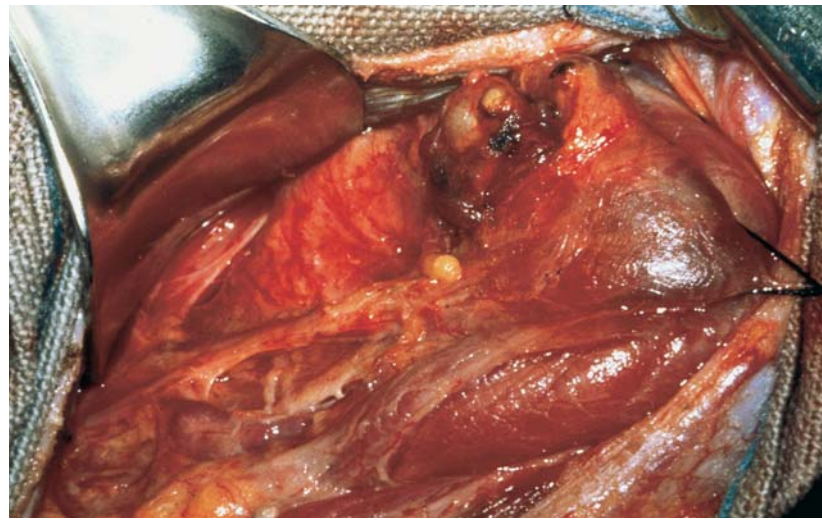


Figure 7–2. Neck dissection with parathyroid mass.

earlier than the peak onset for benign parathyroid disease.[13] Like thyroid carcinoma in which external beam radiation is a clear predisposing event, there have been a few reports of parathyroid abnormalities developing after exposure to neck radiation, more often causing benign adenoma than parathyroid carcinoma.[14,15]

Given the rarity of the disease, little is known about the molecular pathogenesis. Parathyroid carcinoma is likely to follow the type of multistep carcinogenesis best described in colon cancer. It is quite likely that a series of mutations will confer a survival or growth advantage to a specific parathyroid cell and its clone of progenitor cells. The types of mutations that lead to this growth advantage include the ones that result in the overexpression of normal genes and of normal growth receptors to growth-stimulating factors. Other mutations can result in alterations in deoxyribonucleic acid (DNA) methylation, which, in turn, can alter the expression of key controlling genes, leading to reduced activity of genes responsible for the control of the growth of the cell.

Cyclin D1 (*PRAD1*) is an oncogene on chromosome 11q13 whose protein product, a cell-cycle regulator, is overexpressed in 18 to 40% of parathyroid adenomas[16–18] and in 66 to 91% of parathyroid carcinomas.[16,18] In addition, a clonal chromosomal inversion has been observed in a small subset (5%) of parathyroid adenomas, resulting in the juxtaposition of the controlling region of the parathyroid hormone gene (on chromosome 11p15) to the cyclin D1 oncogene (on 11q13).[19,20] This rearrangement leads to the overexpression of cyclin D1, which results in increased cell proliferation. What is not clear is whether cyclin D1 is a causative factor in parathyroid disease, but it deserves further study as a potential therapeutic target.

RET-activating mutations, which account for tumor development through the uncontrolled activation of the receptor tyrosine kinase in multiple endocrine neoplasia (MEN) type II syndrome, are being considered as possibly involved in parathyroid tumorigenesis. The *RET* proto-oncogene is located on chromosome 10q11. Specific *RET*

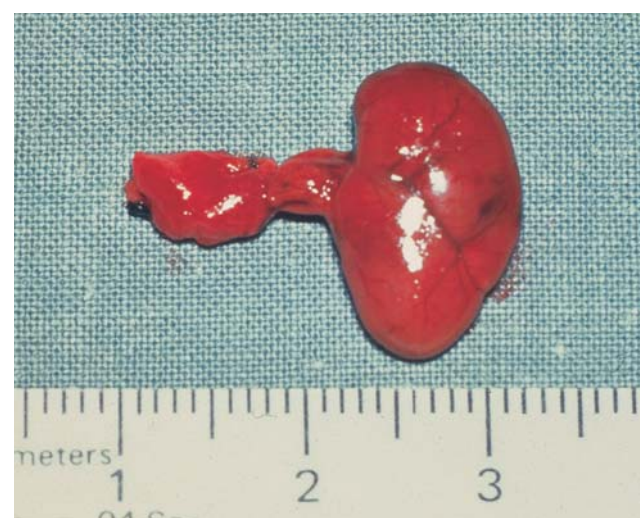


Figure 7–3. Resected parathyroid carcinoma mass.

Table 7–1. COMPARISON OF THE FEATURES OF ADENOMA/HYPERPLASIA VERSUS PARATHYROID CARCINOMA

Findings	Adenoma/Hyperplasia	Parathyroid Carcinoma
Incidence	1/2,000–5,000	30 cases per year or ≤ 0.5% of all cases of primary hyperparathyroidism
Age	3rd to 4th decade	5th to 6th decade
Gender distribution	Moderate female preponderance (2.5:1)	No gender dominance
Presence of a neck mass	Unlikely (≤ 4%)	Common, with mass measuring ≥ 3 cm (≥ 50%)
Presence of hypercalcemic crisis	Less common (≤ 1%)	Common (≥ 30%)
Serum calcium level	11 to 12 mg/dL	14 to 15 mg/dL
Serum parathyroid level	2 to 3 times the upper limit	5 to 10 times (or more)
Presence of renal *and* skeletal manifestations	Uncommon (≈ 15%)	Common (≈ 75%)
Surgical appearance	No invasion into surrounding structures	Clear invasion into surrounding structures

proto-oncogene mutations at codon 634 seem to correlate with involvement of parathyroid tissue. This suggests a possible role for this proto-oncogene in the development of parathyroid tumorigenesis. However, analysis of samples of sporadic (nonfamilial) parathyroid carcinoma have not yet revealed a *RET* mutation.[21,22]

Primary hyperparathyroidism is more common in MEN type I syndrome and is associated with mutations that inactivate the tumor suppressor gene *MEN1*, located on chromosome 11q13. However, *MEN1* inactivations do not appear to be common in parathyroid carcinoma.[23] Parathyroid cancer is more common also in patients with familial hyperparathyroidism and jaw tumor syndrome (HPT-JT).[22,24] HPT-JT syndrome is a distinct disorder with an autosomal dominant inheritance pattern. In these patients, hyperparathyroidism is associated with ossifying fibromas of the jaw. A number of neoplasms, including parathyroid carcinomas, Wilms' tumors, polycystic renal disease, and renal hamartomas, have also been associated with the HPT-JT syndrome. The gene responsible for HPT-JT, *HRPT2*, has been mapped to a region on the long arm of chromosome 1, between chromosome 1q25 and chromosome q31.[25]

Inactivation of the retinoblastoma (*RB*) tumor suppressor gene on chromosome 13q has been described in parathyroid carcinoma but less frequently in parathyroid adenoma or hyperplasia, suggesting that *RB* inactivation may be a causative event in tumorigenesis.[26,27] Large deletions of chromosome 13 have also been frequently observed by comparative genomic hybridization in parathyroid carcinoma, but it is unclear which gene at this locus will turn out to be the primary tumor suppressor in the pathogenesis of parathyroid carcinoma.[23,28] The *P53* tumor suppressor gene has also been examined as a potential causative factor, but inactivations or abnormal protein expression have not been shown to be frequent events in parathyroid carcinoma.[29,30]

Recent comparative genomic hybridization studies have identified several new potential oncogenes on chromosomes 1q, 5q, 9q, 16p, and 19p, as well as tumor suppressor genes on chromosomes 1q, 3q, 4q, 13q, and 21q.[23,28,31] These tumor-specific gains or losses of genetic material are found frequently in parathyroid carcinomas and rarely or never in adenomas. Finally, there is one study showing expression of platelet-derived growth factor β-receptors in a parathyroid carcinoma, a potential therapeutic target that deserves further exploration.[32]

Despite several reports of parathyroid carcinoma occurring within a parathyroid adenoma or hyperplastic gland,[33,34] a large pathologic review found no evidence for malignant transformation in benign lesions.[35] In addition, the lack of *MEN1* inactivations in parathyroid carcinoma versus frequent *MEN1* inactivations in parathyroid adenomas indicates that parathyroid carcinomas likely arise de novo and not in preexisting adenomas.

PATHOLOGY

There have been multiple descriptions of the histologic appearance of parathyroid carcinoma (Figures 7–4 and 7–5). The cells appear to have a tendency to form pseudorosettes around capillaries. The nuclei of the cells are typically enlarged; occasionally, this results in the presence of macronuclei. Mitotic figures

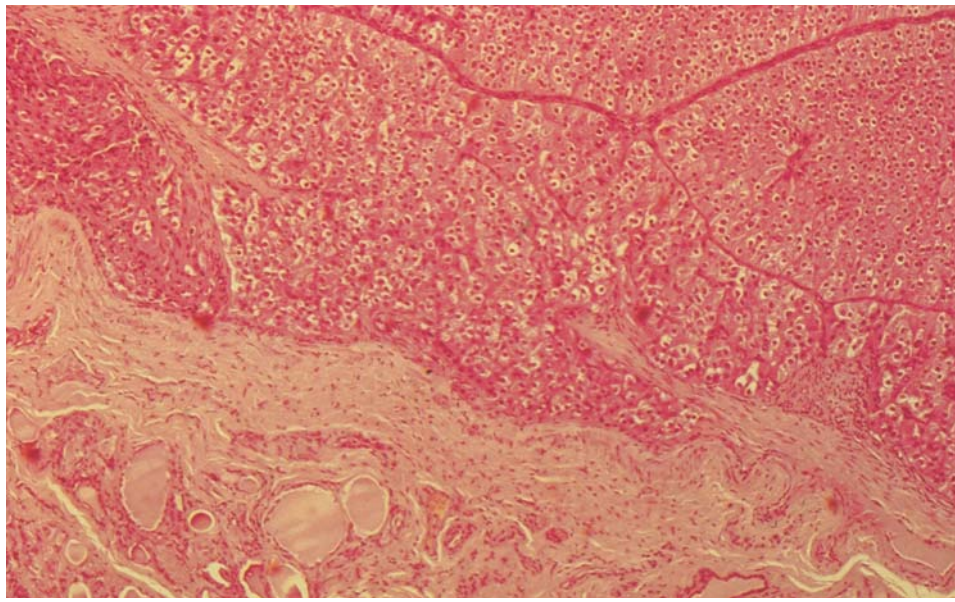


Figure 7–4. Intermediate power view of parathyroid carcinoma illustrating rosette formation (hematoxylin and eosin).

can be seen. It may be difficult to distinguish parathyroid carcinoma from medullary thyroid carcinoma or other neuroendocrine-derived carcinomas (small cell carcinoma of the lung or esophagus or pheochromocytoma). These other entities tend to exhibit the presence of argyrophillic granules. Parathyroid carcinomas tend to be associated with the presence of lipophages (cells that have a high lipid content). One can exclude thyroid carcinoma and small cell carcinomas when lipophages are detected in the specimen. On electron microscopy, parathyroid carcinoma cells tend to have an almost round and central nucleus that has a prominent nucleolus. Most tumor cells also are loosely packed with multiple mitochondria spread throughout the cytoplasm. Immunohistochemical stains for parathyroid hormone can help identify the

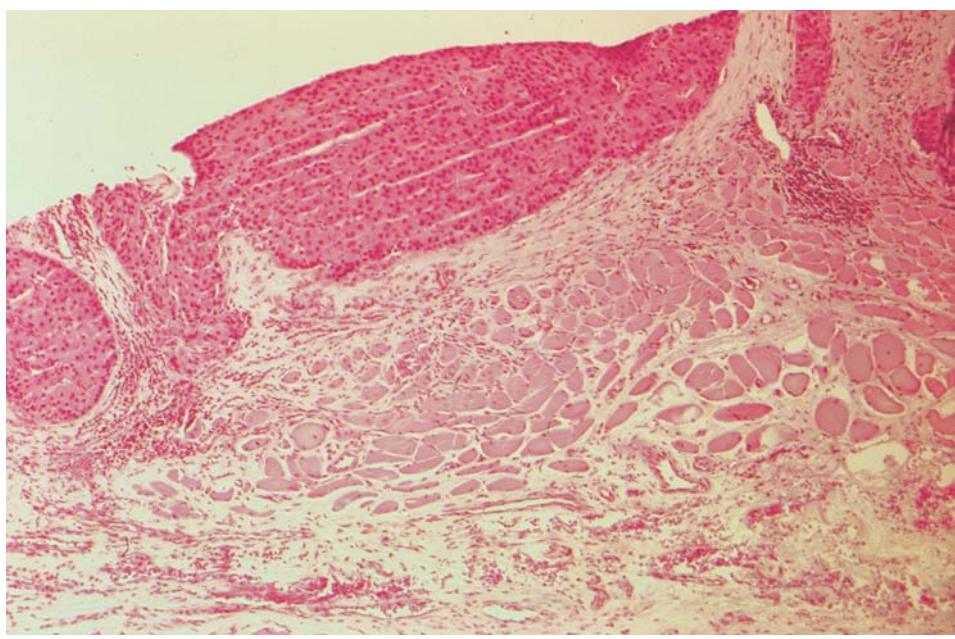


Figure 7–5. Parathyroid carcinoma, low-power view, illustrating invasion into surrounding structures (hematoxylin and eosin).

tumor as being of parathyroid origin. However, the presence of a positive parathyroid hormone stain does not distinguish between a benign adenoma and a malignant carcinoma. One can also aspirate the presumed parathyroid tissue and determine the level of parathyroid hormone concentration in the tissue. It should be markedly increased (> 1,500 ng/L) in parathyroid neoplasm, in contrast to low or absent levels in nonparathyroid neoplastic tissue. Finally, immunohistochemical staining for RB protein or the cell cycle–associated antigen Ki-67 may prove useful in distinguishing parathyroid carcinoma from benign parathyroid disease.[26,27,36]

Over the years, there has been some debate concerning criteria to establish an accurate diagnosis of parathyroid carcinoma. The tumors themselves are firm, grayish-white, and frequently lobulated, with adherence to adjacent tissues. Most authors agree that one should note the presence of fibrous trabeculae, associated with vascular invasion, neovascularization, and mitotic figures. At least 50% of parathyroid carcinoma tumors are surrounded by a dense fibrous capsule, which reveals microscopic invasion by the neoplastic cells. In addition, there is frequent invasion of the tumor cells into contiguous structures such as the thyroid, strap muscles, recurrent laryngeal nerve, esophagus, or trachea. Schantz and Castleman established a set of histologic criteria for parathyroid carcinoma including uniform sheets of chief cells in a lobular pattern with fibrous trabeculae, evidence of capsular or vascular invasion, and mitotic figures within tumor parenchymal cells.[35]

The presence of metastatic deposits to either regional lymph nodes or distant organs confirms the diagnosis. Local recurrence with spread to contiguous structures in the neck is common. Approximately one-third of parathyroid carcinomas will present with distant metastases, most typically to the lungs (40%) (Figures 7–6 and 7–7), cervical lymph nodes (30%), and liver (10%) and less commonly to the bones (Figure 7–8), pleura, pancreas, or pericardium.

The diagnostic workup of patients for persistent or recurrent parathyroid carcinoma includes sestamibi radioactive scanning. Parathyroid cells contain a great deal of mitochondria that will preferentially concentrate sestamibi. Single-photon emission computed tomography with radioactive sestamibi gives a good

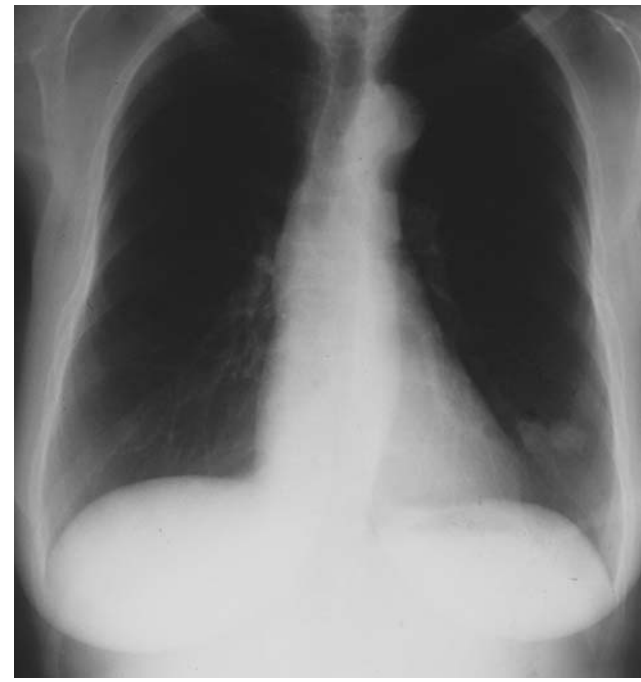


Figure 7–6. Posteroanterior chest radiograph of pulmonary metastases.

three-dimensional view of the location of the parathyroid tumor. Magnetic resonance imaging (MRI) of the neck can also be used to help explore anatomic relationships and tissue planes in the neck (Figure 7–9). One should also consider including a computed tomographic scan of the chest to look for the presence of pulmonary or mediastinal metastases (see Figure 7–7). An example of multiple resected pulmonary metastases is seen in Figure 7–10.

Staging definitions for parathyroid carcinoma have not been determined clearly. The typical tumor, node, metastasis schema used for most tumors does

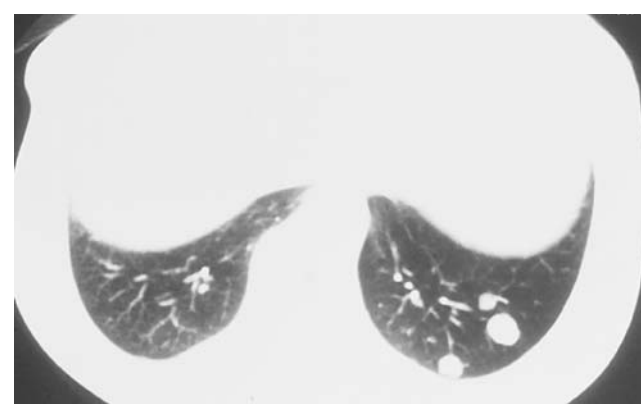


Figure 7–7. Computed tomography scan appearance of pulmonary metastases from parathyroid carcinoma.

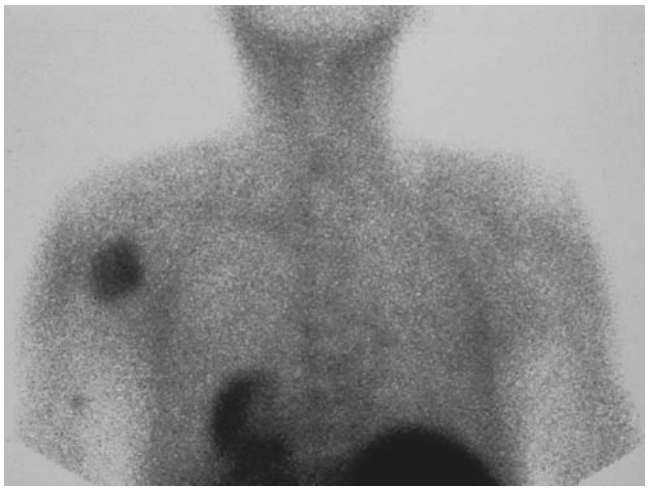


Figure 7–8. Positron emission tomograph demonstrating intense uptake in a parathyroid cancer metastasis located in the right humoral head.

not lead to clear correlations with survival in parathyroid carcinoma. It would appear that the extent of resection and the inherent biology of the underlying disease are more important determining factors. The natural history of the disease is determined by the severity of the underlying hyperparathyroidism and the underlying hypercalcemia. Uncontrolled hypercalcemia will result in severe end-organ damage, which will result in life-threatening complications.

Treatment for parathyroid carcinoma is largely surgical, and the most effective therapy is complete resection at the initial operation. There is some controversy as to the ideal extent of the resection that should be employed. All four parathyroid glands should be carefully explored and examined. Most authors agree that the primary surgery should remove the whole tumor en bloc, with the associated ipsilateral lobe of the thyroid and isthmus, as well as any structures that are directly invaded by the tumor, including the recurrent laryngeal nerve if necessary.[13] The capsule of the tumor should remain intact as rupture increases the likelihood of local seeding. The extent of nodal dissection remains controversial. Some authors feel that an extensive lymph node dissection should be undertaken. Most authors feel that because lymph node involvement is relatively uncommon in this disease, a prophylactic or extensive lateral lymph node dissection is not warranted.[37] An ipsilateral central neck dissection as well as resection of all abnormal nodes should be performed. If the diagnosis of parathyroid carcinoma is made postoperatively, with evidence of vascular or capsular invasion or persistent hypercalcemia, the neck should be re-explored with complete resection and ipsilateral central neck dissection.

Postoperatively, patients should have careful monitoring of serum calcium and parathyroid hormone every 3 months. Symptomatic hypocalcemia should be treated with supplemental calcium and vitamin D as necessary until recovery of normal remaining parathyroid glands. Recurrent hypercalcemia is evaluated promptly with localizing studies including neck ultrasonography and technetium Tc 99m sestamibi scanning. MRI is helpful for recurrent disease in the chest and mediastinum, and selective venous catheterization is useful for suspected

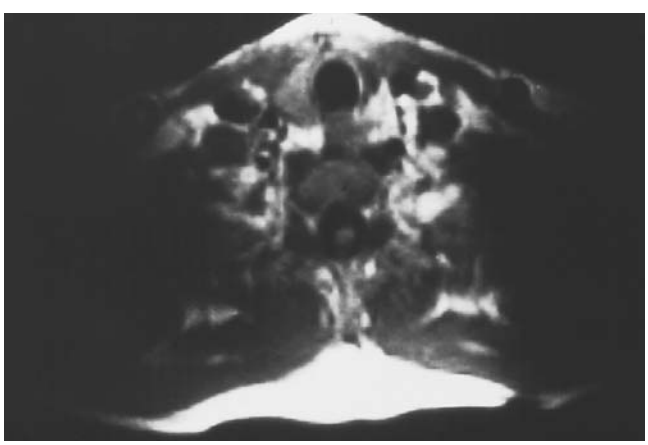


Figure 7–9. Magnetic resonance image of parathyroid mass.

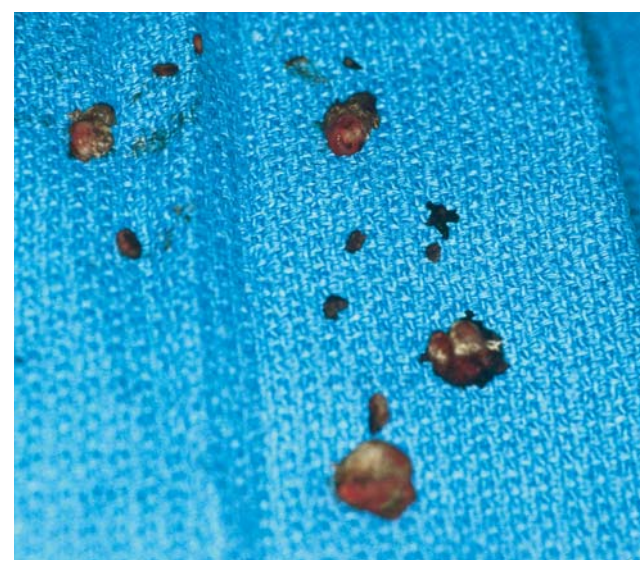


Figure 7–10. Gross specimen of resected metastases.

recurrence when localizing studies are negative. Recurrent tumor should be widely resected. Significant palliation of hypercalcemia may be provided by resection of distant metastases.[38]

The rarity of parathyroid carcinoma has not permitted the formal studying of either radiation therapy or chemotherapy as treatment modalities for the management of this diagnosis. The literature has several case reports of attempts at controlling parathyroid carcinoma with either single agents or combinations of agents. With rare exceptions, these reports suggest that parathyroid carcinoma is not sensitive to older chemotherapeutic agents.[39,40] Case reports have shown some partial responses to different regimens of dacarbazine, 5-fluorouracil, cyclophosphamide, methotrexate, doxorubicin, and lomustine.[41–43] The effectiveness of newer agents released in the past 5 years or so has not been formally evaluated.

The effectiveness of radiation therapy has not been formally evaluated in parathyroid carcinoma. Here, too, most of our information is gleaned from individual case reports. Once again, we are left with the general impression that radiation therapy is not particularly effective.[4,35] Newer techniques such as intraoperative radiation and three-dimensional conformal planning have not been evaluated to date. The role of these newer techniques may be worth studying further.

Hypercalcemia associated with parathyroid carcinoma must be managed aggressively. Once the diagnosis of hypercalcemia is made, the first step in management is to restore the depleted intravascular volume and to induce a sodium diuresis. For that purpose, patients should be treated agressively (200 to 300 cc/hour) with normal saline intravenous hydration. The use of loop diuretics such as furosemide should be postponed until the intravascular volume has been restored.

To achieve a fairly rapid reduction in the serum calcium, one can administer calcitonin (3 to 6 U/kg subcutaneously every 12 hours) and glucocorticoids (300 mg hydrocortisone). Calcitonin inhibits osteoclast-mediated bone resorption and increases urinary calcium excretion. Glucocorticoids inhibit gastrointestinal calcium absorption. The use of calcitonin by itself is unlikely to correct the calcium imbalance fully, but it will decrease the serum calcium by 2 to 4 mg/dL rapidly, allowing for initial stabilization. The long-term use of calcitonin to control hypercalcemia is limited by the development of tachyphylaxis. Glucocorticoids have a fairly delayed onset of action so that they are limited in the short term but help prevent or ameliorate the calcitonin tachyphylaxis.

One of the more effective ways to manage hypercalcemia is to use an intravenous bisphosphonate compound such as pamidronate. The bisphosphonate compounds bind competitively to the bony matrix and interfere with osteoclast-induced bone resorption. Pamidronate is quite effective at a dose of 90 mg intravenously. The effects of pamidronate are noted within the first 24 hours. If the serum calcium fails to decline after a first dose of pamidronate, it can be repeated. More recently, zoledronic acid has been compared with pamidronate in the management of hypercalcemia of malignancy. Double-blind, randomized clinical trials have shown that a 4 to 8 mg rapid infusion (over 8 minutes) of zoledronic acid is equivalent to a 2- to 4-hour 60 to 90 mg infusion of pamidronate.

The prognosis of parathyroid carcinoma remains reasonable. The National Cancer Database recently reported 5-year survival rates of 85% and 50% at 10 years.[7] The best prognosis is achieved with early diagnosis and complete resection during the initial operation. The median time to local recurrence is 3 years.[13] Although these numbers are optimistic, their accuracy remains to be verified in formal clinical trials. Such trials will need to involve many institutions with an interest in this disease to enrol sufficient numbers of patients with this rare but debilitating and sometimes lethal disorder.

REFERENCES

1. Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: an update and review. World J Surg 1991;15:738–44.
2. Obara T, Fujimoto Y. Functioning parathyroid carcinoma: clinicopathologic features and rational treatment. Semin Surg Oncol 1997;13:134–41.
3. Favia G, Lumachi F, Polistina F, D'Amico DF. Parathyroid carcinoma: sixteen new cases and suggestions for current management. World J Surg 1998;22:1225–30.
4. Cohn K, Silverman M, Corrado J, Sedgewick C. Parathyroid carcinoma: the Lahey clinic experience. Surgery 1985;98: 1095–100.
5. Hakaim AG, Esselstyn CB Jr. Parathyroid carcinoma: 50-year experience at The Cleveland Clinic Foundation. Cleve Clin J Med 1993;60:331–5.

6. Wang CA, Gaz RD. Natural history of parathyroid carcinoma: diagnosis, treatment and results. Am J Surg 1985;149: 522–7.
7. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1999;86:538–44.
8. Wynne AG, van Heerden J, Carney JA, Fitzpatrick LA. Parathyroid carcinoma: clinical and pathological features in 43 patients. Medicine 1992;71:197–205.
9. Heath H 3rd, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity and potential economic impact in a community. N Engl J Med 1980;302: 189–93.
10. Silverberg SJ, Shane E, de la Cruz L, et al. Skeletal disease in primary hyperparathyroidism. J Bone Miner Res 1989; 4:283–91.
11. Silverberg SJ, Shane E, Jacobs TP, et al. Nephrolithiasis and bone involvement in primary hyperparathyroidism. Am J Med 1990;89:327–34.
12. Levin KE, Galante M, Clark OH. Parathyroid carcinoma versus parathyroid adenoma in patients with profound hypercalcemia. Surgery 1987;101:649–60.
13. Sandelin K, Tullgren O, Farnebo LO. Clinical course of metastatic parathyroid cancer. World J Surg 1994;18:594–8.
14. Christmas TJ, Chapple CR, Noble JG, et al. Hyperparathyroidism after neck irradiation. Br J Surg 1988;75:873–4.
15. Ireland JP, Fleming SJ, Levison DA, et al. Parathyroid carcinoma associated with chronic renal failure and previous radiotherapy to the neck. J Clin Pathol 1985;38:1114–8.
16. Hsi ED, Zukerberg LR, Yang WI, Arnold A. Cyclin D1/PRAD1 expression in parathyroid adenomas: an immunohistochemical study. J Clin Endocrinol Metab 1996;81:1736–9.
17. Tominaga Y, Tsuzuki T, Uchida K, et al. Expression of PRAD1/cyclin D1, retinoblastoma gene products, and Ki67 in parathyroid hyperplasia caused by chronic renal failure versus primary adenoma. Kidney Int 1999;55: 1375–83.
18. Vasef MA, Brynes RK, Sturm M, et al. Expression of cyclin D1 in parathyroid carcinomas, adenomas, and hyperplasias: a paraffin immunohistochemical study. Mod Pathol 1999;12:412–6.
19. Arnold A, Kim HG, Gaz RD, et al. Molecular cloning and chromosomal mapping of DNA rearranged with the parathyroid hormone gene in a parathyroid adenoma. J Clin Invest 1989;83:2034–40.
20. Mallya SM, Arnold A. Cyclin D1 in parathyroid disease. Front Biosci 2000;5:D367–71.
21. Streeten EA, Weinstein LS, Norton JA, et al. Studies in a kindred with parathyroid carcinoma. J Clin Endocrinol Metab 1992;75:362–6.
22. Wassif WS, Moniz CF, Friedman E, et al. Familial isolated hyperparathyroidism: a distinct genetic entity with increased risk of parathyroid cancer. J Clin Endocrinol Metab 1993;77:1485–9.
23. Imanishi Y. Molecular pathogenetic analysis of parathyroid carcinoma. J Bone Miner Res 1999;14 Suppl 1:S405.
24. Dinnen JS, Greenwoood RH, Jones JH, et al. Parathyroid carcinoma in familial hyperparathyroidism. J Clin Pathol 1977;30:966–75.
25. Szabo J, Heath B, Hill VM, et al. Hereditary hyperparathyroidism-jaw tumor syndrome: the endocrine tumor gene HRPT2 maps to chromosome 1q21-q31. Am J Hum Genet 1995;56:944–50.
26. Cryns VL, Thor A, Xu HJ, et al. Loss of the retinoblastoma tumor-suppressor gene in parathyroid carcinoma. N Engl J Med 1994;330:757–61.
27. Subramaniam P, Wilkinson S, Shepherd JJ. Inactivation of retinoblastoma gene in malignant parathyroid growths: a candidate genetic trigger? Aust N Z J Surg 1995;65:714–6.
28. Kytola S, Farnebo F, Obara T, et al. Patterns of chromosomal imbalances in parathyroid carcinomas. Am J Pathol 2000; 157:579–86.
29. Hakim JP, Levine MA. Absence of p53 point mutations in parathyroid adenoma and carcinoma. J Clin Endocrinol Metab 1994;78:103–6.
30. Cryns VL, Rubio MP, Thor AD, et al. p53 abnormalities in human parathyroid carcinoma. J Clin Endocrinol Metab 1994;78:1320–4.
31. Agarwal SK, Schrock E, Kester MB, et al. Comparative genomic hybridization analysis of human parathyroid tumors. Cancer Genet Cytogenet 1998;106:30–6.
32. Funa K, Papanicolaou V, Juhlin C, et al. Expression of platelet-derived growth factor β-receptors on stromal tissue cells in human carcinoid tumors. Cancer Res 1990; 50:748–53.
33. Haghighi P, Astarita RW, Wepsic HT, Wolf PL. Concurrent primary parathyroid hyperplasia and parathyroid carcinoma. Arch Pathol Lab Med 1983;107:349–50.
34. Desch CE, Arsensis G, Woolf PD, et al. Parathyroid hyperplasia and carcinoma within one gland. Am J Med 1984; 77:131–4.
35. Schantz A, Castleman B. Parathyroid carcinoma: a study of 70 cases. Cancer 1973;31:600–5.
36. Abbona GC, Papotti M, Gasparri G, Bussolati G. Proliferative activity in parathyroid tumors as detected by Ki-67 immunostaining. Hum Pathol 1995;26:135–8.
37. Vetto JT, Brennan MF, Woodruf J, Burt M. Parathyroid carcinoma: diagnosis and clinical history. Surgery 1993;114: 882–92.
38. Obara T, Okamoto T, Ito Y, et al. Surgical and medical management of patients with pulmonary metastasis from parathyroid carcinoma. Surgery 1993;114:1040–8.
39. Anderson BJ, Samaan NA, Vassilopoulou-Sellin R, et al. Parathyroid carcinoma: features and difficulties in diagnosis and management. Surgery 1983;94:906–15.
40. Grammes CF, Eyerly RC. Hyperparathyroidism and parathyroid carcinoma. South Med J 1980;73:814–6.
41. Bukowski RM, Sheeler L, Cunningham J, Esselstyn C. Successful combination chemotherapy for metastatic parathyroid carcinoma. Arch Intern Med 1984;144:399–400.
42. Calandra DB, Chejfec G, Foy BK, et al. Parathyroid carcinoma: biochemical and pathologic response to DTIC. Surgery 1984;96:1132–7.
43. Chahinian AP, Holland JF, Nieburgs HE, et al. Metastatic nonfunctioning parathyroid carcinoma: ultrastructural evidence of secretory granules and response to chemotherapy. Am J Med Sci 1981;282:80–4.

8

Primary Hyperaldosteronism

WEN T. SHEN, MD
QUAN-YANG DUH, MD

Primary hyperaldosteronism affects approximately 1 of every 200 hypertensive patients and is characterized by hypertension, hypokalemia, elevated plasma aldosterone, and low plasma renin activity.[1,2] The most common cause of primary hyperaldosteronism is an aldosterone-secreting adrenal adenoma; other causes include bilateral adrenal hyperplasia and rarer entities such as glucocorticoid-responsive hyperaldosteronism, primary unilateral adrenal hyperplasia, and adrenal cortical carcinoma. Primary hyperaldosteronism caused by an adrenal adenoma is a surgically correctable disease.

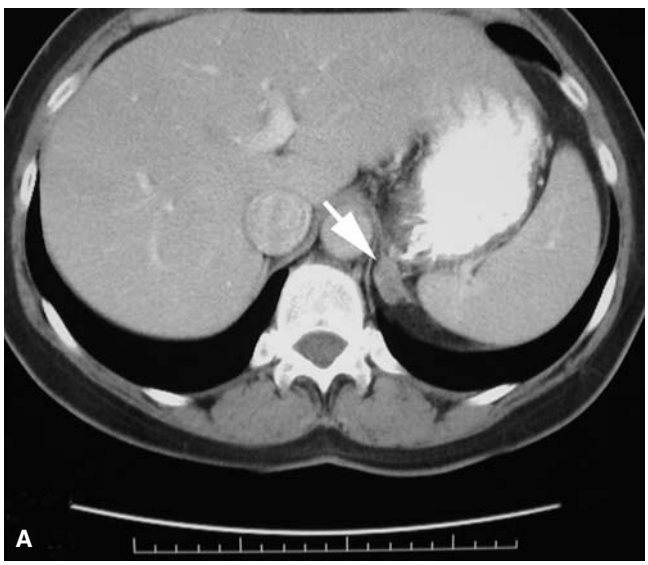
The syndrome of primary hyperaldosteronism was first described in 1954 by Jerome Conn of the University of Michigan.[2] Conn's first patient was a 34-year-old hypertensive woman who had severe hypokalemia, metabolic alkalosis, and elevated urinary aldosterone. Conn reasoned that the patient's condition was attributable to mineralocorticoid excess and recommended adrenalectomy to correct her metabolic abnormalities. The patient's operation was performed by urologist William Baum, who identified and resected a right adrenal cortical adenoma measuring 4 cm. Following this operation, the patient's biochemical abnormalities resolved, and she became normotensive over time. The outcome of this and subsequent cases led Conn to recommend electrolyte testing in hypertensive patients and adrenalectomy in those with elevated aldosterone levels; in the following years, primary hyperaldosteronism became recognized worldwide as a cause of surgically correctable hypertension. The disease is still referred to as Conn's syndrome by many physicians.

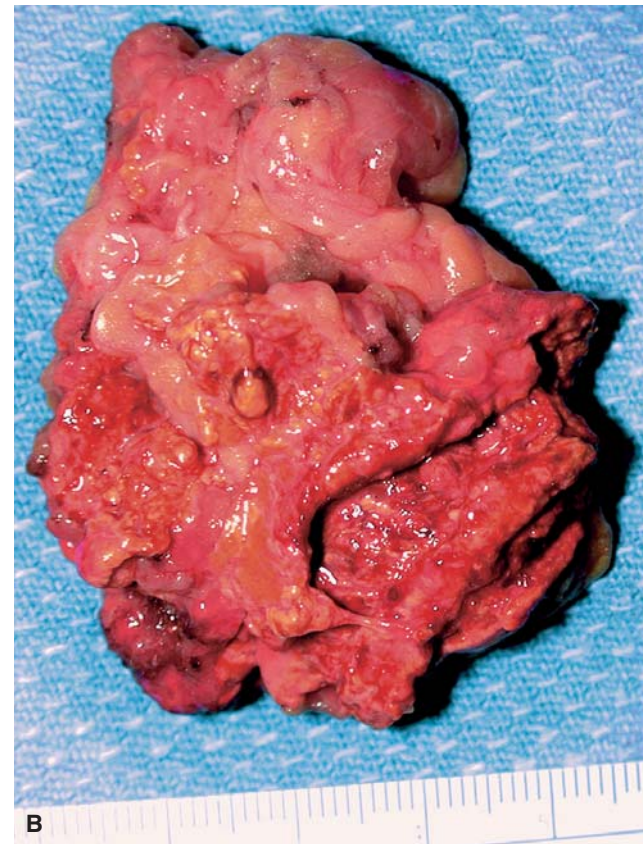
In the decades that followed Conn's initial work in the 1950s, primary hyperaldosteronism was diagnosed, and the distinction between adenoma and hyperplasia was made largely on the basis of biochemical tests. However, recent improvements in computed tomography (CT) have facilitated the identification of adrenal tumors and have altered the traditional diagnostic algorithms used in the workup of primary hyperaldosteronism.[3] Currently, endocrinologists and surgeons use CT in close conjunction with biochemical tests in diagnosing and formulating a treatment plan for primary hyperaldosteronism (Figure 8–1). In addition, the introduction of laparoscopic adrenalectomy in the 1990s has altered the surgical approach to this disease.[4,5] In this chapter, we outline the clinical and biochemical features of primary hyperaldosteronism, review the currently recommended laboratory and radiographic diagnostic tests, and describe the approaches to surgical management of this disease; we also discuss the changes in the clinical presentation and workup of patients with primary hyperaldosteronism that have been observed over the past decade with improvements in CT and the introduction of laparoscopic adrenalectomy.

DEMOGRAPHICS AND CLINICAL FEATURES

Primary hyperaldosteronism typically affects patients between 30 and 50 years of age and is twice as common in women as in men.[1] In recent studies, the disease affects up to 5% of patients evaluated in hypertension clinics.[1,2] These patients usually present with hypertension of variable severity and duration that is indistinguishable from hypertension caused by other diseases and often exhibit symptoms and signs of hypokalemia (muscle weakness, muscle cramps,

Figure 8–1. A 45-year-old woman with a 4-year history of severe hypertension. Workup showed a serum aldosterone level of 86, a renin activity level of 0.4, and a ratio of 215. A thin-cut computed tomographic scan showed a homogeneous 2 cm left adrenal tumor (*arrow*) and a normal right adrenal gland. *A*, She underwent a laparoscopic left adrenalectomy. Pathology showed a 2 cm adrenal cortical adenoma with focally prominent zona glomerulosa consistent with an aldosteronoma. *B*, Her hypertension improved after the operation with no need for medication.





electrocardiographic changes). In some cases, the patients have been worked up for other causes of hypertension and are usually taking antihypertensive medications. Eating black licorice can mimic primary hyperaldosteronism. Primary hyperaldosteronism almost always occurs sporadically but, in rare cases, may be associated with other endocrine disorders, including hyperparathyroidism, prolactinoma, and multiple endocrine neoplasia (MEN) type I.

We recently reviewed the medical records of 42 patients with surgically correctable primary hyperaldosteronism who were treated in the 1990s[6]; interestingly, our patient demographic profiles were markedly different from those of previous studies. The gender breakdown of our 42 patients included 29 men and 13 women, a complete reversal of typical gender ratios seen in this disease. In addition, the median age of the patients in our series was 50 years (range 23 to 72 years), which is slightly higher than the age of patients reported by other authors. These differences in demographics may have been a result of our small sample size but could also reflect changing patterns in the diagnosis and selection of patients for surgical treatment. High-resolution CT has facilitated the localization of adrenal adenomas (Figure 8–2), which has resulted in the diagnosis of patients with tumors that may have previously been missed; surgeons may thus be operating on a different patient population with this disease than in past decades.[3] In addition, the introduction of laparoscopic adrenalectomy may have altered the referral patterns of primary care physicians and endocrinologists[4,5]; these physicians may perceive the laparoscopic procedure to be less invasive and thus less dangerous for patients and may therefore be more willing to refer older patients and patients with less severe disease, patients whom they would previously have treated with medications.

PATHOLOGY

Approximately 65 to 75% of cases of primary hyperaldosteronism are caused by a solitary aldosterone-secreting adrenal adenoma. These adenomas are usually small (< 2 cm in diameter), encapsulated tumors of the adrenal cortex. On gross examination, the adenomas appear bright golden yellow in color;

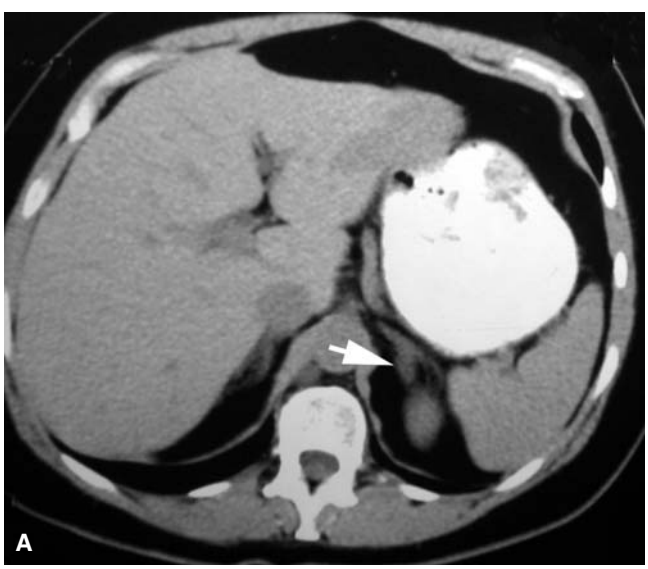
on histologic examination, lipid-laden cortical cells are seen. In previous decades, the radiologic diagnosis of aldosterone-secreting adenomas was difficult because of the relatively small size of these tumors, but the introduction of high-resolution focused CT (3 mm sections) has facilitated the identification of aldosteronomas (Figure 8–3). The small size of aldosterone-secreting adenomas also makes them ideal tumors for resection via laparoscopic adrenalectomy.[4–7]

Twenty-five to 30% of cases of primary hyperaldosteronism are caused by bilateral adrenal hyperplasia (also called idiopathic hyperaldosteronism). This condition is usually characterized by areas of macro- or micronodules interspersed throughout both adrenal glands. Patients with bilateral adrenal hyperplasia rarely improve in hypertension or biochemical abnormalities following surgery, unless both adrenal glands are removed, and are best managed with medical treatment, whereas patients with adenomas are best treated with surgical resection. Thus, the accurate differentiation between unilateral and bilateral disease is a crucial step in the selection of treatment modalities for patients with primary hyperaldosteronism.[1,2,8]

Other rarer causes of primary hyperaldosteronism include glucocorticoid-responsive hyperaldosteronism, primary unilateral adrenal hyperplasia, and adrenal cortical carcinoma. Glucocorticoid-responsive hyperaldosteronism is an uncommon familial condition in which adrenocorticotropic hormone (ACTH) stimulation results in the hypersecretion of aldosterone because of a specific genomic mutation that places the ACTH-responsive promoter before the aldosterone synthase. Administration of exogenous glucocorticoids suppresses ACTH and thus suppresses the hypersecretion of aldosterone.

DIAGNOSIS

Aldosterone facilitates the exchange of sodium for potassium in the distal nephron and plays a key role in the regulation of the body's fluid and electrolyte composition. The secretion of aldosterone from the adrenal cortex is normally determined by the renin-angiotensin system in response to changes in the



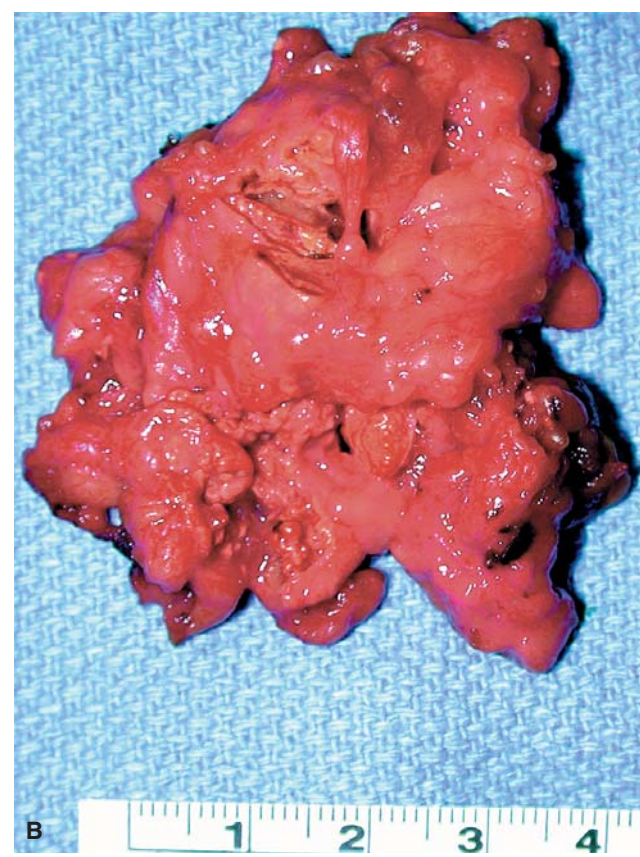
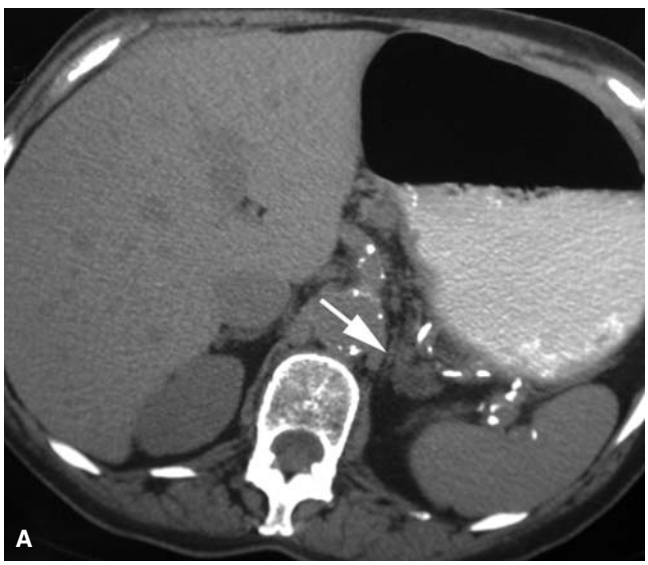
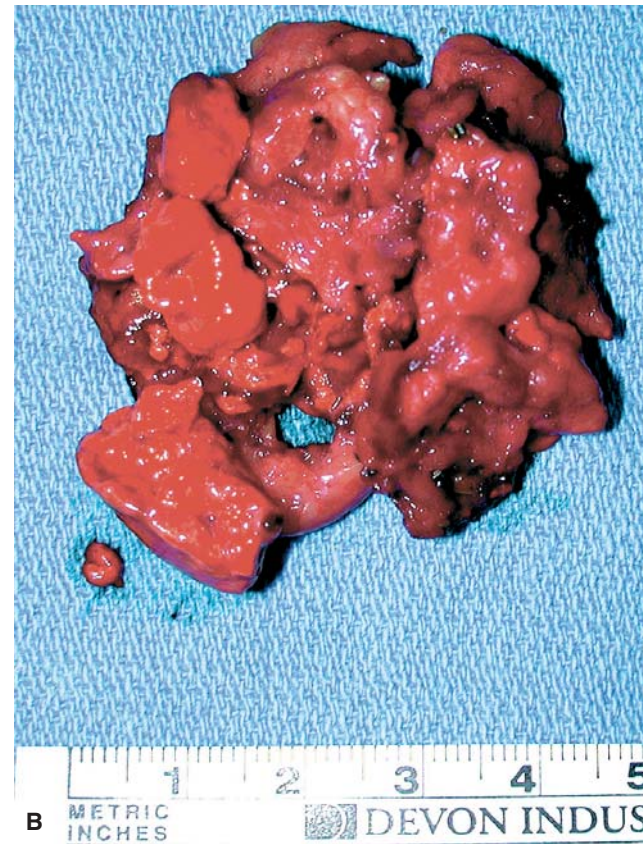


Figure 8–2. A 50-year-old woman with chronic severe hypertension and hypokalemia. Workup showed a serum aldosterone level of 20, a renin activity level of 0.4, and a ratio of 50. A thin-cut computed tomographic scan showed a homogeneous 1.5 cm left adrenal tumor in the posterior limb (*arrow*) and a normal right adrenal gland. *A*, She underwent a laparoscopic left adrenalectomy. Pathology showed a 1.5 cm adrenal cortical adenoma and micronodules with clear fascicular-type cells consistent with cortical hyperplasia. *B*, Her hypertension improved after the operation with no need for medication.

Figure 8–3. A 70-year-old woman with chronic severe hypertension and hypokalemia. Workup showed a serum aldosterone level of 24, a renin activity level of 0.27, and a ratio of 88. A thin-cut computed tomographic scan showed a 1.8 cm left adrenal tumor (*arrow*) and a normal right adrenal gland. *A*, She underwent a laparoscopic left adrenalectomy. Pathology showed adrenal cortical adenoma and nodular adrenal cortical hyperplasia. *B*, Her hypertension improved after the operation with fewer medications required.





body's serum sodium concentration. Hypersecretion of aldosterone leads to decreased serum potassium levels, increased body sodium, and resultant hypertension. Through negative feedback, it also lowers renin production from the kidneys. The biochemical hallmarks of primary hyperaldosteronism are hypokalemia, elevated plasma aldosterone, and low plasma renin activity. Secondary hyperaldosteronism is characterized by elevated plasma renin activity in response to an extra-adrenal stimulus for mineralocorticoid secretion and is usually seen in the setting of renal vascular disease or in patients treated with certain antihypertensive medications.[2]

Primary hyperaldosteronism should be suspected in patients presenting with hypertension and hypokalemia (potassium ≤ 3.2 mg/dL). In most cases, the diagnosis of primary hyperaldosteronism is delayed for months to years, and these patients will usually be taking one or more antihypertensive medications.[1,2] Because some of these medications (diuretics, angiotensin-converting enzyme inhibitors) may affect the renin-angiotensin system, patients undergoing workup for primary hyperaldosteronism should stop their antihypertensive medications for at least 2 weeks prior to biochemical testing. This is usually not dangerous as malignant hypertension is rare in these patients. The finding of elevated plasma aldosterone and decreased plasma renin activity in a hypertensive patient with hypokalemia is highly suggestive of primary hyperaldosteronism; a plasma aldosterone-to-plasma renin activity ratio of greater than 30 to 1 is considered by many to be diagnostic for this disease. Hypokalemia following a sodium challenge (1 g sodium chloride with meals for 4 days) is also characteristic of primary hyperaldosteronism.[1]

Differentiating between solitary adenoma and bilateral adrenal hyperplasia in patients with primary hyperaldosteronism is of utmost importance because adenomas are generally responsive to surgical treatment, whereas hyperplasia is best managed medically (Figure 8–4).[8] In previous decades, endocrinologists relied on various stimulatory tests to differentiate between adenoma and hyperplasia; adenomas tend to secrete aldosterone autonomously, whereas hyperplasias appear to retain normal control by the renin-angiotensin system. The most com-

monly used stimulatory test is the measurement of plasma aldosterone levels in response to postural change.[9] In this test, the plasma aldosterone level is first measured while the patient is in the supine position; the plasma aldosterone is then measured again after the patient has been upright for 4 hours. In patients with hyperplasia, the plasma aldosterone level will typically increase after standing because of the normal renin-angiotensin system control, whereas patients with an aldosterone-secreting adenoma will exhibit a paradoxical decrease or no change in plasma aldosterone level because the tumor is autonomously functioning. Despite the widespread use of postural stimulation studies in past decades, this test unfortunately results in a high false-negative rate in patients with adenomas (from 15 to 40% in various reports) and thus cannot be relied on as the single diagnostic test for differentiating between hyperplasia and adenomas in patients with primary hyperaldosteronism. Improved localization studies within the past decade have facilitated the identification of adrenal tumors and have reduced the role of stimulatory biochemical testing in the differentiation between adenomas and hyperplasia in patients with primary hyperaldosteronism.

All patients who are diagnosed with primary hyperaldosteronism on the basis of biochemical tests should undergo a localization study to distinguish between adrenal adenoma and hyperplasia. High-resolution (3 mm sections) abdominal CT scanning is the initial localization study of choice (see Figures 8–1 to 8–4).[3] The sensitivity of CT in identifying adrenal adenomas in patients with primary hyperaldosteronism ranges from 82 to 97%. The typical appearance of an aldosteronoma on CT scan is a unilateral, homogeneous tumor measuring between 0.5 and 2 cm in diameter. Although CT is highly sensitive for identifying adrenal adenomas, it cannot be used alone to diagnose hyperplasia. Patients with bilateral adrenal tumors identified on CT, as well as those with no enlargement of their adrenal glands, should undergo further localization studies. We recommend the measurement of plasma aldosterone levels via selective adrenal vein catheterization to differentiate bilateral hyperplasia from a small unilateral adenoma in patients with negative or equivocal CT scans.[10,11] Cortisol must be measured concurrently with aldosterone during the adrenal venous sampling to correct for the position of the catheter. Other authors have recommended the use of the NP-59 (iodomethylnorcholesterol) scan, which is an adrenal isotope scan using radiolabeled iodine.[3] Prior to undergoing NP-59 scanning, patients require suppression of the normal adrenal cortex with dexamethasone as well as thyroid blockade to prevent iodine uptake in the thyroid gland. Because the accuracy of NP-59 is lower for adenomas smaller than 1 cm in diameter, it is considered to be less useful in patients who have a negative abdominal CT scan.

SURGICAL TREATMENT OF PRIMARY HYPERALDOSTERONISM

The treatment of choice for patients with primary hyperaldosteronism caused by an aldosterone-secreting adrenal adenoma is surgical resection. Preoperative preparation of patients for adrenalectomy should include correction of hypokalemia and control of hypertension. Spironolactone, a competitive antagonist of aldosterone, is an effective agent for controlling blood pressure and also helps to increase serum potassium levels; oral potassium supplements can be used in conjunction with spironolactone to achieve normokalemia. A good blood pressure response to spironolactone is also an excellent predictor of a good

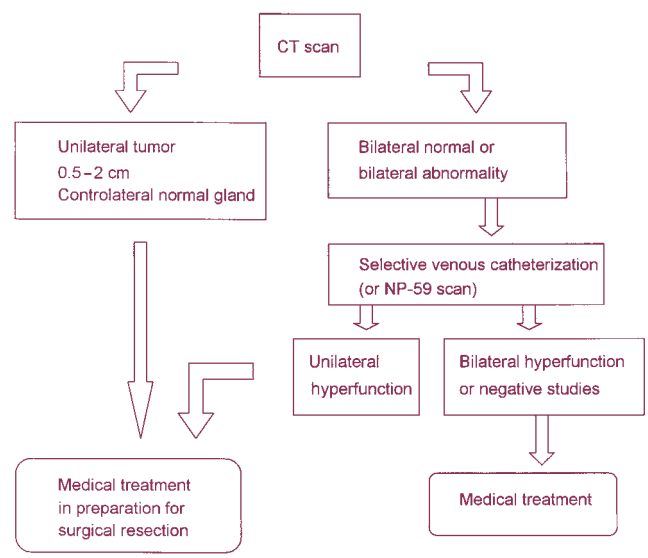


Figure 8–4. Algorithm for the diagnosis of primary hyperaldosteronism and differentiation between adenoma and hyperplasia. CT = computed tomography.

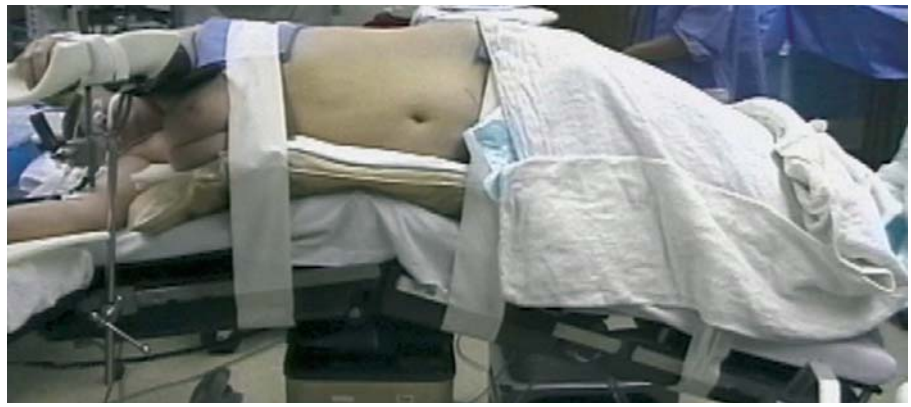


Figure 8–5. Intraoperative photograph of a laparoscopic adrenalectomy.

response to adrenalectomy. An alternative medication to spironolactone is amiloride, which is a potassium-sparing diuretic. Patients may require other antihypertensive medications if their hypertension is refractory to spironolactone or amiloride. Some patients may benefit from a sodium-restricted diet.

In previous decades, the favored surgical approach to resection of aldosterone-secreting adenomas was unilateral open adrenalectomy, using either a posterior (Hugh-Young) or lateral flank incision. The introduction of laparoscopic adrenalectomy in 1992 dramatically altered the surgical approach to primary hyperaldosteronism.[4–6,12,13] Currently, unilateral laparoscopic adrenalectomy is the procedure of choice for resection of aldosteronomas (Figure 8–5). These tumors are well suited for laparoscopic resection because they are relatively small and are almost always benign, and their location is usually known prior to operation from CT or other localization studies. The advantages of laparoscopic adrenalectomy include smaller incisions, decreased postoperative pain, fewer incisional hernias, and shorter duration of hospitalization. In our recent study comparing patients who underwent laparoscopic adrenalectomy with patients who underwent open adrenalectomy for primary hyperaldosteronism, we found that laparoscopic adrenalectomy resulted in fewer postoperative complications than open adrenalectomy.[6] In addition, patients undergoing laparoscopic adrenalectomy were equally likely to improve in blood pressure (≅ 75%) and hypokalemia (98%) when compared with patients treated with the open technique.

The technique for laparoscopic adrenalectomy has been well described in other publications. Aldosteronomas may be resected laparoscopically either by the posterior or the lateral approach.[14] The choice of approach depends largely on surgeon preference and experience. Regardless of the approach that is selected for laparoscopic adrenalectomy, this operation should be performed by an experienced laparoscopic surgeon.

POSTOPERATIVE OUTCOMES

Following unilateral adrenalectomy for primary hyperaldosteronism caused by an adenoma, patients normally do not require corticosteroid or electrolyte replacement. There is usually minimal blood loss during and after the operation, and postoperative fluid imbalances are usually not severe.[12] A rare patient will experience transient aldosterone deficiency following adrenalectomy if the normal contralateral adrenal gland was suppressed by the adenoma; this can be corrected with administration of exogenous aldosterone (fludrocortisone 0.1 mg/d orally). Most patients who have been well prepared with spironolactone prior to operation need to stay in the hospital only overnight.

The majority of patients who undergo adrenalectomy for the treatment of primary hyperaldosteronism will correct their blood pressure and electrolyte abnormalities.[6,7,12,13] Hypertension may not correct immediately and, in some cases, may persist for a year or more following operation before becoming normal. In our recent series, 88% of patients became normotensive following operation and did not require antihypertensive medications.[6] Serum potassium values were normal and ranged from 3.5 to 4.9 mg/dL following operation in this series of patients.

CONCLUSION

The hallmarks of primary hyperaldosteronism are hypertension, hypokalemia, elevated plasma aldosterone, and decreased plasma renin activity. The cause of primary hyperaldosteronism is an adrenal adenoma in 65 to 75% of cases; bilateral hyperplasia is the cause in the majority of the other cases. The diagnosis of primary hyperaldosteronism is made by demonstrating an increased plasma aldosterone level and low plasma renin activity level (or plasma aldosterone/plasma renin activity ratio of greater than 30:1). High-resolution CT scanning of the abdomen will differentiate between adenoma and hyperplasia in most cases; the differentiation between adenoma and hyperplasia is important because adenomas are best treated with surgical resection, whereas hyperplasias are best managed medically. Laparoscopic unilateral adrenalectomy has become the surgical treatment of choice in patients with primary hyperaldosteronism caused by an aldosterone-secreting adrenal adenoma.

REFERENCES

1. Blumenfeld JD, Sealey JE, Schlussel Y, et al. Diagnosis and treatment of primary hyperaldosteronism. Ann Intern Med 1994;121:877–85.
2. Ganguly A. Primary aldosteronism. N Engl J Med 1998; 339:1828–34.
3. Bornstein SR, Stratakis CA, Chrousos GP. Adrenocortical tumors: recent advances in basic concepts and clinical management. Ann Intern Med 1999;130:759–71.
4. Gagner M, Heniford BT, Pharand D, et al. Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. Ann Surg 1997;226:238–47.
5. Staren ED, Prinz RA. Adrenalectomy in the era of laparoscopy. Surgery 1996;120:706–11.
6. Shen WT, Lim RC, Siperstein AE, et al. Laparoscopic versus open adrenalectomy for the treatment of primary hyperaldosteronism. Arch Surg 1999;134:628–32.
7. Celen O, O'Brien MJ, Melby JC, Beazley RM. Factors influencing outcome of surgery for primary aldosteronism. Arch Surg 1996;131:646–50.
8. Gleason PE, Weinberger MH, Pratt JH, et al. Evaluation of diagnostic tests in the differential diagnosis of primary aldosteronism: unilateral adenoma versus bilateral micronodular hyperplasia. J Urol 1993;150:1365–8.
9. Feltynowski T, Ignatowska-Switalska H, Wocial B, et al. Postural stimulation test in patients with aldosterone producing adenomas. Clin Endocrinol 1994;41:309–14.
10. Sheaves R, Goldin J, Reznek RH, et al. Relative value of computed tomography scanning and venous sampling in establishing the cause of primary hyperaldosteronism. Eur J Endocrinol 1996;134:308–13.
11. Young WF, Stanson AW, Grant CS, et al. Primary aldosteronism: adrenal venous sampling. Surgery 1996;120:913–20.
12. Lo CY, Tam PC, Kung AWC, et al. Primary aldosteronism: results of surgical treatment. Ann Surg 1996;224:125–30.
13. Weigel RJ, Wells SA, Gunnells JC, Leight GS. Surgical treatment of primary hyperaldosteronism. Ann Surg 1994;219: 347–52.
14. Duh QY, Siperstein AE, Clark OH, et al. Laparoscopic adrenalectomy: comparison of the lateral and posterior approaches. Arch Surg 1996;131:870–6.

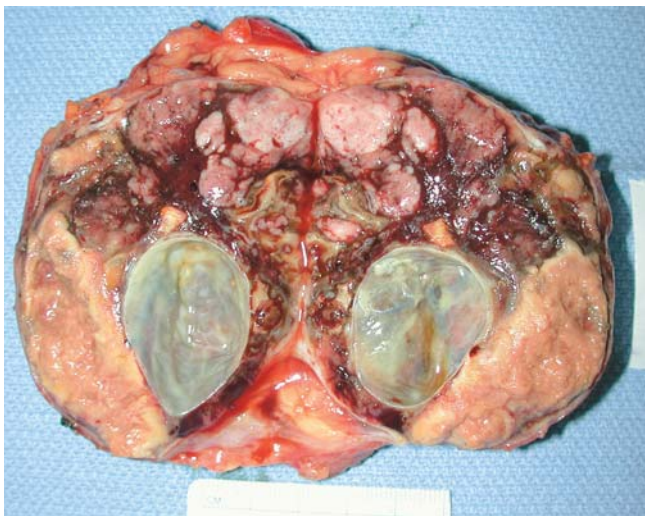


Figure 9–2. Cut surface of the right adrenal pheochromocytoma specimen showing areas of necrosis and cysts. Courtesy of Quan-Yang Duh, MD.

normetanephrine excretion in 1958.[1] Initially, fluorometric assays were used but suffered from nonspecificity. More recently, high-pressure liquid chromatography (HPLC) with electrochemical detection has been used to determine urinary concentrations of fractionated catecholamines and metanephrines (see below).

Surgical techniques progressed from open laparotomy to unilateral posterior or flank approaches, with the aid of preoperative localization with computed tomography (CT) or magnetic resonance imaging (MRI). More recently, laparoscopic removal of most pheochromocytomas has become possible, further reducing perioperative morbidity (see below).

CATECHOLAMINE BIOSYNTHESIS AND CATABOLISM

Catecholamines are molecules with a catechol nucleus (benzene with two hydroxyl side groups) plus a side chain with an amine.[1] Catecholamines include dopamine, epinephrine, and norepinephrine.

Sympathetic nerves (paraganglia) and the adrenal medulla belong to a family of secretory cells characterized by amine and amine precursor uptake and decarboxylation (APUD). Sympathetic nerves and adrenal medullary cells actively take up tyrosine. Intracytoplasmic tyrosine is then converted to L-dihydroxyphenylalanine (dopa) by the enzyme tyrosine hydroxylase. Dopa is then changed to dopamine (L-dihydroxyphenylethylamine) by dopa decarboxylase. Dopamine enters granulated vesicles, where it is hydroxylated to norepinephrine by the enzyme dopamine β-hydroxylase. Norepinephrine is stored in the vesicle. The granulated storage vesicle migrates to the cell surface and secretes its contents via exocytosis. After secretion, most norepinephrine is avidly recycled back into the nerve via a reuptake mechanism. Normally, most circulating norepinephrine originates from nonsecretory diffusion out of nonadrenal sympathetic nerve cells.

Norepinephrine in storage vesicles can diffuse into the cytoplasm. In certain cells (particularly the adrenal medulla), norepinephrine is converted to epinephrine in the cytoplasm, catalyzed by 4-phenylethanolamine-*N*-methyltransferase (PNMT). (Once formed, epinephrine may then return to the vesicle, diffuse from the cell, or undergo catabolism.) The expression of PNMT is enhanced by cortisol, which is present in high concentrations in areas of the adrenal medulla, owing to venous blood flow from the adjacent adrenal cortex. This accounts for the fact that, in the normal human adrenal medulla, about 80% of the catecholamine content is epinephrine, whereas only 20% is norepinephrine. Serum epinephrine concentrations fall dramatically after resection of both normal adrenals, whereas norepinephrine concentrations do not decline.[1]

Catecholamines are metabolized quickly to inactive compounds (the metanephrines, VMA, conjugated catecholamines). This occurs as follows: excess intracellular norepinephrine is inactivated primarily by intramitochondrial deamination by monoamine oxidase (MAO) and aldehyde dehydrogenase to an aldehyde that is then oxidized to 3,4-dihydroxymandelic acid; the latter is eventually converted via catechol *O*-methyltransferase (COMT) to VMA. Circulating norepinephrine is metabolized largely to normetanephrine by COMT, with the methyl donor being *S*-adenosylmethionine. COMT is an enzyme found in most tissues, especially blood cells, liver, kidney, and vascular smooth muscle. Epinephrine is similarly catabolized to metanephrine, which is then partly converted to VMA.

In normal individuals, the urine catecholamines/metabolites are approximately 50% metanephrines,

9

Pheochromocytoma and Paraganglioma

PAUL A. FITZGERALD, MD

HISTORY OF PHEOCHROMOCYTOMA

In 1886, Fränkel described bilateral adrenal tumors discovered at the autopsy of an 18-year-old woman who died suddenly following a year of retinitis and episodic palpitations, pounding heart, pallor, headaches, and vomiting. Her postmortem examination also revealed nephrosclerosis and myocardial hypertrophy.[1]

In 1896, Manasse demonstrated that such a tumor turned dark brown when exposed to chromium salts (the chromaffin reaction), a characteristic of adrenal medullary tissue; these tumors were subsequently termed "chromaffin" tumors. In 1901, the substance causing the chromaffin reaction was chemically identified as 3,4-dihydroxyphenyl-2-methylaminoethanol by two different researchers: Takamine, publishing in the *Journal of Physiology* in London, called the substance "adrenaline"; Aldrich, publishing in the *American Journal of Physiology*, coined the term "epinephrine."[2] In 1908, Alezais and Peyronin described chromaffin tumors of the paraganglia as "paragangliomas." In 1912, Pick introduced the term "pheochromocytoma," derived from the Greek words *phaios* (dark), *chromo* (color), and *kytos* (cell). It refers to the histologic color change that characterizes most such tumors: dichromate fixatives (eg, Zenker's, Orth's, or Helly's) produce a yellowish-brown coloration of cells with neurosecretory granules. Cells containing epinephrine turn dark brown, whereas cells containing norepinephrine turn pale yellow.[3] A dilute Giemsa-Schmorl stain turns these cells green. Pheochromocytomas frequently become cystic and hemorrhagic (Figures 9–1 and 9–2).

Pheochromocytomas were first resected successfully in 1926 by Roux in Switzerland and by Mayo at the Mayo Clinic. In 1929, Rabin discovered a pressor substance in pheochromocytomas that could explain the clinical syndrome. In 1939, a patient with a pheochromocytoma was documented to have high blood levels of epinephrine.[4]

Ulf Svante von Euler, a pioneer in catecholamine research, discovered norepinephrine in the heart in 1946 and found that it was the neurotransmitter for the sympathetic nervous system. By 1950, von Euler and Engel reported the diagnostic usefulness of urinary epinephrine and norepinephrine in the diagnosis of pheochromocytoma. (In 1970, von Euler was awarded the Nobel Prize for Physiology.) In 1957, Armstrong reported the urinary excretion of vanillylmandelic acid (VMA), a urinary metabolite of catecholamines. LaBrosse described urinary

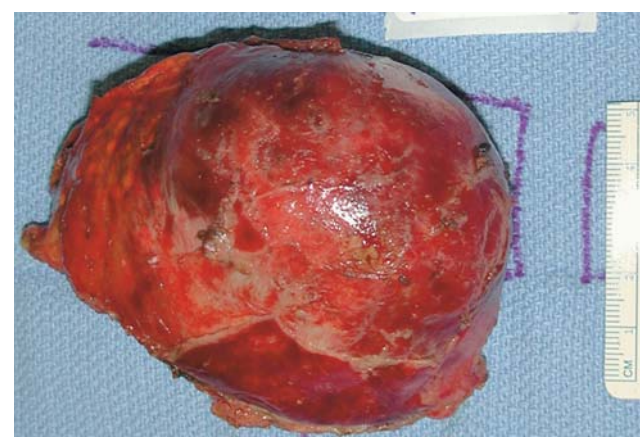


Figure 9–1. A 55-year-old man with chronically controlled hypertension suddenly developed multisystem failure ("pheocrisis") and was found to have a 9 cm right adrenal pheochromocytoma. Laparoscopic adrenalectomy was attempted but was converted to open because the tumor was too large. Courtesy of Quan-Yang Duh, MD.

35% VMA, 10% conjugated catecholamines and other metabolites, and < 5% free catecholamines.

CATECHOLAMINE ACTIONS

Dopamine is important mainly as a neurotransmitter and as a precursor to norepinephrine. Circulating dopamine is not normally a significant catecholamine; the presence of dopamine in the urine is largely attributable to high renal concentrations of dopa decarboxylase. At significant circulating levels, dopamine stimulates vascular D_1 receptors, causing vasodilatation and, particularly, increasing renal blood flow. Very high serum levels of dopamine are required to activate vascular alpha receptors sufficiently to cause vasoconstriction.

Norepinephrine is found in the adrenal medulla and the paraganglia, where it is stored in granulated vesicles. Norepinephrine is also found in brain and spinal cord nerve cells. However, most norepinephrine is found in the synaptic vesicles of postganglionic autonomic nerves in organs that have rich sympathetic innervation: the salivary glands, heart, vascular smooth muscle, liver, spleen, kidneys, and muscles. A sympathetic nerve may have up to 25,000 bulges along the length of its fibers; each synthesizes norepinephrine and stores it in adrenergic storage vesicles, adjacent to target cells.[1]

Norepinephrine's stimulation of α_1-adrenergic receptors increases the flux of calcium into the target cell. Alpha$_1$-adrenergic receptors are found in the vascular smooth muscle, heart, and pupillary dilator muscles; activation results in hypertension, some increased force of cardiac contraction, and pupillary dilation. It also stimulates sweating from nonthermoregulatory apocrine "stress" sweat glands (located variably on the palms, axillae, and forehead). Norepinephrine's activation of β-adrenergic receptors causes an increased flux of calcium into the target cell. Norepinephrine has great affinity for β_1-adrenergic receptors (increases cardiac contraction and rate); stimulation of heart rate is counteracted by simultaneous vagal stimulation. Norepinephrine has less affinity for β_2-adrenergic receptors (vasodilation, hepatic glycogenolysis). With higher norepinephrine levels, hypermetabolism and hyperglycemia are noted. Norepinephrine also activates β_3-adrenergic receptors (fat cells), causing lipolysis and increased serum levels of free fatty acids.

Epinephrine also stimulates α_1-adrenergic receptors, causing "stress" sweating, pupil dilatation, some increased force of cardiac contraction, and vasoconstriction in skin and kidneys. Epinephrine also activates β_1-receptors, increasing cardiac rate and force of contraction. However, simultaneous activation of β_2-receptors causes vasodilation in skeletal muscles. Thus, epinephrine has a variable effect on blood pressure, ranging from hypertension to hypotension (rare). Increased hepatic glycogenolysis causes hyperglycemia, which is usually mild. Lipolysis results in increased serum levels of free fatty acids. It also increases the basal metabolic rate. Epinephrine crosses the blood-brain barrier poorly, but hypothalamic stimulation occurs with high serum levels.[5] This causes unpleasant sensations, ranging from nervousness to an overwhelming feeling of impending doom. These manifestations are distinct from those of noncatecholamine amphetamines, which enter the central nervous system more readily and have other effects.[6]

NORMOTENSION DESPITE HIGH PLASMA NOREPINEPHRINE LEVELS

Some patients with pheochromocytoma are not hypertensive, despite having chronically elevated levels of serum catecholamines. This phenomenon is described by several terms: desensitization, tolerance, or tachyphylaxis. Desensitization can occur in certain patients who are homozygous for certain genetic polymorphisms of β_2-adrenergic receptors. Such genetic polymorphisms allow continued β_2-adrenergic–mediated vasodilation, thus counteracting the α-adrenergic pressor effects of circulating epinephrine and norepinephrine.[7] The adrenergic receptors may undergo sequestration, down-regulation, or phosphorylation.[6] Desensitization does not account for all patients who are normotensive in the face of elevated serum levels of norepinephrine; some of these patients can still have hypertensive responses to norepinephrine. Cosecretion of dopa may reduce blood pressure through a central nervous system action. Similarly, cosecretion of dopamine may directly dilate mesenteric and renal vessels and thus

modulate the effects of norepinephrine.[8] Adrenergic desensitization also appears to be one cause for the cardiovascular collapse that can occur abruptly following the removal of a pheochromocytoma in some patients.

PHEOCHROMOCYTOMA PHYSIOLOGY

Pheochromocytomas synthesize catecholamines at a high rate, up to 27 times the normal adrenal medulla.[9] Pheochromocytoma cells ordinarily contain more norepinephrine than epinephrine, the opposite of the normal adrenal medulla. In adults, about 90% of pheochromocytomas arise from the adrenal medulla. Pheochromocytomas that secrete epinephrine are even more likely to be located in the adrenal medulla. Paragangliomas rarely secrete epinephrine.

The serum concentration of catecholamines does not correlate well with the size of the tumor. This is attributable to several factors, including the fast production and secretion of catecholamines by small tumors and the slower secretion of catecholamines by larger tumors. Additionally, larger tumors tend to undergo necrosis and cystic degeneration (Figure 9–3).

The persistent oversecretion of catecholamines by most pheochromocytomas is likely owing to the lack of feedback inhibition on tyrosine kinase. Catecholamines are produced in quantities that exceed the vesicular storage capacity. Catecholamines outside the storage vesicles are subject to intracellular metabolism; the excess catecholamines and their metabolites diffuse out of the pheochromocytoma cell into the circulation.

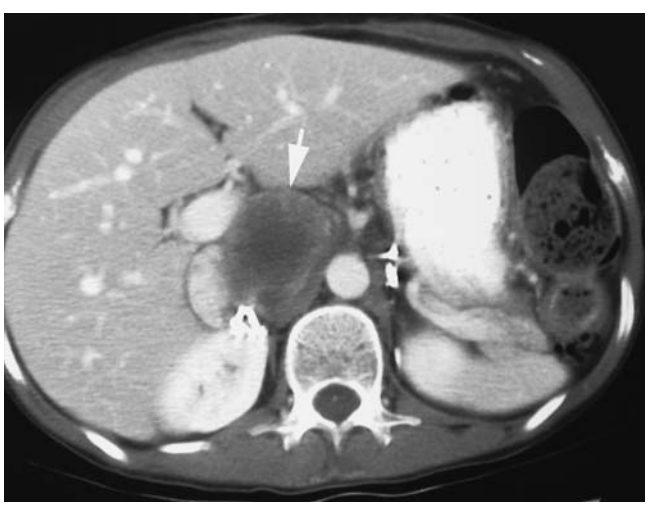


Figure 9–3. The abdominal computed tomographic scan shows a recurrent cystic right adrenal pheochromocytoma (*arrow*), medial to the inferior vena cava, in a 27-year-old woman with multiple endocrine neoplasia type IIB 1 year after bilateral adrenalectomy for pheochromocytoma. This cystic adrenal tumor was reresected successfully. Courtesy of Quan-Yang Duh, MD.

Paroxysms of severe hypertension occur in most patients with pheochromocytoma. Exocytosis of catecholamines from the pheochromocytoma appears to play a small role in such paroxysms, as evidenced by the minimal sympathetic innervation of pheochromocytomas. Instead, hypertensive crises can result from spontaneous hemorrhages within the tumor or from the release of catecholamine-rich blood from sinusoids within the tumor, caused by physical stimuli such as bending or twisting or micturition in patients with bladder paragangliomas and, of course, manipulation of such tumors during surgery.

Additionally, in the presence of the persistently high circulating levels of catecholamines in most patients with pheochromocytomas, the normal sympathetic nervous system may become saturated with catecholamines, owing to normal neuronal reuptake mechanisms. This may explain the paroxysms that are triggered by pain, emotional upset, intubation, anesthesia, or surgical skin incision. It may also account for the intermittent elevation in serum and urine catecholamines for 10 days or longer after the successful surgical resection of a pheochromocytoma.

Pheochromocytomas also secrete neuropeptide Y (NPY), a 36–amino acid oligopeptide that is a potent nonadrenergic vasoconstrictor and vascular growth factor. It is a constituent of neurosecretory granules and is cosecreted with norepinephrine. About 59% of adrenal pheochromocytomas secrete NPY during surgical resection. NPY appears to contribute to hypertension in most patients with pheochromocytoma.[10,11] However, few patients with paraganglioma secrete NPY.[12]

INCIDENCE OF PHEOCHROMOCYTOMA

Hypertension, defined as either a systolic or diastolic blood pressure over 140/90 mm Hg, is extremely common, affecting about 20% of adults

and over 50% of adults over age 60 years in the United States. It affects about 30% of blacks and about 72% of blacks over age 60 years.[13] The incidence of pheochromocytoma is estimated to be < 0.1% of the entire hypertensive population but is higher in those with moderate to severe hypertension. About two new cases per million people are discovered yearly. The reported prevalence in autopsy series varies from about 250 cases per million to 1,300 cases per million in a Mayo Clinic autopsy series.[13] Obviously, the great majority of pheochromocytomas are not discovered during life. Retrospectively, 61% of patients whose pheochromocytomas were discovered at autopsy were known to have had hypertension; about 91% had the typical but nonspecific symptoms associated with active pheochromocytomas. Pheochromocytomas occur in both sexes and at any age but are most common in the fourth and fifth decades.

MANIFESTATIONS OF PHEOCHROMOCYTOMA

At least 35% of pheochromocytomas cause death before the tumor is diagnosed at autopsy. This is attributable to the protean manifestations of pheochromocytoma. In one autopsy study of pheochromocytoma, a large number presented with nonclassic symptoms such as abdominal pain, vomiting, dyspnea, heart failure, or hypotension. Others presented with a fatal arrhythmia or stroke.[14]

Symptoms of Pheochromocytoma

Most adult patients have paroxysmal symptoms, lasting minutes to hours, consisting of headache (80%), perspiration (70%), and palpitations (60%); other symptoms are commonly present, such as anxiety (50%), a sense of dread, tremor (40%, with epinephrine-secreting tumors), or paresthesias. Recurrent chest discomfort, abdominal pain, and vomiting are also frequent symptoms. The abdominal pain may be caused by ischemic enterocolitis. Sweating (initially palms, head, and shoulders) usually occurs. Drenching sweats can occur, even in a cool environment, usually as an attack subsides. The reflex eccrine sweating that occurs later in an attack is thermoregulatory, dissipating heat that was acquired during prolonged vasoconstriction during a paroxysm. Constipation is common, and toxic megacolon has rarely occurred. Many patients have visual changes during acute attacks. Paroxysms usually begin abruptly and subside slowly. The episodes may not recur for months or may recur many times daily. Each patient tends to have a particular pattern of symptoms, with the frequency or severity of episodes usually increasing over time. Attacks can occur without provocation or may occur with certain activities, such as bending, rolling over in bed, exertion, abdominal palpation, or micturition (with bladder paragangliomas). The interindividual variability in manifestations is striking; most patients have dramatic symptoms, but others with incidentally discovered secretory pheochromocytomas are completely asymptomatic. Patients who develop pheochromocytomas as part of multiple endocrine neoplasia (MEN) type II are especially prone to be normotensive and asymptomatic.

Children with pheochromocytoma are more prone to diaphoresis and visual changes than are adults. They are prone to have sustained (instead of paroxysmal) hypertension. Nausea, vomiting, headache, weight loss, polydipsia, polyuria, and convulsions occur frequently in children with pheochromocytoma. Children with pheochromocytoma may develop edema and erythema of the hands, a condition rarely found in adults.[15] Children are more prone to having multiple tumors; in one series, 39% had bilateral adrenal pheochromocytomas, an adrenal pheochromocytoma plus a paraganglioma, or multiple paragangliomas; single paragangliomas were reported in an additional 14% of children.[16]

Physical Signs of Pheochromocytoma

Most patients with diagnosed pheochromocytomas have hypertension (90%), which may be intermittent, remittent, or persistent. In children, blood pressure normally rises with age, so standards for hypertension are age dependent and based on the 95th percentile for age: < 6 months, 110/60 mm Hg; 3 years, 112/80 mm Hg; 5 years, 115/84 mm Hg; 10 years, 130/92 mm Hg; 15 years, 138/95 mm Hg. Paroxysms of severe hypertension occur in about

50% of adults and in about 8% of children with pheochromocytoma. Hypertension can be mild or severe and may be resistant to usual antihypertensive medications. Severe hypertension may be noted during induction of anesthesia for unrelated surgeries. Although hypertension usually accompanies paroxysmal symptoms and may be elicited by the above activities, this is not always the case. Patients with sustained hypertension usually exhibit orthostatic changes in blood pressure. Blood pressure may drop, even to hypotensive levels, after arising from a supine position and standing for 3 minutes; such orthostasis, especially when accompanied by a rise in heart rate, is characteristic of pheochromocytoma.[4] Orthostasis appears to be caused by a vasomotor adrenergic receptor desensitization; some patients may also have a diminished blood volume.

Tachycardia is common; frequently, the heart rate will increase when standing. During a paroxysm, there may be an initial tachycardia, followed by a reflex bradycardia. During a hypertensive crisis, intense peripheral vasoconstriction may cause the radial pulse to become thready or even nonpalpable. Vasoconstriction is also responsible for the pallor and mottled cyanosis that is frequently associated with paroxysms of hypertension. Facial flushing can occur, usually following a paroxysm, owing to reflex vasodilatation following an attack. After an intense and prolonged attack of hypertension, shock may ultimately occur. This may be attributable to low plasma volume, arrhythmias, cardiac damage, or loss of vascular tone.

During pregnancy, a maternal pheochromocytoma can cause sustained hypertension or paroxysmal hypertension and/or symptoms, sudden peripartum shock, or postpartum fever. These manifestations can easily be confused respectively with eclampsia, rupture of the uterus, or infection.[17]

Epinephrine secretion from a pheochromocytoma may cause episodic hypotension and even syncope. Hypertensive retinopathy can be observed in the majority of patients who have sustained hypertension. Most patients lose some weight. More severe weight loss (> 10% of basal weight) occurs in about 15% of patients overall and in 41% of those with sustained and prolonged hypertension.[18] Fevers are quite common and may be mild or severe, even as high as 41°C; up to 70% of patients have unexplained low-grade elevations in temperatures of 0.5°C or more.[8] Fevers appear to be caused by secretion of interleukin 6 (IL-6) by the tumor. Distention of the neck veins is common during an attack, and the thyroid may increase in size transiently. Large pheochromocytomas or their metastases may be palpable. Some may grow so large that they impinge the renal artery, causing concomitant renovascular hypertension. Pheochromocytomas and perirenal paragangliomas may be mistaken for renal cell carcinoma. Left-sided tumors may be mistaken for carcinoma of the tail of the pancreas.

Patients with pheochromocytomas often develop left ventricular hypertrophy. Additionally, a dilated cardiomyopathy may develop owing to catecholamine-induced myocarditis; full recovery from severe cardiomyopathy can occur after successful resection of a pheochromocytoma. In other patients, the cardiomyopathy is irreversible, owing to cardiac scarring and fibrosis.[19] Sudden arrhythmias often occur and may be fatal. Other complications include cerebrovascular accident, malignant nephrosclerosis, and hypertensive retinopathy.

Metastases can cause a variety of problems: for example, hepatomegaly, bone fractures, or spinal cord impingement. Metastases to the skull or mandible may be palpable. Pulmonary or mediastinal metastases may cause dyspnea, hemoptysis, Horner's syndrome, or pleural effusion; chylothorax may occur owing to damage to the thoracic duct.

ECTOPIC PEPTIDES

Pheochromocytomas produce mostly catecholamines or their metabolites, but they can also secrete other peptide hormones: ectopic adrenocorticotropic hormone production can cause Cushing's syndrome. Secretion of parathyroid hormone–related peptide can cause hypercalcemia.[20] Erythropoietin secretion can cause erythrocytosis. Neuropeptide Y can contribute to hypertension. Most pheochromocytomas secrete chromogranin A, making serum levels of chromogranin A useful as a tumor marker. Pheochromocytomas can also secrete other peptides listed in Table 9–1.

Table 9–1. PEPTIDES SECRETED BY PHEOCHROMOCYTOMAS*

Catecholamines
Metanephrines
Dopamine
Adrenocorticotropic hormone
Atrial natriuretic hormone
β-Endorphin
Calbindin
Calcitonin
Cholecystokinin
Chromogranin A
Enkephalins
Erythropoietin
Galanin
Gonadotrophin-releasing hormone
Growth hormone
Motilin
Neuron-specific enolase
Neuropeptide Y
Neurotensin
Parathyroid hormone–related peptide
Renin
Serotonin
Somatostatin
Substance P
Substance peptide histidine isoleucine
Vasoactive intestinal polypeptide

*Pheochromocytomas are variable in their secretion of peptide hormones.

BIOCHEMICAL TESTING

Catecholamines

HPLC with electrochemical detection has become the preferred method for assaying urine or plasma for catecholamines and metanephrines. This method has proved superior for ease of use and specificity. Misleadingly elevated levels of at least one catecholamine or metanephrine determination are found in over 10% of patients with hypertension. These elevations are typically mild, usually < 50% above the maximum normal, and are usually normal on retesting. In contrast, patients with pheochromocytomas typically have elevations of catecholamines or metanephrines that are at least 100% above normal.

Urine Catecholamines and Metanephrines

Urine is collected for 24 hours in a container with 10 to 25 mL of 6 N hydrochloride preservative for the catecholamines. The metanephrines may be collected in the same container but do not absolutely require acidification. (The acid preservative may be omitted for children, for safety reasons, in which case, the specimen should be kept refrigerated and processed immediately.) The laboratory requisition form should request (1) assays for fractionated catecholamines, fractionated metanephrines, and creatinine performed on the same specimen and (2) assays by an endocrine reference laboratory using HPLC followed by electrochemical detection.

Alternatively, a single voided urine specimen may be obtained (without acid preservative) on first morning void or following a paroxysm. For such collections, the patient is instructed to void and discard the urine immediately at the onset of a paroxysm and then collect the next voided urine. The laboratory requisition should request: "spot urine for total metanephrine (by HPLC and electrochemical detection) and creatinine concentrations." It is prudent to contact the laboratory technologist and explain that the specimen is meant to be a single voided urine and not a 24-hour specimen, or else the specimen may be rejected. Patients with pheochromocytomas generally excrete > 2.2 μg metanephrine/mg creatinine.

Plasma Catecholamine or Metanephrine

These levels are rarely required, except as screening tests for patients with MEN type II or von Hippel-Lindau (VHL) disease (see below). Plasma concentrations of norepinephrine do not correlate with blood pressure.[15] Stimulation or suppression tests are not recommended.

Although no single test is absolutely diagnostic for pheochromocytoma, urinary metanephrines have a sensitivity of about 97%. Sensitivities of other tests are somewhat lower: urinary norepinephrine, 93%; plasma norepinephrine, 92%; urinary VMA, 90%; plasma epinephrine, 67%; urinary epinephrine, 64%; plasma dopamine, 63%.[21]

Serum Chromogranin A

Chromogranins are constituents of neurosecretory granules. These acidic glycoproteins have been categorized into three classes: A, B (secretogranin I), and C (secretogranin II).[2] Plasma levels of chromo-

granin A are usually elevated in patients with pheochromocytoma, even in "biochemically silent" tumors.[22] A high serum level of chromogranin A, along with high plasma or urine catecholamines or metabolites, is highly specific for pheochromocytoma.[23] Serum chromogranin A may be a useful tumor marker.[24] In patients with normal renal function, serum chromogranin A determination carries a sensitivity of 83% and a specificity of 96%.[25] However, the usefulness of serum chromogranin A levels is negated by any degree of renal failure, owing to its excretion by the kidneys; even mild azotemia causes serum levels to be elevated.[18] Chromogranin A undergoes extensive tumor-specific cleavages, such that only some serum radioimmunoassays are useful for clinical diagnosis.[26]

Other Laboratory Tests

Measurements of urinary VMA or dopamine do not add any additional useful diagnostic information. However, some centers have traditionally used a combination of urinary VMA and metanephrine determinations, with good result.[27] Clonidine suppression testing of plasma catecholamines is unnecessary and cumbersome. Glucagon stimulation testing is dangerous and no longer useful.

Leukocytosis up to 23,600 $\times$ 10^3 cells/μL has been reported. Hyperglycemia is noted in about 35%. The erythrocyte sedimentation rate is elevated in some patients with pheochromocytoma.

Factors Causing Potential Misleading Biochemical Testing for Pheochromocytoma

Various assays for catecholamines use different methods and internal standards for HPLC and electrochemical detection. These assays can suffer interference from an unexpectedly large and diverse number of drugs**,** foods, and stress. Not all HPLC assays are the same, and the potential for such interference will depend on the particular HPLC method employed. Therefore, it is best to check with each laboratory. Laboratory personnel can often detect a possible interference by observing an unusual shape of the peak on the chromatogram.[28]

Drugs

See Table 9–2 for a list of factors potentially causing misleading catecholamine or metanephrine results. Methylglucamine, contained in some radiocontrast media used during CT scanning, can falsely lower urinary metanephrine determinations by chromatography for up to 72 hours following administration; diatrizoate sodium (Hypaque) does not cause such interference. The older fluorometric methods of assaying catecholamines and VMA are particularly prone to interference by many drugs and foods.

Foods

Even using newer assay techniques of HPLC with electrochemical detection, some foods can misleadingly alter assays for catecholamines and metanephrines. Coffee is converted into certain catechol metabolites (namely, dihydrocaffeic acid), which may result in confounding peaks on a high-pressure liquid chromatogram.[29] Caffeine itself can cause persistent elevation in norepinephrine. (Caffeine inhibits the action of adenosine; one action of adenosine is to inhibit the release of catecholamines.) Bananas contain considerable amounts of tyrosine, which leads to an increase in local supply and conversion to dopamine by the central nervous sytem. Dopamine is then further converted to epinephrine and norepinephrine. Dietary peppers contain 3-methoxy-4-hydroxybenzylamine, a compound that can interfere with the internal standard used in certain assays for metanephrines.

Diseases

Increased production of catecholamines and metanephrines results from any severe stress. Other diseases cause reduced catecholamine production (malnutrition, dysautonomia, quiescent quadriplegia) or excretion (renal failure) (see Table 9–2).

DIFFERENTIAL DIAGNOSIS FOR PHEOCHROMOCYTOMA

Many conditions have manifestations in common with pheochromocytoma, including the following

Table 9–2. FACTORS POTENTIALLY CAUSING MISLEADING CATECHOLAMINE OR METANEPHRINE RESULTS: HIGH-PRESSURE LIQUID CHROMATOGRAPHY WITH ELECTROCHEMICAL DETECTION

Drugs	Foods	Conditions
Acetaminophen‡	Bananas*	Amyotrophic lateral sclerosis*
Methyldopa‡	Caffeine*	Brain lesions*
Amphetamines*	Coffee‡	Carcinoid*
Bronchodilators*	Peppers‡	Eclampsia*
Buspirone‡		Emotion—severe*
Captopril‡		Exercise—vigorous*
Clozapine*		
Cocaine*		Guillain-Barré syndrome*
Cimetidine‡		Hypoglycemia*
Codeine‡		Lead poisoning*
Decongestants*		Myocardial infarct—acute*
Ephedrine*		Pain—severe*
Fenfluramine†		Porphyria—acute*
Isoproterenol*		Psychosis—acute*
Levodopa‡		Quadriplegia*
Labetalol*‡		Renal failure†
Mendelamine‡		
Metoclopramide‡		
Nitroglycerin*		

Reproduced with permission from Fitzgerald P. Endocrine disorders. In: Tierney LM, Whooley MA, McPhee SJ, Papadakis MA, editors. Current medical diagnosis and treatment. 42nd ed. New York: McGraw Hill; 2003. p. 1134.
*Increases catecholamine excretion.
†Decreases catecholamine excretion.
‡May cause confounding peaks on high-pressure liquid chromatograms.

common examples: anxiety attacks, essential hypertension, renal artery stenosis, renal parenchymal disease, vascular or cluster headaches, hyperthyroidism, mastocytosis, vasomotor instability of hypogonadism (eg, menopause), cardiac arrhythmias, and unstable angina. The differential diagnosis also includes intracranial lesions, toxemia of pregnancy, clonidine withdrawal, hypertensive crisis of MAO inhibitors, hypoglycemia, pork sensitivity, autonomic epilepsy, acute intermittent porphyria, lead poisoning, encephalitis, and tabetic crisis. Factitious symptoms may be caused by surreptitious self-administration of various drugs. Hyperthyroidism can cause sweating, systolic hypertension with widened pulse pressure, and palpitations. Patients with erythromelalgia may have hypertension but suffer from flushing rather than pallor; acute episodes of pedal pain and swelling are relieved by application of ice. Carcinoid syndrome causes flushing but not usually hypertension.

Patients who have intermittent bizarre symptoms may have their blood pressure and pulse checked during a symptomatic episode with a home blood pressure meter or an ambulatory blood pressure monitor. Those who are normotensive during an attack are unlikely to have a pheochromocytoma. Similarly, patients who are exhausted for more than 2 hours following an attack or who live in dread of the next attack are more likely to have a panic disorder than a pheochromocytoma.[18]

LOCATION AND PATHOLOGY OF PHEOCHROMOCYTOMAS

Most pheochromocytomas are located in the adrenal glands (90% in adults and 70% in children), occurring more frequently on the right than on the left. In one series, right-sided pheochromocytomas have been described as producing paroxysmal hypertension more often than sustained hypertension, whereas the opposite is true for tumors arising from the left adrenal gland.[18] Adrenal pheochromocytomas are bilateral in about 10% of adults and 35% of children. They may present at any age but are more common in the fourth and fifth decades.

In familial cases, pheochromocytomas typically are discovered at an earlier age, and about 70% of adrenal pheochromocytomas are bilateral when discovered; extra-adrenal paragangliomas are often also present concomitantly. Eventually, in familial cases, nearly all patients will develop bilateral pheochromocytomas or medullary hyperplasia.[15]

Most sporadic pheochromocytomas are circumscribed and encapsulated by either a true capsule or a pseudocapsule of the adrenal capsule. At surgery, pheochromocytomas are firm in texture. They are often opaque, with yellow areas of remaining adrenal cortex and brown areas of periadrenal fat. Hemorrhages within the tumor may impart a mottled or dark red appearance. Larger tumors frequently have large areas of hemorrhagic necrosis that undergo cystic degeneration (see Figure 9–1). Viable tumor may be found in the cyst wall. Calcification may be present. Pheochromocytomas may rarely invade adjacent tissue or the adrenal vein, extending into the vena cava and resulting in pulmonary emboli.[2] Pheochromocytomas vary enor-

mously in size, ranging from microscopic to 3,600 g. The "average" pheochromocytoma weighs 100 g and is 4.5 cm in diameter.

Paragangliomas (extra-adrenal pheochromocytomas) account for about 10% of pheochromocytomas in adults and about 30% in children. These tumors arise from sympathetic ganglia. About 85% are intra-abdominal, where they are typically located in the juxtarenal or para-aortic region, particularly in the perinephric, periaortic, and bladder regions. Retroperitoneal paragangliomas are more likely to be malignant (30 to 50%) and present with pain or a mass[15]; about 36% of such tumors are functional. Functional status is not known to affect survival.[30] Nonfunctional paragangliomas frequently concentrate metaiodobenzylguanidine (MIBG) or cause increased serum levels of chromogranin A. Paragangliomas of the bladder cause symptoms on micturition. Large perinephric tumors can cause renal artery stenosis. Vaginal tumors can cause dysfunctional vaginal bleeding.

Paragangliomas may also arise in the anterior or posterior mediastinum or the heart.[31] Central nervous system locations include the sella turcica, petrous ridge, and pineal region; cauda equina paraganglioma can cause increased intracranial pressure.[32] Nonchromaffin paragangliomas of neuroectodermal chemoreceptors are known as chemodectomas or glomus tumors; they are typically found in the head and neck, particularly near the carotid body, glomus jugulare, or jugulotympanic region or in the lung. Chemodectomas rarely secrete catecholamines.[33]

Carney's triad generally presents in women under age 40. It consists of the triad of multicentric paragangliomas, indolent gastric leiomyosarcomas, and pulmonary chondromas.

LOCALIZATION STUDIES FOR PHEOCHROMOCYTOMA

MIBG selectively accumulates in tissues that store catecholamines in neurosecretory granules. The uptake of MIBG into a tissue is proportional to the concentration of neurosecretory granules.[34] Scintigraphy using radioactive iodine (^{123}I)-MIBG or ^{131}I-MIBG is useful for imaging an occult pheochromocytoma, paraganglioma, or neuroblastoma or for confirming that a certain mass is a neuroendocrine tumor (Figure 9–4).[35] It is also useful for screening patients for metastases. MIBG uptake does occur in apparently nonfunctioning pheochromocytomas. The isotope that is preferable for precise imaging is ^{123}I-MIBG because ^{123}I has a more useful photon flux, with lower-energy gamma emissions than ^{131}I, allowing for clearer images and single-photon emission computed tomography (SPECT). ^{123}I-MIBG SPECT scanning is more sensitive than ^{123}I-MIBG planar imaging for imaging small metastases.[36] However, most centers use ^{131}I-MIBG because it has a longer half-life than ^{123}I-MIBG and is also less expensive.[37] The overall sensitivity of ^{123}I-MIBG for pheochromocytomas is about 85%; it is more sensitive for unilateral, adrenal, benign, capsular-invasive, and sporadic pheochromocytomas. Scanning with ^{123}I-MIBG is less sensitive for bilateral, malignant, extra-adrenal, noninvasive, and pheochromocytomas related to MEN types IIA and IIB.[38]

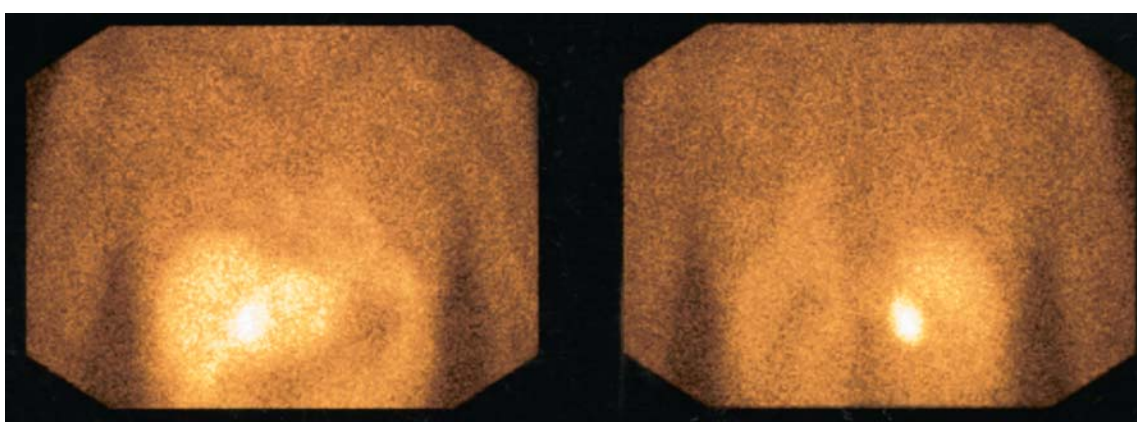


Figure 9–4. Anterior and posterior views of a radioactive iodine (^{123}I)-metaiodobenzylguanidine scan showing a right adrenal pheochromocytoma.

To block the thyroid's uptake of free ^{123}I or ^{131}I, Lugol's solution (potassium iodide [KI], 5 drops orally three times daily) is given before the injection and daily for 7 days afterward. The ^{123}I-MIBG is given intravenously, and gamma camera scanning may be performed between 1 and 3 days afterward.

False-negative scans occur in about 15% of both benign and malignant pheochromocytomas. False-negative scans are more common in patients who, within 6 weeks, have taken tricyclic class drugs, for example, antidepressants or cylcobenzaprine (Flexeril). Other drugs can cause false-negative scans if taken within 2 weeks: amphetamines, cocaine, phenylpropanolamine hydrochloride, haloperidol, phenothiazines, thiothixene, reserpine, nasal decongestants, and diet pills. Labetalol causes some decreased uptake, but the scan can still be done with reasonable sensitivity (Table 9–3).

False-positive scans do occur. Uptake in the normal adrenal medulla and renal pelvis and bladder is commonly seen on day 1[39]; the scan is then repeated on days 3 and 5. Uptake in the salivary glands is the rule. Some uptake of ^{123}I-MIBG by the heart and liver is common. Skin contaminated by urine can also cause a false-positive scan.

Computed Tomography

When a pheochromocytoma is suspected on clinical and biochemical grounds, the patient can be imaged with full abdominal CT scanning, from the diaphragm through the pelvis. Thin sections are obtained through the adrenals (Figure 9–5). Glucagon should not be used because it may provoke a hypertensive crisis. Hypertension should be treated prior to CT scanning because intravenous contrast can also cause hypertensive crisis. If no mass is discovered, either a ^{123}I-MIBG scan may be obtained and/or the CT scan may be extended into the chest and thoracic spine in search of a paraganglioma. The overwhelming majority of pheochromocytomas are greater than 2 cm in diameter, well within the resolution of the CT scan. The overall sensitivity of CT scanning for an adrenal pheochromocytoma is about 90% and over 95% for pheochromocytomas over 0.5 cm diameter.[40] However, it is less sensitive for the detection of extra-adrenal paragangliomas, metastases, and recurrent small tumors in the adrenal bed.

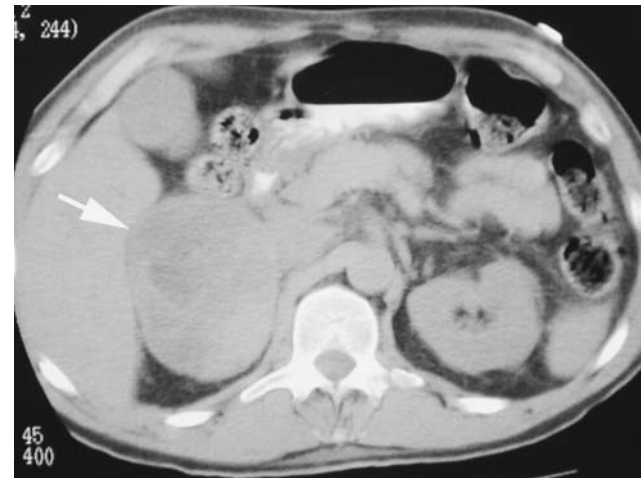


Figure 9–5. Abdominal computed tomographic scan showing a 9 cm right adrenal tumor. Courtesy of Quan-Yang Duh, MD.

Table 9–3. FACTORS INHIBITING MIBG UPTAKE BY PHEOCHROMOCYTOMA

Inhibitors of type I catecholamine uptake: cocaine, tricyclic drugs, labetalol (2–6 wk)
Stimulants of catecholamine discharge: reserpine (2 wk)
Displacement of catecholamines from intracellular stores and competition with uptake of MIBG: all amphetamines; nasal decongestants—oral or nasal (2 wk)
Others: phenothiazines, haloperidol, thiothixene (2 wk)

MIBG = metaiodobenzylguanidine.

Magnetic Resonance Imaging

MRI has the advantage of not requiring intravenous iodinated contrast, thereby minimizing the risk of hypertensive crisis. The lack of radiation makes it the localizing procedure of choice during pregnancy. MRI can visualize and confirm metastases to bone suspected on MIBG imaging. It can help determine whether an adrenal mass is a pheochromocytoma when biochemical studies are inconclusive. The T_2-weighted signal is usually (75%) hyperintense to the liver (Figure 9–6). However, some adrenal adenomas may have the same appearance, so the MRI scan lacks true specificity. MRI of the abdomen has a sensitivity of about 95% for adrenal pheochromocytomas over 0.5 cm diameter.[40] However, MRI is less sensitive for the detection of extra-adrenal paragangliomas, metastatic disease, and recurrent small tumors in the adrenal surgical bed.

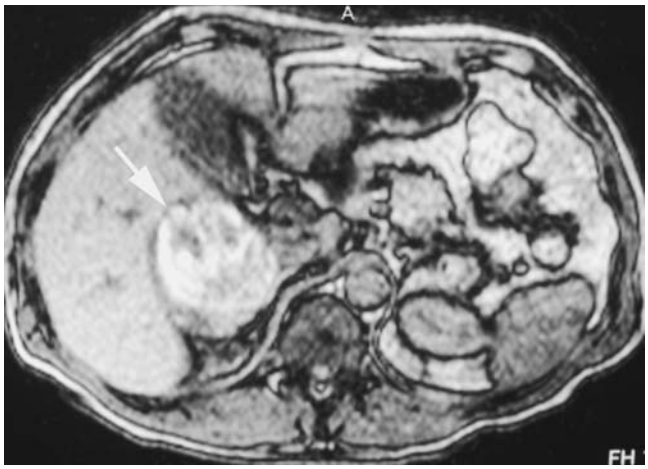


Figure 9–6. Magnetic resonance image showing a heterogeneous right adrenal tumor that enhanced on T_2-weighted image (*arrow*). Courtesy of Quan-Yang Duh, MD.

Positron Emission Tomography

Positron emission tomography (PET) uses isotopes that emit positrons during their decay; positron-electron collisions emit gamma rays traveling in precisely opposite directions. Sensitive gamma detectors surround the patient; simultaneous activation of two gamma detectors indicates that the source is located directly between them. Multiple such detections allow three-dimensional CT of tumors to better determine their location and volume (Figure 9–7). Deoxyglucose may be tagged with radioactive rubidium (^{82}Rb) or radioactive fluoride (^{18}F) (fluorodeoxyglucose [FDG]) and has successfully imaged malignant pheochromocytoma.[41] However, [^{18}F]FDG PET scanning detects other tumors besides pheochromocytoma and localizes in other tissues with a high metabolic rate, including inflammation or shivering muscles; it is thus less specific for pheochromocytoma than is MIBG scanning.

PET with radiolabeled dopamine, 6-[^{18}F]fluorodopamine, is under investigation. It is more specific for paraganglioma and metastatic pheochromocytoma than is [^{18}F]FDG because dopamine is a substrate for the norepinephrine transporter in tumor tissue.[42]

PET has some advantages over MIBG scanning in that PET can be carried out almost immediately, whereas MIBG scanning must be delayed for 24 to 48 hours after MIBG injection to allow dissipation of background radiation. PET does not require pretreatment with iodine to protect the thyroid, as is necessary with MIBG scanning. However, PET is very expensive and has not been directly compared with ^{123}I-MIBG or ^{131}I-MIBG scanning for sensitivity and specificity.

Other Imaging

Somatostatin receptor imaging (SRI) with indium-111 (^{111}In)-labeled octreotide has a sensitivity of only 25% for adrenal pheochromocytomas. However, octreotide scanning detects 87% of pheochromocytoma metastases and is also a sensitive technique for detecting paragangliomas of the head and neck (chemodectomas). Octreotide scanning detects some metastases not visible on MIBG scanning and vice versa. Octreotide scanning has been reported to detect a cardiac paraganglioma that was not visible on MIBG scanning.[43] When occult metastases are suspected but MIBG scanning is negative, SRI may be useful.[44]

Bone scans can usually detect skeletal metastases of malignant pheochromocytomas but are not as specific as ^{123}I-MIBG scanning.

GENETIC CONDITIONS ASSOCIATED WITH PHEOCHROMOCYTOMAS

Pheochromocytomas are usually sporadic. However, at least 10% are hereditary and may occur as part of

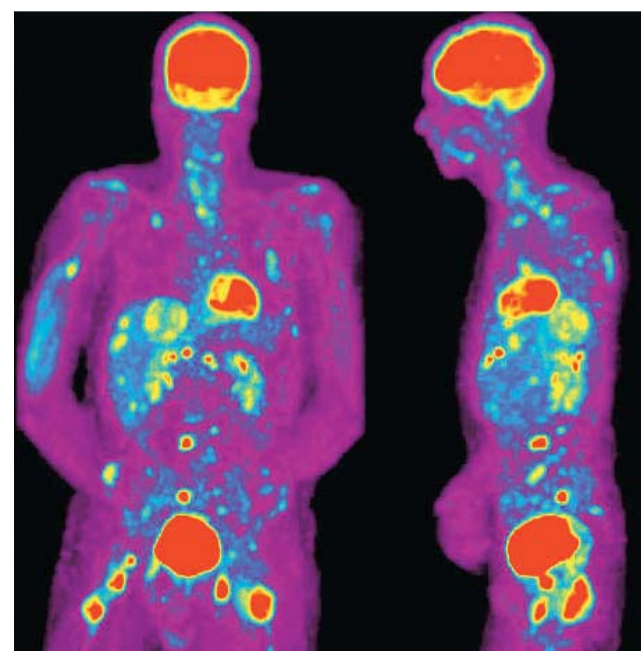


Figure 9–7. Positron emission tomographic scan showing metastatic pheochromocytomas.

certain familial syndromes. MEN type II is an autosomal dominant disorder with two distinct subtypes: MEN type IIA (Sipple's syndrome): medullary thyroid carcinoma, hyperparathyroidism, pheochromocytoma, or adrenal medullary hyperplasia, lichen planus amyloidosis, and Hirschsprung's disease; MEN type IIB: mucosal neuromas, intestinal ganglioneuromas, thick corneal nerves, marfanoid habitus, medullary thyroid carcinoma, and pheochromocytoma or adrenal medullary hyperplasia.[45]

In patients with a MEN type IIA genetic defect, the ultimate occurrence of medullary thyroid carcinoma is nearly 100%. However, the incidence of pheochromocytoma varies in different kindreds, ranging from 6 to 100% (average 40%), depending on the kindred. Pheochromocytomas tend to present in middle age, often without hypertension. The incidence of hyperparathyroidism has also varied, averaging 35%.[46,47] Pheochromocytomas that arise in patients with MEN type IIA or IIB are usually located in the adrenal glands; extra-adrenal paragangliomas are rare. Individuals who belong to kindreds with MEN type IIA (Figure 9–8) or IIB (Figure 9–9) should have *RET* proto-oncogene mutation analysis prior to age 6 years for MEN type IIA and at diagnosis in suspected MEN type IIB to determine if they carry the autosomal dominant trait and require thyroidectomy and close surveillance for these tumors. Each specific type of mutation in the *RET* gene determines each kindred's idiosyncrasies, such as the age of onset and aggressiveness of medullary thyroid carcinoma.[52] Patients with the 634-point mutation are more prone to pheochromocytoma and hyperparathyroidism.[48] Plasma concentrations of metanephrine are elevated early in most patients with pheochromocytoma associated with MEN type II.[49]

About 1% of patients with von Recklinghausen's neurofibromatosis ultimately develop pheochromocytomas. These tend to be at an older age. However, such patients are prone to develop vascular anomalies such as coarctation of the aorta and renal artery stenosis, which can also produce hypertension and mimic pheochromocytoma. Patients usually have areas of café au lait skin pigmentation.

In VHL disease, a mutation of the tumor suppressor *VHL* gene causes an autosomal dominant predisposition to hemangioblastomas in the cerebellum, spinal cord, and retina. About 10 to 20% of patients with VHL ultimately manifest a pheochromocytoma; such patients are usually those with *VHL* gene missense mutations rather than those with deletion or frame-shift mutations. Pancreatic cysts, kidney cysts, and renal cell carcinoma also occur. In a series of 36 French patients with pheochromocytoma and VHL disease, pheochromocytoma was the presenting tumor in 53%. Pheochromocytomas were bilateral in

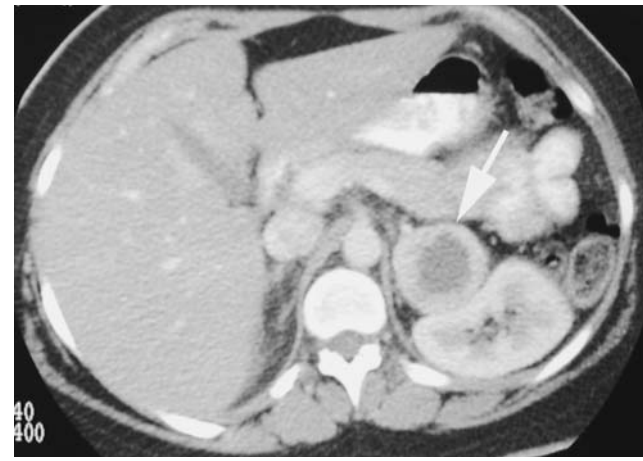


Figure 9–8. Abdominal computed tomographic scan in a 30-year-old woman with multiple endocrine neoplasia type IIA showing a left adrenal pheochromocytoma (*arrow*) with characteristic central necrosis. Courtesy of Quan-Yang Duh, MD.

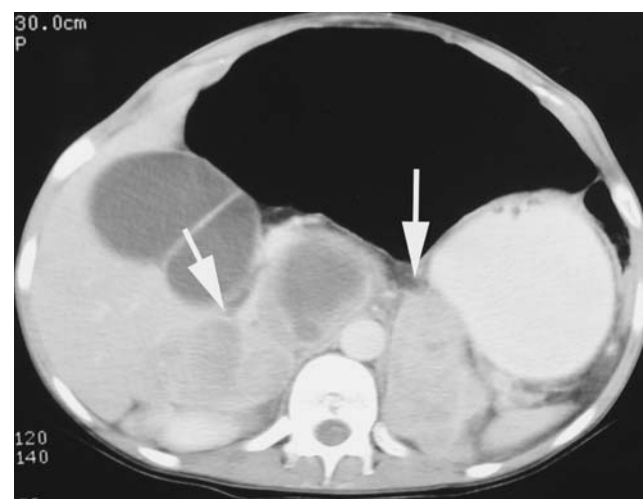


Figure 9–9. A 26-year-old woman had severe constipation and developed multisystem failure. She was found to have a thyroid nodule and cervical lymphadenopathy. Abdominal computed tomographic scan showed bilateral adrenal tumors (*arrows*). Biochemical workup was consistent with pheochromocytoma, and the patient underwent open bilateral adrenal resection for pheochromocytomas followed by thyroidectomy for medullary thyroid cancer. Genetic study confirmed the clinical diagnosis of multiple endocrine neoplasia type IIB. Courtesy of Quan-Yang Duh, MD.

42% and concurrent paragangliomas were present in 11%. Three had malignant pheochromocytoma. In 18%, pheochromocytoma was the only manifestation of the disease.[50] Plasma normetanephrine levels are usually elevated when patients with VHL disease develop a pheochromocytoma.[49]

Pheochromocytomas may also occur as an isolated familial genetic syndrome. Pheochromocytomas occurring as part of any familial syndrome are more likely to be bilateral or associated with adrenal medullary hyperplasia than are those occurring sporadically. Hereditary paragangliomas have been attributed to mutations in three genes (*SDHB*, *SDHC*, *SDHD*). Individuals with such genetic proclivity require frequent clinical and biochemical screening for pheochromocytoma.[49]

Carney's triad generally presents in women under age 40. It consists of the triad of multicentric paragangliomas, gastric leiomyosarcomas, and pulmonary chondromas.

Genetic screening is indicated for all patients with a family history of pheochromocytomas or paragangliomas, bilateral pheochromocytomas, or other manifestations of the genetic syndromes noted above. Such screening can be done for MEN type II *RET* proto-oncogene mutations, *VHL* mutations, and *SDHB*, *SDHC*, and *SDHD* mutations.[51]

ADRENAL PERCUTANEOUS FINE-NEEDLE ASPIRATION BIOPSY

Fine-needle aspiration (FNA) biopsy is rarely required to diagnose a pheochromocytoma, which can usually be readily identified by their clinical, biochemical, and radiologic presentation. However, pheochromocytomas may be discovered incidentally on abdominal CT or ultrasonography and may be clinically and biochemically silent. Biopsy of such pheochromocytomas without alpha-blockade has produced hypertensive crisis as well as hemorrhage, resulting in death.[52] The cytologic material derived from biopsy of pheochromocytomas often is misinterpreted as a metastatic tumor or another malignancy, owing to pleomorphic and hyperchromic nuclei.[2] A left-sided pheochromocytoma has been misdiagnosed as carcinoma of the tail of the pancreas, based on CT and biopsy.[53]

PREOPERATIVE TREATMENT OF PATIENTS WITH PHEOCHROMOCYTOMAS

It is ideal for patients to be hemodynamically stable on oral antihypertensives (see below) prior to surgery. During outpatient titration of antihypertensive doses, patients should have daily orthostatic measurements of blood pressure and pulse. Additionally, patients should measure their blood pressure at the time of paroxysmal symptoms. However, prolonged preoperative preparation of greater than 7 days is no more effective at preventing intraoperative hypertension than are shorter preparation times of 4 to 7 days.[54] In fact, some hypertensive patients can be admitted emergently for hypertension control and hydration, stabilized, and taken directly to surgery with an intravenous infusion of a vasodilator drug, for example, nicardipine, nitroprusside, and nitroglycerin (see below).[55]

Calcium channel blockers are effective antihypertensive agents for patients with pheochromocytoma and are preferred in many centers. Patients generally better tolerate calcium channel blockers than α-blockers. Perioperative fluid requirements are lower among patients pretreated with calcium channel blockers than with α-blockers.[56] In a French series, 70 patients with pheochromocytoma were safely prepared for surgery using oral calcium channel blockers (usually nicardipine).[57] Nicardipine may be given in doses of 20 to 40 mg orally every 8 hours. Nifedipine may be given as a slow-release preparation (eg, Adalat CC) in doses of 30 to 60 mg orally once daily. For hypertensive paroxysms, nifedipine 10 mg (chewed pierced capsule) is usually a quick and effective treatment. Chewed nifedipine is generally safe for use by patients with pheochromocytoma, who may self-administer it at home during paroxysms, but only with close blood pressure monitoring. Nifedipine carries an advantage of having been demonstrated to cause a reduction in the mitotic index of pheochromocytoma cells in vitro[57] and to improve uptake of MIBG into some tumors.[57,58] Another option is to use verapamil sustained release 120 to 240 mg orally once daily.

Alpha-adrenergic blockade has traditionally been used for most patients with pheochromocytoma in preparation for surgery. Patients who are normoten-

sive are also usually treated (carefully) preoperatively. Phenoxybenzamine (Dibenzyline, 10 mg capsules), an oral nonselective α-blocker, is the most commonly used α-blocker; it is given orally in a starting dose of 10 mg daily and increased by 10 mg every 3 to 5 days until the blood pressure is < 140/90 mm Hg. Hydration should be encouraged. Patients must be monitored for worsening orthostatic hypotension. Other adverse effects are common, including dry mouth, headache, diplopia, inhibition of ejaculation, and nasal congestion. (Patients are cautioned not to use nasal decongestants if urinary catecholamines or ^{123}I-MIBG scanning is planned, but antihistamines are acceptable.) Phenoxybenzamine crosses the placenta and can cause hypotension and respiratory depression in the newborn for several days following birth.[60] Most patients require 30 to 60 mg/day, but the dosage is sometimes escalated to as high as 120 mg/day. Excessive alpha-blockade with phenoxybenzamine is undesirable because it worsens postoperative hypotension. Furthermore, excessive alpha-blockade may deny a critical surgical indicator: a drop in blood pressure after complete resection of the tumor and aggravation of hypertension during palpation of the abdomen in case of multiple tumors or metastases. Alternatively, a short-acting selective α-blocker (eg, prazosin*)* appears to cause less reflex tachycardia and less postoperative hypotension.[61] The starting dose of prazosin is 0.5 mg/day, increasing up to 10 mg twice daily if necessary.

Angiotensin-converting enzyme (ACE) inhibitors have been used successfully to treat hypertension in patients with pheochromocytoma. Catecholamines stimulate renin, thereby stimulating the production of angiotensin II. ACE inhibitors counteract this aspect of catecholamine hypertension.[62]

Metyrosine (Demser, α-methylparatyrosine) inhibits tyrosine hydroxylase, the first step in catecholamine biosynthesis. Owing to its potential side effects, it is usually used only to treat hypertension in patients with metastatic pheochromocytoma. However, it may be used in hypertensive patients with pheochromocytoma for preoperative preparation. Metyrosine is administered orally as 250 mg capsules, beginning with one every 6 hours; the dose is titrated upward every 3 to 4 days according to blood pressure response and side effects. The maximum dosage is 4 g/day. Catecholamine excretion is usually reduced by 35 to 80%. Preoperative treatment with metyrosine tends to reduce intraoperative hypertension and arrhythmias; however, postoperative hypotension is likely to be more severe for several days. Side effects of metyrosine include sedation, psychiatric disturbance, extrapyramidal symptoms, and potentiation of sedatives and phenothiazines. Crystalluria and urolithiasis can occur, so adequate hydration is mandatory.[63] Metyrosine does not inhibit MIBG uptake by the tumor, allowing concurrent ^{123}I-MIBG scanning or high-dose ^{131}I-MIBG treatment.

Beta-adrenergic blockade may be considered for β-adrenergic symptoms such as flushing or tachycardia once there is adequate alpha-blockade. It is important to institute alpha-blockade first because blocking vasodilating β_1-adrenergic receptors without also blocking vasoconstricting α_1-adrenergic receptors can lead to hypertensive crisis if serum norepinephrine levels are high. Even labetalol, a mixed α/β-blocker, has been reported to cause an unexpected exacerbation of hypertension. Propranolol 10 to 40 mg orally four times daily is occasionally required. Propranolol crosses the placenta and can cause intrauterine growth retardation. Newborns of mothers taking propranolol at delivery exhibit bradycardia, respiratory depression, and hypoglycemia.

Octreotide (SMS 201-995) 300 μg/day has been reported to reduce hypertensive episodes and catecholamine excretion in a man with pheochromocytoma whose hypertensive episodes were uncontrolled using other means.[64]

Nonsteroidal anti-inflammatory drugs, such as naproxen, can be used to treat fevers caused by the release of IL-6 by the tumor.

PERIOPERATIVE MANAGEMENT OF PHEOCHROMOCYTOMAS

It is important for patients to have fully repleted intravascular volumes prior to surgery. Some surgeons admit patients for intravenous fluids one day prior to surgery and predonate blood for autologous transfusion and infuse two units of blood within 12 hours preoperatively.[61] It is not usually necessary.

All adrenal masses of unknown pathology should be managed with the extreme care rendered to a pheochromocytoma. Constant invasive blood pressure monitoring requires an arterial line.[47] A central venous pressure line is sometimes necessary to monitor fluid replacement. A pulmonary artery (Swan-Ganz) line is inserted in selected high-risk patients with congestive heart failure or coronary artery disease to further optimize fluid replacement. Constant electrocardiographic monitoring is mandatory. Severe hypertension is frequently encountered, even in "fully blocked" patients, on bladder catheterization, intubation, surgical incision, and pneumoperitoneum for laparoscopy or during manipulation of the tumor.[65] During laparoscopic surgery, catecholamine release is especially stimulated by pneumoperitoneum and by tumor manipulation.[66] Therefore, all medication that may be required should be ready in advance. Laparoscopic operations, however, cause less fluctuation of catecholamine levels than open operations.

A balanced anesthetic technique is usually used. Agents such as intravenous propofol, enflurane, isoflurane, sufentanil, and nitrous oxide appear to be effective and safe.[67,68] Muscle relaxants with the least hypertensive effect are used (eg, vecuronium).[47] Hypertension is managed by increasing the depth of anesthesia and by vasodilators for blood pressure over 160/90 mm Hg. The infusion rates are adjusted to control blood pressure. Catecholamine levels drop abruptly on clipping of the adrenal vein; therefore, the vasodilator infusion is stopped immediately before ligation of the adrenal vein. This reduces the chance of sudden hypotension after resection of the pheochromocytoma.

Nicardipine, a calcium channel blocker, is effective as an intravenous infusion in doses of 2 to 6 μg/kg/minute. Nicardipine was successfully used as the sole intraoperative vasodilating agent in one series of 70 patients and another series of 19 patients.[56,69]

Sodium nitroprusside intravenous infusion is effective in managing hypertensive episodes. Advantages to its use include its short duration of action and its widespread familiarity. The usual dose is 0.3 to 10 μg/kg/minute. The maximal infusion rate should be given for no longer than 10 minutes because with prolonged (over 6 hours) nitroprusside infusion rates above 2 μg/kg/minute, cyanide may accumulate to toxic concentrations. Coadministration of sodium thiosulfate (1 g/100 mg nitroprusside) prevents cyanide accumulation.[70]

Nitroglycerin intravenous infusion is effective for treating perioperative hypertension. The required dosage ranges from 5 to 100 μg/minute. However, nitroglycerin adheres to polyvinyl chloride tubing, so appropriate dilutions, dosing, and infusion sets must be used. Side effects include headache and hypotension. Methemoglobinemia has rarely occurred during prolonged, high-dose infusions and is manifested by cyanosis in the presence of a normal arterial oxygen partial pressure. The treatment for methemoglobinemia consists of stopping the nitroglycerin and giving methylene blue, 1 to 2 mg/kg intravenously.

Phentolamine mesylate (Regitine) is a short-acting α-adrenergic blocker with an intravenous half-life of 19 minutes. Bolus doses of 5 to 15 mg (1 to 3 mg for children) are administered intravenously for blood pressure control. Phentolamine may also be given as an intravenous infusion at a rate of 0.5 to 1 mg/minute. Side effects include hypotension, tachycardia, cardiac arrhythmias, nasal stuffiness, nausea, and vomiting.

Lidocaine 50 to 100 mg intravenously may be used to treat cardiac ventricular arrhythmias. Atrial tachyarrhythmias may be treated with intravenous boluses of atenolol 1 mg or by constant infusion of a short-acting β-blocker such as esmolol.

Immediately after resection of a pheochromocytoma, severe hypotension and cardiovascular collapse can occur, particularly in patients with norepinephrine-secreting tumors. This hypotension is largely owing to desensitization of α_1-adrenergic receptors, persistence of antihypertensives, and low plasma volume. Preoperative preparation with calcium channel blockers and/or alpha-blockade and forced hydration attenuate this effect. Treatment of shock consists of large volumes of intravenous saline or colloid. Intravenous norepinephrine (Levophed) is sometimes required in high doses. Immediately following resection of the pheochromocytoma, intravenous 5% dextrose should be infused at a constant rate of about 100 mL/hour to prevent hypoglycemia that is otherwise frequently encountered postoperatively.

Labetalol infusion is not recommended for perioperative or intraoperative management of pheochromocytoma because it aggravates postresection hypotension, owing to its long half-life. It may also paradoxically initially aggravate hypertension (see above). Additionally, labetalol inhibits MIBG uptake and causes false elevations in urinary catecholamine determinations.[71,72] Diazoxide (Hyperstat) infusion is also not recommended for hypertension management. Atropine premedication may cause arrhythmias and hypertension despite preoperative α-adrenergic blockade.[8]

SURGICAL APPROACH FOR PHEOCHROMOCYTOMA

Laparoscopic resection is now the procedure of choice for resecting most adrenal tumors under 6 cm in diameter. The techniques of laparoscopic adrenalectomy have been described in detail.[73] This technique has largely replaced open laparotomy, owing to the accuracy of preoperative localization procedures. However, tumors > 6 cm are more difficult to resect laparoscopically and are more likely to be malignant. For such large tumors, a lateral laparoscopic approach can still be done as it allows greater space for exploration and examination of the liver for metastases. Use of laparoscopic adrenalectomy in suspected malignant tumors is controversial. A lateral laparoscopic approach may be converted to an open laparotomy if required. A posterior laparoscopic approach can be used for patients with smaller tumors or a history of prior abdominal surgery.[47,74] Laparoscopic adrenal surgery is usually accomplished through four subcostal ports of 10 to 12 mm.

The laparoscope provides magnified views of the tumor and vasculature (Figure 9–10). The anesthesiologist is notified when the tumor is about to be manipulated in order to prepare for the expected hypertension. Tumors are "bagged" to avoid fragmentation and intraperitoneal or port site spread of tumor cells. Very large tumors can also be removed through a small incision that allows the surgeon's hand to assist (laparoscopic hand-assisted adrenalectomy). On average, the surgery time is about 1 hour longer with the laparoscopic approach compared with open surgery. However, with experience, the surgical time can be reduced (about 2 to 3 hours). With the laparoscopic technique, the frequency and severity of hypertensive episodes are not reduced; however, hypotensive episodes are less frequent and less severe. Laparoscopic adrenalectomy offers additional advantages compared with open adrenalectomy: reduced postoperative pain, quicker return to oral food intake (median 1.5 versus 4 days), and shorter average hospital stays (median 3 versus 7 days).[75,76] This approach is the least invasive for the patient, who can usually begin eating and ambulating by the next day.[77] The laparoscopic approach may also be used during preg-

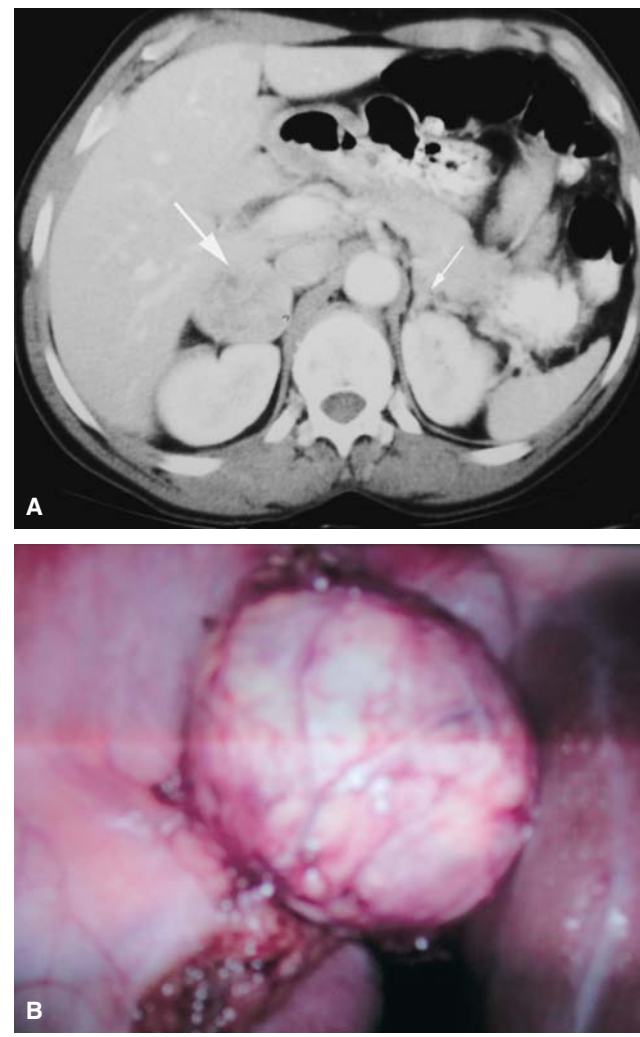


Figure 9–10. An abdominal computed tomographic scan performed in a 63-year-old woman because of mild right upper quadrant pain. *A*, The scan shows a 4 cm right adrenal tumor (*large arrow*) and a normal left adrenal gland (*small arrow*). B, Subsequent biochemical workup confirmed pheochromocytoma. The patient was α-adrenergic blocked, and the right adrenal tumor was resected laparoscopically. Courtesy of Quan-Yang Duh, MD.

nancy.[78] Very large and invasive tumors are best treated with open laparotomy. The surgical mortality is now < 3% in referral centers.[47]

"Needlescopic" adrenalectomy has been reported using three subcostal ports of 2 to 5 mm with a larger umbilical port for tumor removal. In one series of 15 patients, this technique resulted in surgical times and convalescence that improved on the standard laparoscopic approach. Prior experience with laparoscopic surgery is essential.[79]

Familial adrenal pheochromocytomas (a condition distinguished from MEN type II) are rarely malignant. Such pheochromocytomas are usually bilateral. Patients undergoing bilateral total adrenalectomies require lifelong glucocorticoid and mineralocorticoid hormone replacement. To avoid adrenal insufficiency, patients with benign familial or bilateral pheochromocytomas have had successful selective laparoscopic resection of small pheochromocytomas, sparing the adrenal cortex.[80] Unfortunately, recurrent pheochromocytoma has been reported using such an approach.

An open laparotomy may be necessary for patients with very large pheochromocytomas or for those with intra-abdominal metastases that require debulking. An open anterior midline or subcostal approach is preferred and gives adequate exposure.[47]

Overall perioperative mortality is about 2.4%, whereas morbidity rates of up to 24% have been reported. Morbidity includes splenectomy, which is more common with open abdominal exploration than with laparoscopic surgery. Surgical complications are more common in patients with profound hypertension and highly secretory tumors and in those with repeated procedures. Complication risks are reduced by careful preoperative preparation, proper tumor localization, and intraoperative care noted above.[81]

MALIGNANT PHEOCHROMOCYTOMA AND PARAGANGLIOMA

About 10% of patients with an adrenal pheochromocytoma have metastases evident at the time of diagnosis, and another 5% are found to have metastatic disease within 5 years. Patients with MEN have been found to have a higher risk of a pheochromocytoma being malignant.[4] Paragangliomas are commonly malignant (30 to 50%).[15] Once metastases are detected, there is a 50% survival at 4.5 years.

Malignancy can sometimes be detected at the time of initial discovery of the pheochromocytoma or paraganglioma. Metastases are usually evident on the initial CT or MIBG scan. Absent metastases, neither histopathology nor endocrine testing can reliably determine whether a given pheochromocytoma is malignant or benign. Malignancy is more likely under the following circumstances: extra-adrenal location, larger size (≥ 6 cm), confluent tumor necrosis, vascular invasion, extensive local invasion, and high c-myc messenger ribonucleic acid expression.[82,83] In one series, high serum levels of neuron-specific enolase were found in 50% of patients with malignant pheochromocytoma but in none of 13 patients with benign pheochromocytoma. Serum levels of NPY tend to be more highly elevated in malignant versus benign pheochromocytoma but are not helpful in making the diagnosis of malignancy.[84] Malignancy can be definitely determined only by the presence of metastases, which may be visible on whole-body ^{123}I-MIBG scanning or on octreotide, PET, or CT scanning of the abdomen, pelvis, and chest. It is important to closely follow patients after resection of an apparently benign pheochromocytoma because metastases may require 20 years or more to become apparent.[85] In the presence of metastases, urinary norepinephrine and/or normetanephrines and serum chromogranin A may remain elevated after resection of the primary tumor unless metastases are small or nonfunctional.

The differential diagnosis for apparent metastases include incidental benign paragangliomas, second pheochromocytomas, multicentric paragangliomas, intraperitoneal seeding during surgery, and false-positive ^{123}I-MIBG scanning (see above).[86] Malignant pheochromocytomas typically metastasize to bones, retroperitoneal and regional lymph nodes, liver, contralateral adrenal gland, lungs, and, occasionally, brain or muscle. The bones most frequently involved include vertebrae, pelvis and ischium, clavicles, and proximal femurs and humeri; metastases to the cranium also occur, with a predilection for the frontal bone. Prevertebral paragangliomas may cause destruction of adjacent vertebrae. Spinal cord compression can

occur.[87] The 5-year survival rate for patients with metastatic disease is about 50%. However, patients with multiple pulmonary metastases generally have a poorer prognosis. Some metastatic tumors are rather indolent, and prolonged survival has been documented.[88]

It is usually best to surgically resect the primary tumor as well as large metastases. The surgery is guided by CT. However, CT may not visualize small malignant intra-abdominal metastases that are visualized with preoperative ^{123}I-MIBG scanning. In such cases, following preoperative injection of ^{123}I-MIBG, intraoperative use of a portable gamma probe may help locate the tumor.[89] Hypertension must be adequately controlled.

Chemotherapy has been employed for metastatic pheochromocytoma and paraganglioma. One chemotherapy regimen uses cyclophosphamide, vincristine, and dacarbazine.[90] This chemotherapy regimen, given to 12 patients every 21 days, caused complete or partial remissions in 57%. For metastatic paraganglioma, a regimen of cyclophosphamide, doxorubicin, and dacarbazine has caused partial remission or stabilization in most patients.[90] However, tumors usually relapse after cessation of chemotherapy. Chemotherapy has successfully caused temporary clearing of bone marrow metastases in preparation for stem cell harvest before therapy with high-dose ^{131}I-MIBG (see below).

Radiation therapy is employed for symptomatic metastases to the spine, long bones, or central nervous system. Pheochromocytomas are relatively resistant to conventional radiation therapy.

^{131}I-MIBG treatment of malignant pheochromocytomas was first performed in 1983 at the University of Michigan.[91] Subsequently, many other patients have been treated with ^{131}I-MIBG. Most treatment protocols employ repeated doses up to 200 mCi (7.4 GBq) ^{131}I-MIBG.[20,92,93] ^{131}I-MIBG uptake occurs in many nonfunctioning pheochromocytomas and metastases; such treatment can therefore be effective for such nonfunctioning tumors if scanning shows them to be avid for MIBG. Following ^{131}I-MIBG therapy, once background radiation has dissipated, a post-treatment whole-body scan is obtained (Figure 9–11).

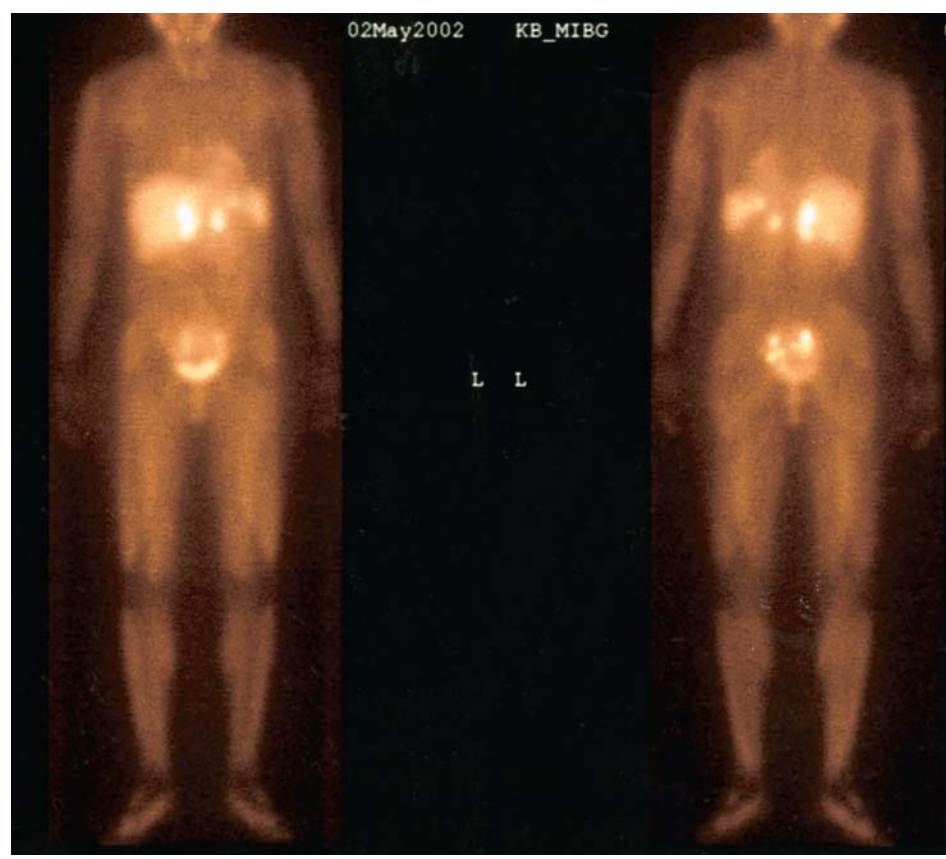


Figure 9–11. Whole-body scan following therapy with radioactive iodine (^{131}I)-metaiodobenzylguanidine in a patient with metastatic pheochromocytoma.

A higher-dose ^{131}I-MIBG treatment protocol has been employed at the University of California-San Francisco. The patient receives an intravenous infusion of ^{131}I-MIBG at a dose of up to 18 mCi/kg to a maximum of 800 mCi (29.6 GBq) over about 2 hours. Certain precautions must be taken for high-dose ^{131}I-MIBG therapy. A bone marrow biopsy is obtained to ensure absence of tumor in the marrow; granulocyte colony-stimulating factor–stimulated stem cell leukophoresis is then obtained for later use in the event of marrow suppression. Patients are hospitalized in a lead-shielded room with radiation precautions. They are medicated with KI and potassium perchlorate ($KClO_4$) to prevent thyroid damage by free ^{131}I. An indwelling Foley catheter is placed to reduce radiation exposure to the bladder area. Patients remain hospitalized until the emitted gamma radiation declines to safe levels, which usually requires about 5 to 7 days.

The majority of patients receiving ^{131}I-MIBG therapy experience partial remissions, stable disease, or symptomatic relief. Complete remissions have occurred uncommonly, usually in patients without a heavy tumor burden. The 5-year survival rate may be improved.[92] Therapy with ^{131}I-MIBG carries certain risks, including bone marrow suppression, infertility, and an increased lifetime risk of second malignancies. Repeated treatments are usually required.

PROGNOSIS AND FOLLOW-UP

With current perioperative management and surgical techniques, the mortality rate for patients undergoing pheochromocytoma resection is < 2%. Morbidity and hospital length of stay have been dramatically improved with laparoscopic surgery. The overall 5-year survival rate for patients with benign pheochromocytomas is 96% but is only 44% for patients with malignant pheochromocytomas and metastases. Even with complete resection of the pheochromocytoma, hypertension persists or recurs in 25%.

Patients require close follow-up. Persistent symptoms or hypertension can signify lack of cure and possibly metastatic disease. About 10% of pheochromocytomas are found to have metastases at the time of diagnosis or soon postoperatively. However, occult metastatic disease is detected, up to 20 years later, in another 5%.[94]

Patients are followed with 24-hour urine collections. Catecholamine excretion often remains high for up to 10 days after successful surgery (see above). Therefore, the first urine collection for fractionated catecholamines, metanephrines, and creatinine is delayed for at least 2 weeks postoperatively. Quarterly urine collections are obtained during the first year postoperatively and then annually or semiannually for at least 5 years. Nonfunctioning tumors may later develop functioning metastases.[95]

Weekly home blood pressure monitoring is recommended for the first year postoperatively and then monthly afterward. A rising blood pressure or recurrence of symptoms should trigger a full workup for recurrent or metastatic pheochromocytoma.

A postoperative ^{123}I-MIBG scan is recommended for all patients, especially those in whom there is any doubt about complete resection of the pheochromocytoma and for any patients with paraganglioma or multiple tumors. Follow-up ^{123}I-MIBG scanning is done for all patients with malignant or nonsecreting pheochromocytoma. In patients with normal renal function, follow-up using chromogranin A as a tumor marker may be helpful, particularly for patients with metastatic or recurrent disease.

REFERENCES

1. Manger WM, Gifford RW Jr. Pheochromocytoma. New York: Springer-Verlag; 1977.
2. Robinson R. Tumours that secrete catecholamines. Their detection and clinical chemistry. New York: John Wiley & Sons; 1980.
3. Lack EE. Adrenal medullary hyperplasia and pheochromocytoma. In: Lack EE, editor. Pathology of the adrenal glands. New York: Churchill Livingstone; 1990.
4. Strömbeck JP, Hedberg TP. Tumor of the suprarenal medulla associated with paroxysmal hypertension. Report of a case preoperatively diagnosed and cured by extirpation after capsular incision. Acta Chir Scand 1939;82:177–89.
5. Weil-Malherbe H, Axelrod J, Tomchick R. Blood-brain barrier for adrenaline. Science 1959;129:1226.
6. Hoffman BB. Adrenoreceptor-activating and other sympathomimetic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 8th ed. New York: McGraw Hill; 2000. p. 120–37.
7. Dishy V, Sofowora GG, Xie H-G, et al. The effect of common polymorphisms of the α_2-adrenergic receptor on agonist-mediated vascular desensitization. N Engl J Med 2001; 345:1030–5.
8. Kirby BD, Ham J, Fairley HB, et al. Normotensive pheochromocytoma. Pharmacologic, paraneoplastic and anesthetic considerations. West J Med 1983;139:221–5.

9. Blaschko H, Born GVR, D'Iorio A, Eade NR. Observations on the distribution of catecholamines and adenosine-triphosphate in the bovine adrenal medulla. J Physiol 1956;133:548–57.
10. Eurin J, Barthelemy C, Masson F, et al. Release of neuropeptide Y and hemodynamic changes during surgical removal of human pheochromocytoma. Regul Pept 2000;86:95–102.
11. Januszewicz W, Wocial B, Ignatowska-Switalska H, et al. Alterations in plasma neuropeptide Y immunoreactivity and catecholamine levels during surgical removal of pheochromocytoma. J Hypertens 1998;16:543–7.
12. DeS Senanayake P, Denker J, Bravo EL, Graham RM. Production, characterization, and expression of neuropeptide Y by human pheochromocytoma. J Clin Invest 1995;96:2503–9.
13. Joffres MR, Hamet P, MacLean DR, et al. Distribution of blood pressure and hypertension in Canada and the United States. Am J Hypertension 2001;14:1099–105.
14. Sutton MG, Shepps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc 1981;56:354–60.
15. Platts JK, Drew PJT, Harvey JN. Death from phaeochromocytoma: lessons from a post-mortem survey. J R Coll Physicians Lond 1995;29:299–306.
16. Gifford RW Jr, Manger WM, Bravo EL. Pheochromocytoma. Endocrinol Metab Clin North Am 1994;23:387–404.
17. Hume DM. Pheochromocytomas in the adult and in the child. Am J Surg 1960;99:458.
18. Ahlawat SK, Jain S, Kumari S, et al. Pheochromocytoma associated with pregnancy: case report and review of the literature. Obstet Gynecol Surg 1999;54:728–37.
19. Gifford RW Jr, Kvale WF, Maher FT, et al. Clinical features, diagnosis and treatment of pheochromocytoma: a review of 76 cases. Mayo Clin Proc 1964;39:281–302.
20. Benowitz NL. Pheochromocytoma—recent advances in diagnosis and treatment. West J Med 1988;148:561–7.
21. Loh KC, Matthay KK, Hoover M, et al. Hypercalcemia in malignant paraganglioma due to parathyroid hormone-related protein. Horm Res 1998;50:217–21.
22. Lucon AM, Pereira MAA, Mendonça BB, et al. Pheochromocytoma: study of 50 cases. J Urol 1997;157:1208–12.
23. Yanaihara H, Hata M, Nishikawa Y, et al. Application of region-specific immunoassay for chromogranin A: substantial clue for detection and measurement of chromogranin A in human plasma. Regul Pept 1999;80:83–90.
24. Canale MP, Bravo EL. Diagnostic specificity of serum chromogranin-A for pheochromocytoma in patients with renal dysfunction. J Clin Endocrinol Metab 1994;78:1139–44.
25. Ferrari L, Seregni E, Bajetta E, et al. The biological characteristics of chromogranin A and its role as a circulating marker in neuroendocrine tumours. Anticancer Res 1999; 19:3415–27.
26. Stridsberg M, Husebye ES. Chromogranin A and chromogranin B are sensitive circulating markers for phaeochromocytoma. Eur J Endocrinol 1997;136:67–73.
27. Jensen TB, Hilsted L, Rehfeld JF. Library of sequence-specific radioimmunoassays for human chromogranin A. Clin Chem 1999;45:549–60.
28. Grant CS. Pheochromocytoma. In: Clark OH, Duh Q-Y, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 513–22.
29. Rosano TG, Swift TA, Hayes LW. Advances in catecholamine and metabolite measurements for diagnosis of pheochromocytoma. Clin Chem 1991;37:1854–67.
30. Goldstein DS, Stull R, Markey SP, Marks ES, Keiser KR. Dihydrocaffeic acid: a common contaminant in the liquid chromatographic-electrochemical measurement of plasma catecholamines in man. J Chromatogr 1984;311:148–53.
31. Sclafani LM, Woodruff JM, Brennan MF. Extraadrenal retroperitoneal paragangliomas: natural history and response to treatment. Surgery 1990;108:1124–30.
32. Odze R, Bégin LR. Malignant paraganglioma of the posterior mediastinum. A case report and review of the literature. Cancer 1990;65:564–9.
33. Paleologos TS, Gouliamos AD, Kourousis DD, et al. Paraganglioma of the cauda equina: a case presenting features of increased intracranial pressure. J Spinal Disord 1998; 11:362–5.
34. Tashiro M, Nagase M, Nakajima T, et al. Malignant paraganglioma. Report of a case and review of the Japanese literature. J Craniomaxillofac Surg 1988;16:324–9.
35. Bomanji J, Levinson DA, Flatman WD, et al. Uptake of iodine-123 MIBG by pheochromocytomas, paragangliomas, and neuroblastomas: a histopathologic comparison. J Nucl Med 1987;28:973–8.
36. Shulkin BL, Shapiro B. Current concepts on the diagnostic use of MIBG in children. J Nucl Med 1998;39:678–88.
37. Tsuchimochi S, Nakajo M, Nakabeppu Y, Tani A. Metastatic pulmonary pheochromocytomas: positive I-123 SPECT with netgative I-131 MIBG and equivocal I-123 MIBG planar imaging. Clin Nucl Med 1997;22:687–90.
38. Shapiro B, Gross MD. Radiochemistry, biochemistry, and kinetics of ^{131}I-metaiodobenzylguanidine (MIBG) and ^{123}I-MIBG: clinical implicationns of the use of ^{123}I-MIBG. Med Pediatr Oncol 1987;15:170–7.
39. van der Harst E, de Herder WW, Bruining HA, et al. [^{123}I]Metaiodobenzylguanidine and [^{111}In]octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metab 2001;86:685–93.
40. Roelants V, Goulios C, Beckers C, Jamar F. Iodine-131-MIBG scintigraphy in adults: interpretation revisited? J Nucl Med 1998;39:1007–12.
41. Francis IR, Gross MD, Shapiro B, et al. Integrated imaging of adrenal disease. Radiology 1992;184:1–13.
42. Neumann DR, Basile KE, Bravo EL, et al. Malignant pheochromocytoma of the anterior mediastinum: PET findings with (^{18}F)FDG and ^{82}Rb. J Comput Assist Tomogr 1996;20:312–6.
43. Pacak K, Eisenhofer G, Carrasquillo JA, et al. 6-[^{18}F]fluorodopamine positron emission tomographic (PET) scanning for diagnostic localization of pheochromocytoma. Hypertension 2001;38:6–8.
44. Lin JC, Palafox BA, Jackson HA, et al. Cardiac pheochromocytoma: resection after diagnosis by 111-indium octreotide scan. Ann Thorac Surg 1999;67:555–8.
45. Meunier JP, Tatou E, Bernard A, et al. Cardiac pheochromocytoma. Ann Thorac Surg 2001;71:712–3.
46. Koch CA, Vortmeyer AO, Huang SC, et al. Genetic aspects of pheochromocytoma. Endocr Regul 2001;35(1):43–52.
47. Howe JR, Norton JA, Wells SA Jr. Prevalence of pheochromocytoma and hyperparathyroidism in multiple

endocrine neoplasia type 2A: results of long-term follow-up. Surgery 1993;114:1070–7.
48. Kebebew E, Duh QY. Benign and malignant pheochromocytoma: diagnosis, treatment, and follow-up. Surg Oncol Clin North Am 1998;7:765–89.
49. Brandi ML, Gagel RF, Angeli A, et al. Consensus guidelines for diagnosis and therapy of MEN type 1 and 2. J Clin Endocrinol Metab 2001;86:5658–71.
50. Eisenhofer G, Lenders JWM, Linehan WM, et al. Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. N Engl J Med 1999; 340:1872–9.
51. Richard S, Beigelman C, Duclos JM, et al. Pheochromocytoma as the first manifestation of von Hippel-Lindau disease. Surgery 1994;116:1076–81.
52. Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med 2002;19:1459–65.
53. McCorkell SJ, Niles NL. Fine-needle aspiration of catecholamine-producing adrenal masses: a possibly fatal mistake. AJR Am J Roentgenol 1985;145:113–4.
54. Lambert MA, Hirschowitz L, Russell RC. Fine needle aspiration biopsy: a cautionary tale. Br J Surg 1985;72:364.
55. Newell KA, Prinz RA, Brooks MH, et al. Plasma catecholamine changes during excision of pheochromocytoma. Surgery 1988;104:1064–73.
56. Boutros AR, Bravo EL, Zanettin G, Straffon RA. Perioperative management of 63 patients with pheochromocytoma. Cleve Clin J Med 1990;57:613–7.
57. Ulchaker JC, Goldfarb DA, Bravo EL, Novick AC. Successful outcomes in pheochromocytoma surgery in the modern era. J Urol 1999;161:764–7.
58. Combemale F, Carnaille B, Tavernier B, et al. Exclusive use of calcium channel blockers and cardioselective beta-blockers in the pre- and peri-operative management of pheochromocytoma. 70 cases. Ann Chir 1998;52:341–5.
59. Starikova AM, Chvanov MA, Pogorelaya NC, Kostyuk PG. Nifedipine-induced morphological differentiation of rat pheochromocytoma cells. Neuroscience 1998;611–7.
60. Blake GM, Lewington VJ, Fleming JS, et al. Modification by nifedipine of ^{131}I-meta-iodobenzylguanidine kinetics in malignant pheochromocytoma. Eur J Nucl Med 1988;14: 345–8.
61. Santeiro ML, Stromquist C, Wyble L. Phenoxybenzamine placental transfer during the third trimester. Ann Pharmacother 1996;30:1249–51.
62. Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. Endocr Rev 1994;15:356–8.
63. Sheps SG, Jiang NS, Klee GG, van Heerden JA. Recent developments in the diagnosis and treatment of pheochromocytoma. Mayo Clin Proc 1990;65:88–95.
64. Steinsapir J, Carr AA, Prisant LM, Bransome ED Jr. Metyrosine and pheochromocytoma. Arch Intern Med 1997; 157:901–6.
65. Koriyama N, Kakei M, Yaekura K, et al. Control of catecholamine release and blood pressure with octreotide in a patient with pheochromocytoma: a case report with in vitro studies. Horm Res 2000;53:46–50.
66. O'Riordan JA. Pheochromocytomas and anesthesia. Int Anesthesiol Clin 1997;35:99.
67. Joris JL, Hamoir EE, Hartstein GM, et al. Hemodynamic changes and catecholamine release during laparoscopic adrenalectomy for pheochromocytoma. Anesth Analg 1999;88:16–21.
68. Hamilton A, Sirrs S, Schmidt N, Onrot J. Anesthesia for phaeochromocytoma in pregnancy. Can J Anaesth 1997; 44:654–7.
69. Kreienmeyer J. Total intravenous anesthesia with propofol and sufentanil for resection of pheochromocytoma. Anaesthesiol Reanim 1997;22:80–2.
70. Colson P, Ryckwaert F, Ribstein J, et al. Haemodynamic heterogeneity and treatment with the calcium channel blocker nicardipine during phaeochromocytoma surgery. Acta Anaesthesiol Scand 1998;42:1114–9.
71. Johanning RJ, Zaske DE, Tschida SJ, et al. A retrospective study of sodium nitroprusside use and assessment of the potential risk of cyanide poisoning. Pharmacotherapy 1995;15:773–7.
72. Khafagi FA, Shapiro B, Fig LM, et al. Labetalol reduces iodine-131 MIBG uptake by pheochromocytoma and normal tissues. J Nucl Med 1989;30:481–9.
73. Feldman JM. Falsely elevated urinary excretion of catecholamines and metanephrines in patients receiving labetalol therapy. J Clin Pharmacol 1987;27:288–92.
74. Gagner M. Laparoscopic adrenalectomy. In: Clark OH, Duh Q-Y, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 535–45.
75. Duh Q-Y, Siperstein AE, Clark OH, et al. Laparoscopic adrenalectomy. Comparison of the lateral and posterior approaches. Arch Surg 1996;131:870–5; discussion 875–6.
76. Winfield HN, Hamilton BD, Bravo EL. Technique of laparoscopic adrenalectomy. Urol Clin North Am 1997;24: 459–65.
77. Sprung J, O'Hara JF Jr, Gill IS, et al. Anesthetic aspects of laparoscopic and open adrenalectomy for pheochromocytoma. Urology 2000;55:339–43.
78. Cheah WK, Clark OH, Horn JK, et al. Laparoscopic adrenalectomy for pheochromocytoma. World J Surg 2002;26: 1048–51.
79. Demeure MJ, Carlsen B, Traul D, et al. Laparoscopic removal of a right adrenal pheochromocytoma in a pregnant woman. J Laparoendosc Adv Surg Techniq 1998; 8:315–9.
80. Gill IS, Soble JJ, Sung GT, et al. Needlescopic adrenalectomy—the initial series: comparison with conventional laparoscopic adrenalectomy. Urology 1998;52:180–6.
81. Neumann HPH, Reincke M, Bender BU, et al. Preserved adrenocortical function after laparoscopic bilateral adrenal sparing surgery for hereditary pheochromocytoma. J Clin Endocrinol Metab 1999;84:2606–10.
82. Duh Q-Y. Editorial: evolving surgical management for patients with pheochromocytoma. J Clin Endocrinol Metab 2001;86:1477–8.
83. Linnoila RI, Keiser HR, Steinberg SM, Lack EE. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. Hum Pathol 1990;21:1168–80.

84. Liu J, Voutilainen R, Kahri AI, Heikkila P. Expression patterns of the c-myc gene in adrenocortical tumors and pheochromocytomas. J Endocrinol 1997;152:175–81.
85. Grouzmann E, Gicquel C, Plouin PF, et al. Neuropeptide Y and neuron-specific enolase levels in benign and malignant pheochromocytoma. Cancer 1990;66:1833–5.
86. Lumachi F, Polistina F, Favia G, D'Amico DF. Extraadrenal and multiple pheochromocytomas. Are there really any differences in pathophysiology and outcome? J Exp Clin Cancer Res 1998;17:303–5.
87. Karasov RS, Sheps SG, Carney JA, et al. Paragangliomatosis with numerous catecholamine-producing tumors. Mayo Clin Proc 1982;57:590–5.
88. Cybulski GR, Nijensohn E, Brody BA, et al. Spinal cord compression from a thoracic paraganglioma: case report. Neurosurgery 1990;28:306–309.
89. Kebebew E, Siperstein AE, Clark OH, Duh QY. Results of laparoscopic adrenalectomy for suspected and unsuspected malignant adrenal neoplasms. Arch Surg 2002;137:948–51; discussion 952–3.
90. Lehnert H, Weber P, Nägele-Wöhrle B, et al. Intraoperative localization of malignant pheochromocytoma by ^{123}I-metaiodobenzylguanidine single probe measurement. Klin Wochenschr 1988;66:61–4.
91. Patel SR, Winchester DJ, Benjamin RS. A 15-year experience with chemotherapy of patients with paraganglioma. Cancer 1995;76:1476–80.
92. Sisson JC, Shapiro B, Beierwaltes WH, et al. Radiopharmaceutical treatment of malignant pheochromocytoma. J Nucl Med 1984;24:197–206.
93. Mukherjee JJ, Kaltsas GA, Islam N, et al. Treatment of metastatic carcinoid tumours, phaeochromocytoma, paraganglioma and medullary carcinoma of the thyroid with ^{131}I-metaiodobenzylguanidine (^{131}I-mIBG). Clin Endocrinol 2001; 55:47–60.
94. Troncone L, Rufini V. Nuclear medicine therapy of pheochromocytoma and paraganglioma. Q J Nucl Med 1999;43:344–55.
95. Tanaka S, Ito T, Tomoda J, et al. Malignant pheochromocytoma with hepatic metastasis diagnosed 20 years after resection of the primary adrenal lesion. Intern Med 1993;32:789–94.
96. Fernandez-Llamazares J, Sabrià-Leal M, Armengol-Carrasco M, et al. Functioning metastases of a nonfunctioning paraganglioma. J Surg Oncol 1988;37:213–4.

10

Adrenocortical Carcinoma

MAHA AL FEHAILY, MD
QUAN-YANG DUH, MD

INCIDENCE AND EPIDEMIOLOGY

Adrenocortical carcinomas account for only 0.05 to 0.2% of all cancers, with an annual incidence of 2 per million. The age of occurrence is bimodal, with the first peak occurring before the age of 5 years and the second peak in the fourth and fifth decades.[1] Most series find a slight preponderance in women (4:3). Adrenocortical carcinomas occur equally in the right and left adrenal glands and are bilateral in 2.4% of patients.[2] Adrenocortical carcinoma is found in 4% of patients with adrenal incidentalomas and in 10% of adrenal incidentalomas larger than 4 cm.[3,4]

MOLECULAR PATHOGENESIS

Adrenocortical carcinoma is associated with several genetic syndromes:

- Multiple endocrine neoplasia (MEN) type I (parathyroid, pancreatic islet cell, and pituitary neoplasms)[5]
- Beckwith-Wiedemann syndrome (exophthalmos, hemihypertrophy, macroglossia, gigantism, nesidioblastosis, and visceral organ hypertrophy); patients may have neonatal adrenocortical carcinomas and childhood tumors, such as Wilms' tumor, and hepatoblastoma[6]
- Li-Fraumeni syndrome (mutation in the *P53* tumor suppressor gene), which is associated with pediatric adrenocortical carcinoma[7]

Adrenocortical carcinomas are monoclonal lesions, indicating that specific loci in the genome are regulated in adrenal tumorigenesis.[8] Although adrenocorticotropic hormone (ACTH) signaling through adenyl cyclase and protein kinase A is important for normal adrenal cellular physiology, this pathway may inhibit the growth of adrenocortical tumors, and inactivation of the ACTH receptor may promote tumor formation.[9] Loss of heterozygosity of the ACTH receptor gene (*MC2R*) in chromosome 18p occurs frequently in adrenocortical carcinoma but not in adenomas, suggesting its role in adrenocortical carcinogenesis.[10,11]

Several other genes, such as *GSP*, *MENIN* (multiple endocrine neoplasia type I), and *APC* (familial adenomatous polyposis), also may play a role in adrenocortical tumorigenesis.[12,13] Expression of growth factor alpha and an epidermal growth factor receptor is markedly elevated in adrenocortical carcinomas but not in adrenocortical adenomas.[14] Somatic *P53* mutations are also common in adrenocortical carcinomas.[15]

CLINICAL AND BIOCHEMICAL EVALUATION

Adrenocortical carcinomas cause symptoms by mass effect or local invasion. Some adrenocortical carcinomas secrete hormones that cause Cushing's syndrome (50%), virilization (34%), and, rarely, feminization or mineralocorticoid excess syndrome.[16,17] Ninety-five percent of patients younger than 5 years old present with virilization.[18] The rapid onset of Cushing's syndrome with virilization strongly suggests adrenocortical carcinoma.

In general, the hormonal pattern in patients with Cushing's syndrome caused by adrenocortical car-

cinomas is similar to that observed in patients with adrenal adenomas. The presence of very high levels of urinary free cortisol and 17-ketosteroid, or elevated levels of intermediary precursors in the steroid biosynthesis or their metabolites, however, strongly suggests adrenocortical carcinomas.[19,20] Tumors secreting multiple hormones, such as cortisol and aldosterone, are usually malignant. Adrenocortical carcinomas that secrete aldosterone are larger and cause higher blood aldosterone levels and more hypokalemia than the usual small (less than 2 cm) benign aldosteronomas.[21,22] Nonfunctioning or minimally functioning tumors may be discovered incidentally on ultrasound or computed tomographic (CT) scans performed for unrelated reasons, so-called incidentalomas. Patients with nonfunctional cortical carcinomas, however, usually present with local symptoms, such as pressure, and invasion of contagious structures. Other associated symptoms include unexplained fever, anemia, and weight loss.[23,24]

RADIOLOGIC EVALUATION

Imaging studies often provide useful information about the nature of adrenal tumors (Figure 10–1). Certain abnormalities suggest adrenocortical carcinomas and may change treatment and surgical approach.

For diagnosis,

- CT and magnetic resonance imaging (MRI) scans can usually diagnose myelolipoma, cysts, and hemorrhage. CT scans with intravenous contrast or chemically shifted MRI scans using gadolinium help to differentiate between adrenocortical adenomas and carcinomas (Table 10–1).[25–33] Combining the information gained from imaging studies along with other diagnostic tests helps to determine whether an adrenal tumor is likely to be malignant. Adrenocortical carcinomas are usually
  1. Larger than 5 cm
  2. Heterogeneous because of necrosis
  3. Irregular and have poorly defined margins
  4. Invasive to the upper pole of the kidney or the inferior vena cava
  5. Associated with adjacent nodal metastasis or liver metastasis
- MRI helps to identify pheochromocytoma, which enhances on T_2-weighted or gadolinium-enhanced images. Adrenocortical carcinomas and metastatic tumors in the adrenal glands, however, also enhance on T_2-weighted images.[27]
- Iodocholesterol scintigraphy (iodomethylnorcholesterol [NP-59]) can determine whether an adrenocortical tumor is functional or nonfunctional. Most adrenocortical carcinomas fail to take up iodocholesterol.[22] Iodocholesterol scinti-

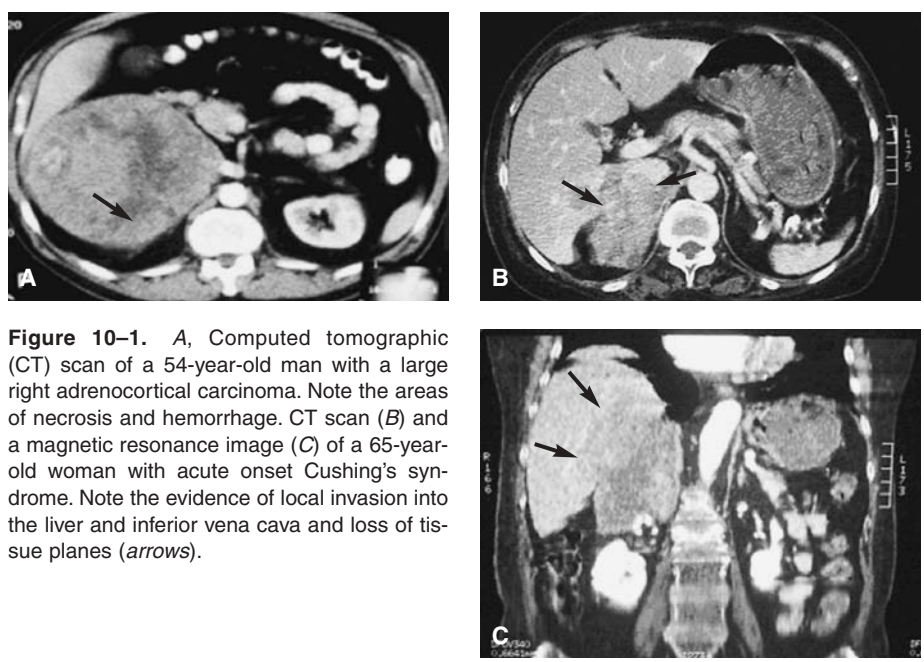


Figure 10–1. *A*, Computed tomographic (CT) scan of a 54-year-old man with a large right adrenocortical carcinoma. Note the areas of necrosis and hemorrhage. CT scan (*B*) and a magnetic resonance image (*C*) of a 65-year-old woman with acute onset Cushing's syndrome. Note the evidence of local invasion into the liver and inferior vena cava and loss of tissue planes (*arrows*).

Table 10–1. IMAGING CRITERIA THAT MAY HELP TO DISTINGUISH ADRENOCORTICAL ADENOMA FROM ADRENOCORTICAL CARCINOMAS

Imaging	Benign	Malignant	Sensitivity (%)	Specificity (%)	Remarks
CT scan	Less than 10 HU	More than 18 HU	73	96	Enhancement is measured in HU
CT scn + contrast	Less than 30 HU; greater than 50% washout within 15 min of contrast injection	More than 30 HU; greater retention of contrast	95	100	Enhancement depends on lipid content; lipid-poor masses are likely to be malignant
MRI (T_1, T_2, CH)	A/L less than 1.4	A/L 1.2–2.8	81–93	92–100	The use of A/L ratio is not reliable because the ratio overlaps in up to 40% of cases
MRI + CH	Lipid-rich adenomas show 34% change in relative signal intensity between in-phase and out-phase imaging		81	100	

A/L ratio = ratio of signal intensity of the adrenal mass to the liver; CH = chemical shift; CT = computed tomography; HU = Hounsfield units; MRI = magnetic resonance imaging.

graphy and CT scan can be used together for the diagnosis of small (less than 4 cm) euadrenal masses; discordant images (CT image on one side and increased uptake on the contralateral side) suggest malignancy.[34]

- Imaging studies can guide fine-needle aspiration biopsy. Biopsy is usually recommended if a metastatic cancer is possible, and documenting such a diagnosis would alter therapy.

To plan management,

- CT and MRI scan help to detect metastases in regional lymph nodes, liver, or lungs. They also help to determine the stage of disease and help with surgical planning.
- Magnetic resonance phlebography or a conventional venogram may be necessary to evaluate large right-sided adrenocortical carcinoma for intracaval thrombi. Cardiopulmonary bypass may be necessary to prevent tumor thromboembolism during the operation in such patients.[35,36]

STAGING

The Sullivan modification of the MacFarlane system is the most widely used staging system for adrenocortical carcinoma (Table 10–2).[37,38] The criteria used reflect the tendency of adrenocortical carcinomas to invade locally. At the time of diagnosis, 20% of adrenocortical carcinomas have already spread locally, and about half of the patients have distant metastases, to the liver (47%), lung (43%), and bone (15%).[17,39] Adrenocortical carcinomas may grow into the right atrium.

Table 10–2. STAGING SYSTEM FOR ADRENOCORTICAL CARCINOMA

Stage	MacFarlane	Sullivan
I	T1 (≤ 5 cm) N0, M0	T1 (≤ 5 cm), N0, M0
II	T2 (> 5 cm) N0, M0	T2 (> 5 cm), N0, M0
III	T3 (local invasion without involvement of adjacent organs) or mobile positive lymph nodes, M0	T3 (local invasion), N0, M0, or T1–2, N1 (positive lymph nodes), M0
IV	T4 (invasion of adjacent organs) or fixed lymph nodes, or M1 (distant metastases)	T4 (local invasion), N0, M0 or T3, N1, M0 or T1–4, N0–1, M1 (distant metastases)

M = metastases; N = lymph nodes; T = tumor size.

PATHOLOGIC FEATURES

It is often difficult to distinguish atypical adrenocortical adenomas from low-grade adrenocortical carcinomas based on histologic features alone. Several criteria are used to distinguish between benign and malignant adrenocortical tumors. Most are based on histologic findings, such as nuclear grade, mitotic rate, atypical mitotic figures, necrosis, and capsular invasion. In addition to diagnosing malignancy, these criteria may predict the behavior of the tumor and the need for adjuvant medical therapy.[40–42] Immunohistochemical staining of adrenocortical carcinoma is almost always positive for vimentin, negative for epithelial membrane antigen, and usually negative for cytokeratin. It is often difficult to distinguish adrenocortical carcinoma from renal cell carcinoma or metastatic adrenocarcinomas by routine histology; the presence of epithelial membrane antigen staining in both renal cell carcinoma and metastatic adenocarcinoma is often helpful in resolving this issue.[43,44]

DECISION-MAKING

Several issues need to be addressed when evaluating patients with adrenal tumors:

- Adrenocortical carcinomas are rare, and little is known about the pathogenesis. There are few large series, and the data provided are limited because of the changing therapeutic strategies during the time of investigation. To date, there are no convincing randomized controlled trials to assess the natural history and the response to different treatments.
- Adrenocortical carcinomas are usually diagnosed late in their course. At diagnosis, about one-third to half of patients already have metastasis, and the average tumor is larger than 12 cm.[45,46] Small adrenocortical carcinomas (less than 5 cm, stage I) are rarely diagnosed because they grow rapidly; thus, the time window to diagnosis is narrow. The histologic diagnosis of small adrenocortical carcinomas is also difficult, and they may be misdiagnosed as adenomas.[47]
- Incidentally discovered adrenal tumors (incidentalomas) are becoming more common. The workup and management of incidentalomas of 3 to 5 cm remain controversial, partly because of the difficulties in differentiating benign from malignant adrenocortical tumors. A suggested approach to incidentalomas is shown in Figure 10–2.
- Clinical features, laboratory findings, and imaging tests help distinguish benign from malignant tumors. To date, however, there are no tumor markers or features that are absolutely diagnostic.
- There is a strong correlation between the size of an adrenocortical tumor and malignancy. Copeland suggested using 6 cm as a size threshold to resect nonfunctioning adrenal tumors, to avoid operating on too many patients with adenomas.[48] When cancer is present, however, fewer patients can be cured.[49,50] Most cancers are at one time smaller than 6 cm. In fact, adrenocortical cancer as small as 1.7 cm has been reported.[50] On the other hand, the vast majority of nonfunctional small adrenocortical tumors (less than 3 cm) are benign and can be safely observed. Adrenocortical carcinomas less than 3 cm are more common in childern and young adults so that even small adrenal tumors should be resected in these patients.[51]
- Complete surgical resection is the only potentially curative treatment for patients with adrenocortical carcinomas. Patients with stage I and stage II cancer have a better prognosis, although it is still relatively poor, and it is easier to resect cancers at an earlier stage.

Indications of surgical resection of adrenal cortical mass are

- Functional adrenal tumors
- Tumors larger than 5 cm in diameter
- Tumors with suspicious imaging characteristics, such as heterogeneity, irregular margins, adjacent nodes, or evidence of invasion

Treatment of 3 to 5 cm tumors that are nonfunctioning and have benign imaging characteristics depends on other factors, such as patient age, tumor characteristics, and comorbidity. The decision to remove such tumors partly depends on whether the patients are willing to accept uncertainty and whether long-term follow-up is possible.

A suggested algorithm for evaluation and management of patients with adrenocortical carcinoma is shown in Figure 10–3.

THERAPEUTIC INTERVENTIONS

Surgery

Surgery is the main treatment for adrenocortial carcinoma and the only option with a potential for cure.

- Surgical resection, preferably complete resection, is the initial step in therapy. Surgical strategy should be planned based on preoperative imaging findings.
- Intraoperative and postoperative administration of steroids is necessary in patients with cortisol-secreting tumors to avoid addisonian crisis.
- A standard open approach is used for most large adrenal tumors. This gives excellent exposure, minimizes tumor spillage, and allows for vascular control of the inferior vena cava, aorta, and renal vessels. For very large tumors, a thoracoabdominal approach provides better exposure. Laparoscopic adrenalectomy for large invasive adrenocortical carcinoma is difficult and risks inadequate resection and capsular rupture with seeding, causing local recurrence.
- Resection is possible in only two-thirds of patients.[52] Invasion into adjacent organs is common and may require en bloc resection of the kidney, portions of the liver, and regional lymph nodes. Thus, preoperative evaluation of the function of the contraleral kidney is absolutely necessary should nephrectomy be required.
- Palliative resection may help to decrease hormone secretion.
- Adrenocortical carcinomas sometimes invade the liver, so segmentectomy or wedge resection may be necessary.
- Patients with recurrent or metastatic adrenocortical carcinomas should undergo reoperation, if possible. Unfortunately, after an apparent curative resection, two-thirds of patients develop recurrence within 1 to 2 years.[17,52,53] Reresection

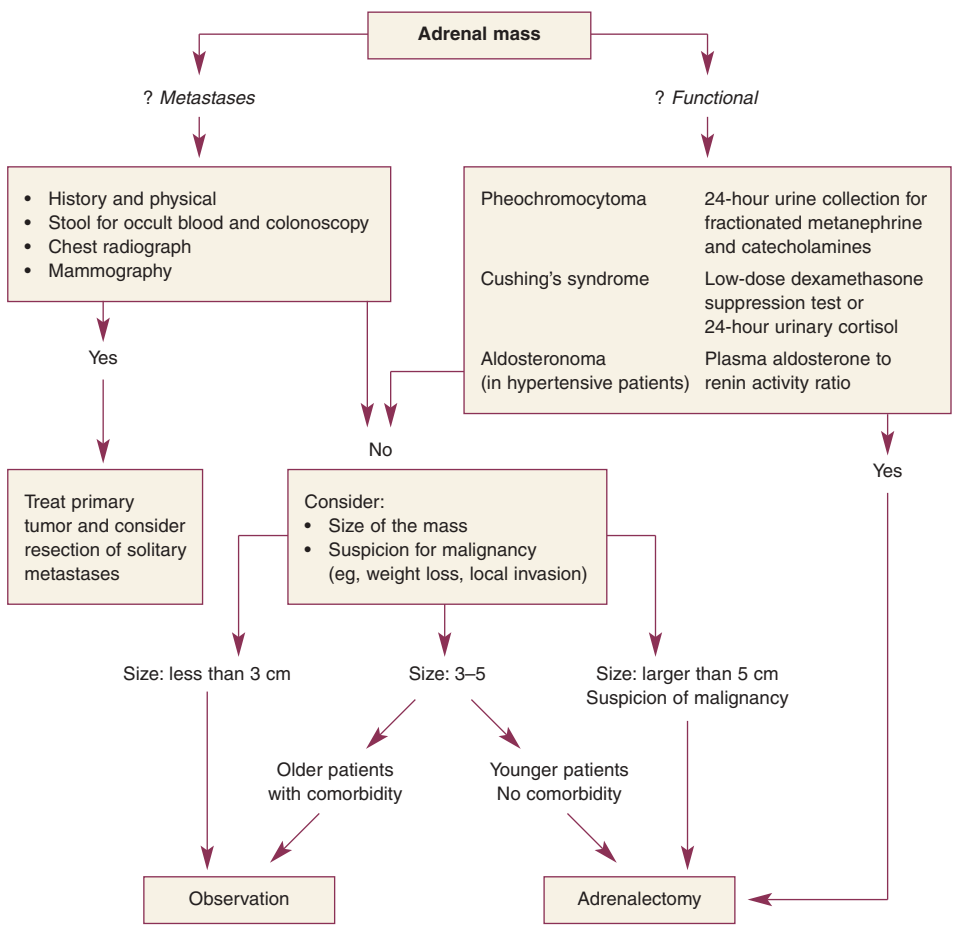


Figure 10–2. Management of patients with adrenal incidentaloma.

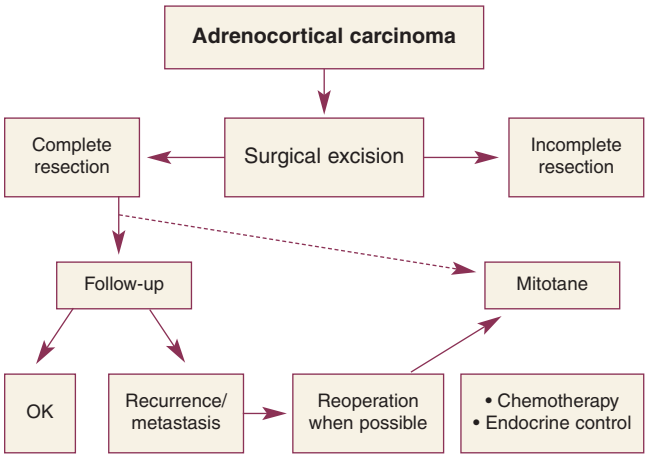


Figure 10–3. Management of patients with adrenocortical carcinoma.

may palliate symptoms and prolong survival (56 months after resection versus 19 months with medical therapy only).[17,54]

Radiation Therapy

Although adrenocortical carcinomas are relatively radioresistant, radiation therapy is used to palliate bony metastases and to treat local recurrences that are not amenable to surgical resection.[55–57]

Medical Therapy

Medical therapy is used, especially in advanced disease, usually as an adjuvant treatment in addition to surgery.

- Mitotane is used to treat patients with metastatic, unresectable, or recurrent adrenocortical cancers. It is an adrenolytic drug that is cytotoxic to steroid-producing cells. It causes necrosis in adrenocortical carcinoma and in normal adrenal cortex. Glucocorticoid replacement is thus necessary when patients are treated with mitotane. The clinical efficacy and outcome of mitotane treatment are unpredictable, with a response rate of 20 to 30%, although the response is dramatic in some patients.[24,58,59] Adjuvant therapy with mitotane may prolong survival, but the side effects, which are dose dependent, are significant. This makes it difficult for patients to tolerate this treatment. Monitoring of blood mitotane levels helps to increase effectiveness and decrease toxicity.[59]
- *Chemotherapy:* Cisplatinum combined with mitotane may improve survival.[60]
- *Endocrine control:* To help control endocrine activity, which may not be adequately treated by surgical resection or mitotane, one may use inhibitors of steroid production, such as ketoconazole and metyrapone.

PROGNOSIS

The prognosis of patients with adrenocortical carcinomas is poor. The mean survival is 18 months for surgically treated patients but only 3 months for untreated patients.[60] Tumor stage and completeness of resection are the most important prognostic factors (Table 10–3).[17,38,61,62]

FOLLOW-UP

Unfortunately, 85% of patients undergoing potentially curable resections eventually develop local recurrences or distant metastases.[17] Local recurrence or metastasis should be resected if technically feasible. Postresection surveillance includes the following:

- Careful history and physical examination
- Chest radiography and CT scan of the chest and abdomen
- Urinary steroid or serum dehydroepiandrosterone sulfate levels for patient with preoperative elevation of these hormones.

Follow-up is continued indefinitely because adrenocortical carcinomas can recur after many years.

Table 10–3. PROGNOSTIC FACTORS IN PATIENTS WITH ADRENOCORTICAL CARCINOMAS

Clinical factors
Early stage and curative resection are the most important factors predicting improved survival rate and recurrence
Better prognosis when age younger than 40 yr
Hormonal activity and type of hormone secretion: no difference in survival rate between patients with functional versus patients with nonfunctional tumors. Androgen-secreting tumors, however, may carry better prognosis.
Pathologic factors
Size of the tumor: tumors > 12 cm have worse prognosis
Presence of more than 6 mitotic figures per high-power field indicates worse prognosis
Other factors that may predict outcome include venous, capsular, adjacent organ invasion; atypical mitosis; and mdm2 overexpression in malignant adrenal tissue

SUMMARY

Adrenocortical carcinomas are rare and are associated with a dismal prognosis. Features that are characteristic of adrenocortical carcinomas (versus adrenocortical adenomas) are size > 6 cm, heterogeneity and irregular margins on CT or MRI scan, rapid onset of Cushing's syndrome, and secretion of multiple hormones and metabolites. Stage and completeness of resection are the most important prognostic factors. Complete resection, although rarely achieved, should be attempted. Reresection of recurrent cancer, if possible, may also prolong survival. Adjuvant treatment with mitotane may be useful.

REFERENCES

1. Norton JA. Adrenal tumors. In: De Vita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. Philadelphia: Lippincott-Raven; 1997. p. 1659–77.
2. Wooten MD, King DK. Adrenal cortical carcinoma. Cancer 1993;72:3145–55.
3. Kloos RT, Gross MD, Francis IR, et al. Incidentally discovered adrenal masses. Endocr Rev 1995;16:460–84.
4. Bernini GP, Miccoli P, Moretti A, et al. Sixty adrenal masses of large dimensions: hormonal and morphologic evaluation. Urology 1998;51:920–5.
5. Skogseid B, Rastad J, Gobl A, et al. Adrenal lesion in multiple endocrine neoplasia type 1. Surgery 1995;118:1077–82.
6. Satge D, Philippe E, Ruppe M, et al Neonatal carcinoma. Bull Cancer 1988;75:373–84.
7. Pivnick EK, Furman WL, Velagaleti GV, et al. Simultaneous adrenocotical carcinoma and ganglioneuroblastoma in a child with Turner syndrome and germline p53 mutation. J Med Genet 1998;35:328–32.
8. Bornstein S, Stratakis CA, Chrousos GP. Adrenocortical tumors: recent advances in basic concepts and clinical management. Ann Intern Med 1999;130:759–71.
9. Kirschner LS. Signaling pathways in adrenocortical cancer. Ann N Y Acad Sci 2002;968:222–39.
10. Reincke M, Mora P, Beuschlein F, et al. Deletion of the adrenocorticotropin receptor gene in human adrenocortical tumors: implication for tumorogenesis. J Clin Endocrinol Metab 1997;82:3054–8.
11. Reincke M. Mutation in adrenocortical tumors. Horm Metab Res 1998;30:447–55.
12. Gortz B, Roth J, Speel EJ, et al. MEN1 gene mutation analysis of sporadic adrenocortical lesions. Int J Cancer 1999; 80:373–9.
13. Reincke M, Karl M, Travis W, et al. No evidence of oncogenenic mutation in guanine nucleotide-binding protein of human adrenocortical neoplasms. J Clin Endocrinol Metab 1993;77:1419–22.
14. Komminoth P, Roth J, Schroder S, et al. Overlaping expression of immunohistochemical markers and synaptophysin mRNA in pheochromocytomas and adrenocortical carcinomas: implication for the differential diagnosis of adrenal gland tumors. Lab Invest 1995;72:424.
15. McNicol AM, Nolan CE, Struthers AJ, Haak HR. Expression of p53 in adrenocortical tumors: clinicopathologic correlations. J Pathol 1997;181:146–52.
16. Miccoli P, Bernini GP. Adrenocortical carcinoma. In: Doherty GM, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott-Raven; 2001. p. 263–71.
17. Pommier RF, Brennan MF. An eleven year experience with adrenocortical carcinoma. Surgery 1992;62:963–70.
18. Stratakis CA, Chrousos GP. Endocrine tumors. In: Pazzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 3rd ed. Philadelphia: Lippincott-Raven; 1997.
19. Daitch JA, Goldfarb DA, Novick AC. Cleveland Clinic experience with adrenal Cushing's syndrome. J Urol 1997; 158:2051–5.
20. Schteingart DE. Adrenal cancer. In: Degroot LJ, Jameson JL, editors. Endocrinology. 4th ed. Philadelphia: WB Saunders; 2001. p. 1767–71.
21. Farge D, Chatellier G, Pagny JY, et al. Isolated clinical syndrome of primary aldosteronism in four patients with adrenocortical carcinoma. Am J Med 1987;83:635–40.
22. Arteaga E, Biglieri EG, Kater CE, et al. Aldosterone-producing adrenocortical carcinoma. Ann Intern Med 1984;101:316–21.
23. Langer P, Bartsch D, Moebius E, et al. Adrenocortical carcinoma—our experience with 11 cases. Langenbecks Arch Surg 2000;385:393–7.
24. Kasperlik-Zaluska AA, Migdalska BM, Zgliczynski S, Makowska AM. Adrenocortical carcinoma: a clinical study and treatment results in 52 patients. Cancer 1995; 73:2587–91.
25. Barnett CC Jr, Varma DG, El-Naggar AK, et al. Limitations of size as a criterion in the evaluation of adrenal tumors. Surgery 2000;128:973–82.
26. Hussain S, Belldegrun A, Seltzer SE, et al. Differentiation of malignant from benign adrenal masses: predictive indices on computed tomography. AJR Am J Roentgenol 1985; 144:61–5.
27. Doppman JL, Reinig JW, Dwyer AJ, et al. Differentiation of adrenal masses by magnetic resonance imaging. Surgery 1987;102:1018–26.
28. Boland GW, Lee MJ. Magnetic resonance imaging of the adrenal gland. Crit Rev Diagn Imaging 1995;36:115–74.
29. Krestin GP, Steinbrich W, Friedmann G. Adrenal masses: evaluation with fast gradient echo MR imaging and Gd-DTPA-enhanced dynamic studies. Radiology 1989;171:675–80.
30. Outwater EK, Siegelman ES, Radecki PD, et al. Distinction between benign and malignant adrenal masses: value of T1-weighted chemical-shift MR imaging. AJR Am J Roentgenol 1995;165:579–83.
31. Korobkin M, Francis IR, Kloos RT, et al. The incidental adrenal mass. Radiol Clin North Am 1996;34:1037–54.
32. Korobkin M, Brodeur FJ, Francis IR, et al. Delayed enhanced CT for differentiation of benign from malignant adrenal masses. Radiology 1996;200:737–42.
33. Korobkin M, Lombardi TJ, Aisen AM, et al. Characterization of adrenal masses with chemical shift and gadolinium enhanced imaging. Radiology 1995;197:414–8.
34. Gross MD, Shapiro B, Bouffard JA, et al. Distinguishing

benign from malignant euadrenal masses. Ann Intern Med 1988;109:613–8.
35. Hedican SP, Marshall FF. Adrenocortical carcinoma with intracaval extension. J Urol 1997;158:2056–61.
36. Moul JW, Hardy MR, Mcleod DG. Adrenal cortical carcinoma with vena cava tumor thrombus requiring cardiopulmonary bypass for resection. Urology 1991;38:179–83.
37. Sullivan M, Boileau M, Hodges CV. Adrenal cortical carcinoma. J Urol 1978;120:660–5.
38. MacFarlane DA. Cancer of the adrenal cortex: the natural history, prognosis and treatment in a study of fifty-five cases. Ann R Coll Surg Engl 1958;23:155–86.
39. Wooten MD, King DK. Adrenal cortical carcinoma: epidemiology and treatment with mitotane and a review of the literature. Cancer 1993;72:3145–55.
40. Kanauchi H, Wada N, Clark OH, Duh Q-Y. Apoptosis regulating genes, bcl-2 and bax, and human telomerase reverse transcriptase (hTERT) mRNA expression in adrenal tumors: possible diagnostic and prognostic importance. Surgery 2002;132:1021–7.
41. Harrison LE, Gaudin PB, Brennan MF. Pathologic features of prognostic significance for adrenocortical carcinoma after curative resection. Arch Surg 1999;134:181–5.
42. Stojadinovic A, Ghossein RA, Brennan MF, et al. Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. J Clin Oncol 2002;20:941–50.
43. Wick MR, Cherwitz DL, McGlennen RC, Dehner LP. Adrenocortical carcinoma. An immunohistochemical comparison wth renal cell carcinoma. Am J Pathol 1986;122:343–52.
44. Fetsch PA, Power CN, Zakowski MF, Abati A. Anti-alpa-inhibin: marker of choice for the consistent distinction between adrenocortical carcinoma and renal cell carcinoma in fine-needle aspiration. Cancer 1999;87:168–72.
45. Kendrick ML, Lloyd R, Erickson L, et al. Adrenocortical carcinoma: surgical progress or status quo? Arch Surg 2001; 136:543–9.
46. Icard P, Goudet P, Proye C. Adrenocortical carcinoma: surgical trend and results of a 253-patients series from the French Association of Endocrine Surgery. World J Surg 2001;25:891–7.
47. Ushiyama T, Suzuki K, Kageyama S, Yoshimi T. A case of Cushing's syndrome due to adrenocortical carcinoma with recurrence 19 months after laparoscopic adrenalectomy. J Urol 1997;157:2239.
48. Copeland PM. The incidentally discovered adrenal mass. Ann Intern Med 1983;98:940–5.
49. Ross NS, Aron DC. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. N Engl J Med 1990;323:1401–5.
50. Barnett CC Jr, Varma DG, El-Naggar AK, et al. Limitations of size as a criterion in the evaluation of adrenal tumors. Surgery 2000;128:973–82.
51. Mayer SK, Oligny LL, Deal C, et al. Childhood adrenocortical carcinoma: case series and reevaluation of prognosis-a 24-year experience. J Pediatr Surg 1997;32:911–5.
52. Crucitti F, Bellantone R, Ferrante A, et al. The Italian Registry for Adrenal Cortical Carcinoma: analysis of a multiinstitutional series of 129 patients. Surgery 1996;119:161–70.
53. Bellantone R, Ferrante A, Marazano L, et al. Role of reoperation in recurrence of adrenal cortical carcinoma: results from 188 cases collected in the Italian national registry for adrenal cortical carcinoma. Surgery 1997;122:1212–8.
54. Schulick RD, Brennan MF. Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. Ann Surg Oncol 1999;6: 719–26.
55. Percarpio B, Knowlton AH. Radiation therapy of adrenal cortical carcinoma. Acta Radiol Ther Phys Biol 1976;15:288.
56. Cohn K, Gottesman L, Brennan M. Adrenal cortical carcinoma. Surgery 1986;100:1170–7.
57. Markoe AM, Serber W, Micaily B, Brady LW. Radiation therapy for adjunctive treatment of adrenal cortical carcinoma. Am J Clin Oncol 1991;14:170–4.
58. Luton JP, Cerdas S, Bricaire H, et al. Clinical features of adrenocortical carcinoma, prognostic factors and the effect of mitotane therapy. N Engl J Med 1990;322: 1195–201.
59. Haak HR, Hermans J, Krans HM, et al. Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. Br J Cancer 1994;69:947–51.
60. Abraham S, Bakke A, Rutt B, et al. A study of combination chemotherapy and surgical resection in the treatment of adrenocortical cancer (ACC): continuous infusion doxorubicin, vincristine and etoposide with daily mitotane before and after surgical resection. Proc Am Soc Clin Oncol 1999;18:191a.
61. Angeli A, Osella G, Ali A, Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the national Italian study group. Horm Res 1997;47:279–83.
62. Proye CAG, Pattou FN. Adrenocortical carcinoma: nonfunctioning and functioning. In: Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 490–6.

Cushing's Syndrome

MAHA AL FEHAILY, MD
QUAN-YANG DUH, MD

In 1932, Harvey W. Cushing described a series of 12 patients with unusual features that formed the basis of the syndrome that now bears his name.[1] Cushing's syndrome is characterized by clinical symptoms and signs caused by excess and inappropriate secretion of glucocorticoid hormones. It is a rare disorder with an incidence of approximately 10 per million people per year.[2] Accurate diagnosis and management are essential because most of the physical features are reversible after curative therapy, and, more importantly, untreated Cushing's syndrome is associated with significant morbidity and a death rate of 51% at 5 years.[3]

Despite the advances in diagnostic and therapeutic measures, the management of Cushing's syndrome continues to be one of the most challenging tasks in clinical endocrinology.

PATHOPHYSIOLOGY

The production of cortisol by the adrenal gland is tightly regulated by the hypothalamus and pituitary gland with the classic feedback inhibition (Figure 11–1). In Cushing's syndrome, the normal feedback control and the normal circadian rhythm are lost. The most common cause of Cushing's syndrome is the prolonged use of glucocorticoid to treat chronic inflammatory disease; steroid inhalers and topical creams must also be considered (exogenous hypercortisolism).[4–7] Endogenous hypercortisolism is either adrenocorticotropic hormone (ACTH) dependent or ACTH independent (Table 11–1).[8–12] Pseudo-Cushing's syndrome state has clinical features similar to hypercortisolism, but successful treatment of the underlying primary condition cures the Cushing's-like state.[13–15]

CLINICAL MANIFESTATION

The signs and symptoms of Cushing's syndrome may be subtle and nonspecific. These clinical manifestations vary depending on the severity and duration of hypercortisolism. Cushing's syndrome

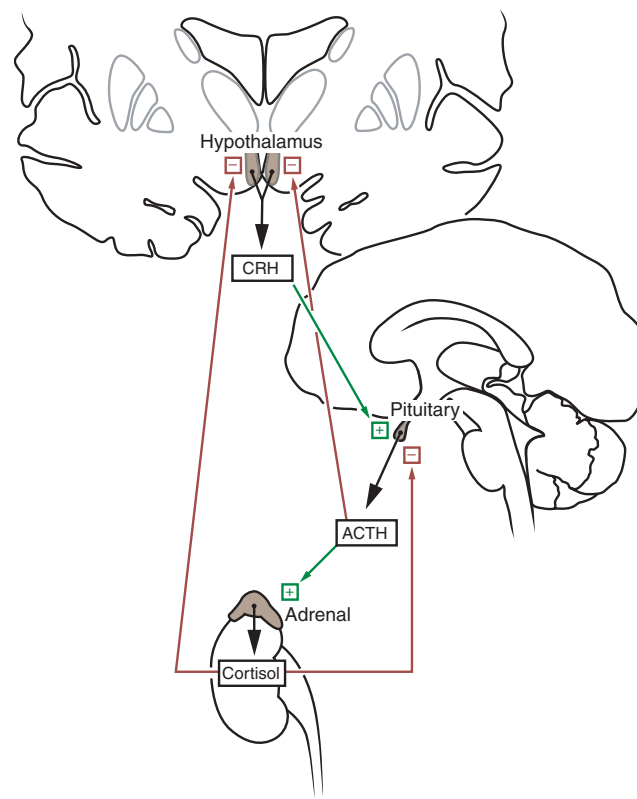


Figure 11–1. Hypothalamus-pituitary-adrenal axis. ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone.

Table 11–1. CAUSES OF CUSHING'S SYNDROME

Exogenous: iatrogenic (the most common cause)
Endogenous
ACTH dependent
Pituitary adenoma, Cushing's syndrome (70%)
Ectopic Cushing's syndrome (15%)
Bronchial carcinoid (25–49%)
Occult (12–16%)
Small cell carcinoma of the lung (10%)
Pancreatic islet cell tumors (4–16%)
Medullary carcinoma of the thyroid gland (8%)
Thymic carcinoid (5–16%)
Pheochromocytoma (3%)
ACTH independent
Adrenal neoplasms (15%)
Nodular adrenal hyperplasia (rare)
Pseudo-Cushing's syndrome
Alcohol
Depression
Others: stress, pregnancy, chronic renal failure, and HIV infection

ACTH = adrenocorticotropic hormone; HIV = human immunodeficiency virus.

may be unrecognized when patients are being treated in rheumatology, psychiatry, and orthopedic clinics. Progressive central weight gain (truncal obesity) is the most universal symptom of patients with Cushing's syndrome. Certain features, such as proximal muscle weakness and purple striae wider than 1 cm, are reliable clues to the diagnosis (Figure 11–2).[16,17] Particular attention should be paid to worsening of signs or symptoms over time and findings atypical for age, such as thinning skin in young men or osteoporosis in children. The hallmark of Cushing's syndrome in a child is growth failure, and timely diagnosis is important to ensure normal growth and puberty.[2,18–20] Certain clinical and biochemical features may suggest a specific cause of Cushing's syndrome (Table 11–2).[8,10,21–24]

ESTABLISHING THE DIAGNOSIS

Two or more highly sensitive tests should be used to diagnose and confirm hypercortisolism (Table 11–3). We recommend 24-hour urinary free cortisol followed by an overnight 1 mg dexamethasone suppression test. Midnight serum cortisol level (for inpatients), midnight salivary cortisol level (outpatients and children), and a corticotropin-releasing hormone (CRH) test are added if the other tests are equivocal.[25–34]

DIFFERENTIAL DIAGNOSIS

Once the diagnosis of Cushing's syndrome is established, it is important to know whether it is ACTH dependent. Plasma ACTH level is measured by immunoradiometric assay. If ACTH is undetectable (ACTH-independent Cushing's syndrome), adrenal imaging is necessary (Figure 11–3). A high or borderline ACTH level (ACTH-dependent Cushing's syndrome) requires further biochemical testing, such as a high-dose dexamethasone suppression test or CRH with dexamethasone suppression.[35–37] Many physicians proceed directly to pituitary imaging and bilateral inferior petrosal sinus sampling (BIPSS) with CRH stimulation.[35,38–42] Pituitary adenomas, as well as other tumors secreting ACTH, are frequently small and can be missed easily by conventional pituitary imaging, including thin-cut high-resolution computed tomography (CT) and magnetic resonance imaging (MRI). In addition, nonfunctional pituitary incidentalomas can cause false-positive studies.[42–45] Distinguishing a central source of ACTH, by BIPSS, from an ectopic source of ACTH prevents unnecessary pituitary operations and possible hypopituitarism.

ACTH-Dependent Hypercortisolism

Cushing's Disease

Overproduction of ACTH by a pituitary adenoma is responsible for 75 to 80% of endogenous hypercortisolism.

- Microadenomas are the most common cause of Cushing's disease. They are usually smaller than 10 mm, making them difficult to detect by pituitary imaging.[13,46]
- Macroadenomas, because of their size, may cause hypopituitarism, as well as visual field defect and headache.

Pituitary hyperplasia is very rare.

Diagnosis. Pituitary adenomas respond to CRH stimulation but are less responsive to glucocorticoid suppression. Thus, pituitary adenomas tend to secrete high levels of ACTH in response to CRH stimulation but are incompletely suppressed

by dexamethasone.[26,27] About half of the pituitary adenomas in patients with Cushing's disease are found on conventional pituitary imaging studies. Those with negative pituitary imaging studies should undergo BIPSS with CRH stimulation. BIPSS is invasive, but it is the best test to differentiate Cushing's disease from occult ectopic ACTH-producing tumors. In addition, lateralization (gradient on the right or left side) can guide the surgeon to selectively explore and remove one side of the pituitary gland even when pituitary imaging studies are negative.[13,40–42]

Treatment. The standard treatment for patients with a pituitary adenoma is transsphenoidal hypophysectomy. Success rate varies between 70% and 98%, depending on the experience of the surgeon and the length of follow-up.[47–51]

Radiation therapy can cure 85% of children and is an option for initial treatment in pediatric patients.[52,53]

The risk of hypopituitarism after radiotherapy can be decreased dramatically by a focused stereotaxic radiosurgery (gamma knife).[53,54] Medical therapy with ketoconazole is not definitive but is often required in conjunction with radiotherapy to control hypercortisolism.[17,55–57] Patients with microadenomas have a good prognosis, but their survival is still less than an age-matched control group, primarily because of cardiovascular diseases.[58] Patients with macroadenomas die from both hypercortisolism and local tumor invasion.[17]

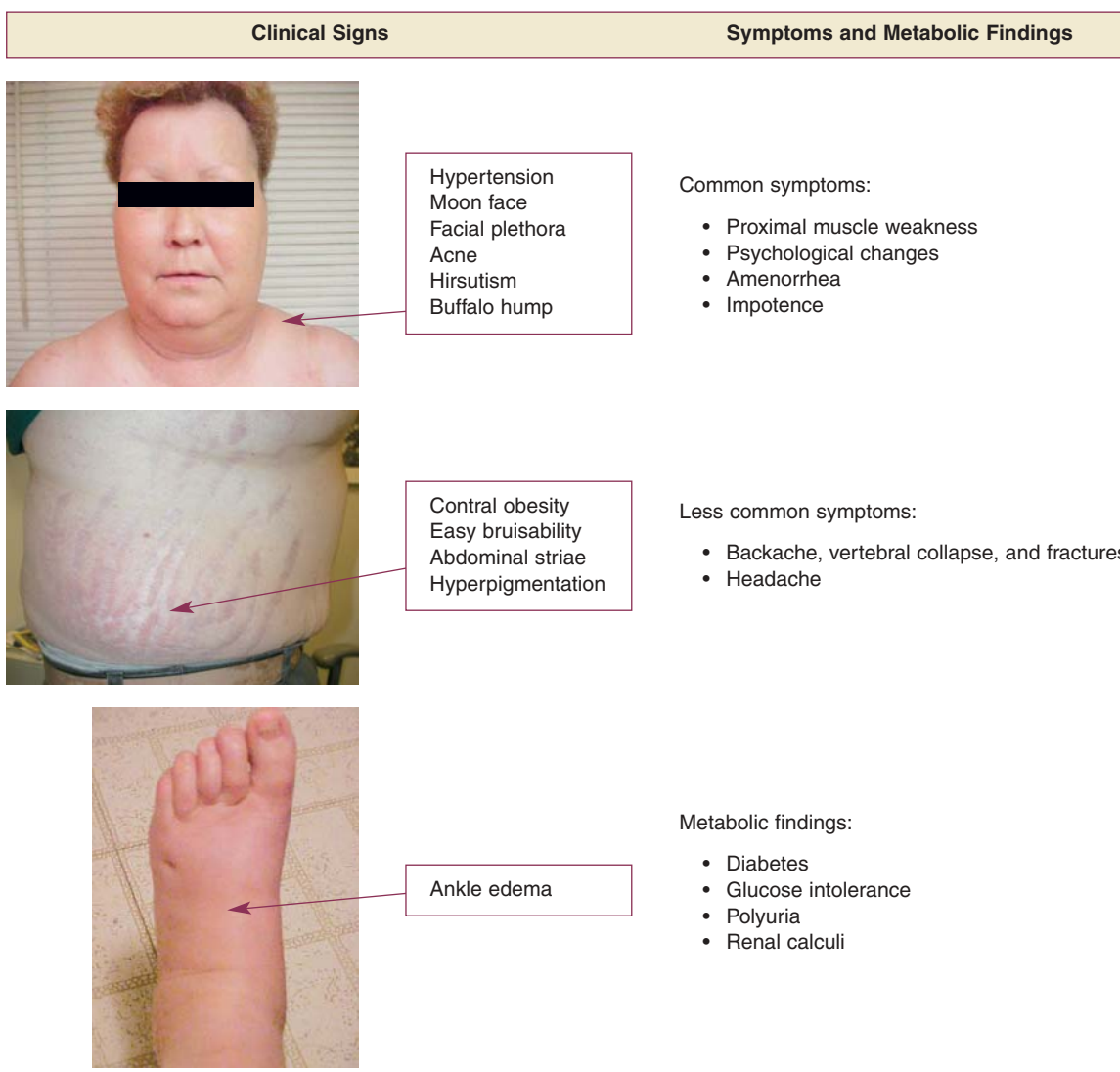


Figure 11–2. Signs and symptoms of Cushing's syndrome.

Table 11–2. FEATURES SUGGESTING A SPECIFIC CAUSE OF CUSHING'S SYNDROME

	Sex	Age (yr)	Progression	Severity	Special Features	Androgenic Features (Hirsutism and Acne)	Pigmentation	Hypokalemia
Cushing's disease	F	20–40	Gradual	Moderate	Classic Cushing's syndrome	Common	Rare	Rare
Ectopic carcinoma	M	40–60	Rapid	Severe	Weight loss, glucose intolerance, weakness	Virilism is common	Common	Common
Ectopic benign	F	36	Gradual	Moderate	Classic Cushing's syndrome	Common	Uncommon	Variable
Adrenal adenoma	F	40	Gradual	Mild	Small tumor 2–5 cm	Rare	Rare	Variable
Adrenal carcinoma	~ F	5–50	Rapid	Severe	Large tumor > 6 cm	Common	Rare	Common

Ectopic ACTH-Secreting Tumors

ACTH secretion from a nonpituitary source accounts for 10 to 15% of endogenous hypercortisolism. Patients usually present with a rapid onset of hypertension, glucose intolerance, and other features of Cushing's syndrome. Those with lung cancer usually have a rapidly progressive course (see Table 11–2). Those with indolent neuroendocrine tumors, such as bronchial carcinoid and medullary thyroid cancer, tend to have a more chronic course. Patients with ectopic ACTH-secreting tumors usually have higher ACTH levels than those with Cushing's disease and are thus more likely to have hyperpigmentation. Hypokalemia is an early clue to the diagnosis. Lung cancers that cause ectopic ACTH syndrome are usually clinically obvious, and survival of these patients is short. Patients with indolent neuroendocrine tumors are usually young and show classic features of Cushing's syndrome. Many of these patients are diagnostically difficult to distinguish from those with Cushing's disease and may have already had a failed pituitary operation.[10–13,59–63] Patients with ectopic ACTH syndrome usually have a rapid and progressive disease and are at risk of dying from sepsis, gastrointestinal perforation, and other complications. Therefore, an aggressive approach is warranted; this includes bilateral adrenalectomy when the primary tumors cannot be identified or completely removed.[17] Rarely, a pheochromocytoma may secrete ACTH or CRH and causes Cushing's syndrome. Unilateral adrenalectomy, resecting the pheochromocytoma, can cure these patients.[64,65]

Localization. The optimal and curative treatment for ectopic ACTH syndrome is to remove the tumor that is secreting ACTH. These tumors are, however, usually small and difficult to find despite the various biochemical testings and imaging studies.

Biochemical testing: Serum levels of 5-hydroxyindoleacetic acid (carcinoid), calcitonin (medullary thyroid cancer), and 24-hour collection of urine for catecholamines and metanephrines (pheochromocytoma) to search for a primary tumor.

Imaging studies: Chest radiography; thin-cut CT of the chest and abdomen; MRI of the chest,

Table 11–3. SCREENING TESTS FOR CUSHING'S SYNDROME

Test	Sensitivity (%)	Specificity (%)	Comment
24-h urinary free cortisol	95–100	94–98	Depends on renal function; may be high in pseudo-Cushing's syndrome
Overnight dexamethasone suppression test	98	87	3% false positive, 3% false negative
Midnight salivary cortisol level	92–100	95	Easy, convenient, especially for children; highly accurate, especially if combined with dexamethasone test
Midnight serum cortisol level	100	77	Used mainly for inpatients with special precautions
Low-dose dexamethasone suppression test with corticotropin-releasing hormone stimulation	100	90	Used mainly for equivocal cases

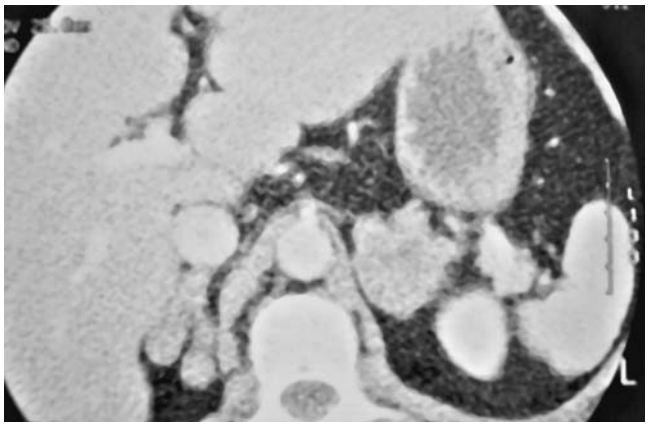


Figure 11–3. Computed tomographic scan of a 52-year-old woman with Cushing's syndrome caused by bilateral adrenal hyperplasia.

mediastinum, and abdomen with gadolinium; ultrasonography of the neck; and octreotide body scan. About 80% of the carcinoid tumors that cause ectopic ACTH syndrome are found above the diaphragm.[12,23]

When an imaging study localized a presumed tumor, fine-needle aspiration cytology with immunoassay of ACTH may confirm the diagnosis.[17]

Treatment. Optimal treatment involves resection or complete destruction of the ACTH-secreting tumor. However, most carcinoid tumors that cause ectopic ACTH syndrome remain occult even after multiple imaging studies,[66,67] so medical or surgical adrenalectomy is usually required to control hypercortisolism. The longer the expected survival, the more important it is to control hypercortisolism. Bilateral adrenalectomy is superior to medical therapy in controlling hypercortisolism caused by disseminated cancer or occult ACTH-secreting tumors.[68] Severe ectopic Cushing's syndrome is associated with poor prognosis over and above that attributable to the tumor itself.

ACTH-Independent Causes of Cushing's Syndrome

About 25% of patients with Cushing's syndrome have adrenal tumors.

Adrenal Adenoma

About 10 to 15% of patients with Cushing's syndrome have an autonomously functioning benign adrenal adenoma. These adenomas are usually less than 5 cm in diameter (Figure 11–4). Adrenalectomy is curative, and the prognosis is excellent.[21] Postoperatively, glucocorticoid should be replaced until complete recovery of the hypothalamus-pituitary-adrenal axis, which usually takes several months but may take as long as 2 years. Mineralocorticoid replacement is rarely needed after unilateral adrenalectomy because the secretion of mineralocorticoid does not depend on the recovery of the pituitary ACTH secretion, and hydrocortisone has some mineralocorticoid effects.

Adrenocortical Carcinoma

Adrenocortical carcinoma causes 5 to 10% of Cushing's syndrome (or 40% of ACTH-independent Cushing's patients, owing to primary adrenal pathology). Adrenocortical carcinoma is rare, with a bimodal age distribution with an initial peak before age 5 years and the second peak at the fourth and fifth decades.[69–71] It occurs rarely as part of multiple endocrine neoplasia type I (parathyroid, pancreatic islet cell, and pituitary neoplasms).[72] It also may occur as part of Li-Fraumeni syndrome (germline mutation of *P53*).[8] Adrenocortical carcinomas are usually larger than 6 cm in diameter and weigh 100 to 5,000 g.[17,73–75] Virilization can occur because of the relatively inefficient cortisol synthesis, resulting in overproduction of androgenic precursors.[76] The only reli-

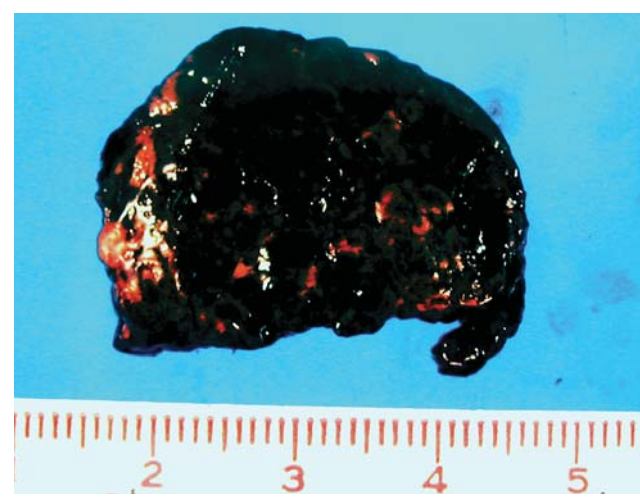


Figure 11–4. Adrenocortical adenoma, gross pathology.

able criteria to differentiate adrenocortical carcinoma from adrenocortical adenoma are nodal or distant metastasis and direct invasion into the adjacent tissues. Carcinomas also tend to be larger and have more mitoses. The mainstay of treatment is an initial complete resection.[77–79] The prognosis of patients with adrenocortical carcinomas is generally poor. The overall mean survival is 18 months, but for untreated patients, it is only 3 months.[80] Tumor stage and completeness of resection are the most important prognostic factors.[80–82] It is controversial whether mitotane therapy improves long-term survival.[83–85] Similar to other hormone-secreting tumors, debulking may be attempted even if complete resection cannot be achieved to minimize the complications caused by hypercortisolism. Prolonged remission has been reported after resection of metastasis or regional recurrences.[86–88]

Hyperplasia

Primary adrenocortical hyperplasia causes 5% of Cushing's syndrome. In contrast to patients with adrenocortical hyperplasia secondary to ACTH secretion by a pituitary tumor or ectopic source, these patients almost always have a very low level of or undetectable plasma ACTH.

Primary adrenocortical hyperplasia may be macronodular or micronodular.

1. The adrenal glands in patients with bilateral macronodular adrenal hyperplasia are very large, with multiple nodules. In contrast, patients with micronodular primary adrenal hyperplasia may have normal or slightly abnormal adrenal glands on CT and MRI.[89–91]
2. Primary pigmented micronodular hyperplasia occurs mainly in children and may have a familial pattern. It may be attributable to a circulating immunoglobulin that stimulates the adrenal gland. Half of these occur as an autosomal dominant disorder known as Carney's complex that is associated with atrial myxoma, blue nevi, and schwannomas.[92–95]
3. Rare patients may have adrenocortical hyperplasia owing to an abnormal or ectopic expression of receptors for various hormones, such as gastric inhibitory polypeptide or β-adrenergic receptors.[96–98]

Bilateral adrenalectomy is required for the treatment of primary adrenocortical hyperplasia.

ADRENALECTOMY

A unilateral adrenalectomy is the standard treatment for adrenocortical adenomas and carcinomas. Bilateral adrenalectomies are indicated in

- Patients with Cushing's disease, whose pituitary surgery and/or radiotherapy fail to control the increased cortisol secretion
- Patients with an ectopic ACTH-secreting tumor that cannot be resected or an occult tumor that cannot be localized
- Primary bilateral adrenal hyperplasia

Preoperative Measures

Appropriate preoperative preparation of patients with Cushing's syndrome is essential to prevent complication. Particular attention should be paid to the following:

- Control hypertension, diabetes, and full assessment of cardiac and respiratory function
- Preoperative therapy with ketoconazole or other adrenalytic drugs[56]
- Deep vein thrombosis prophylaxis
- Prophylactic perioperative antibiotics, because of the higher rate of infection in patients with Cushing's syndrome
- Intraoperative and postoperative steroid coverage to prevent addisonian crisis

Operation

Laparoscopic adrenalectomy is the procedure of choice for nearly all adrenal operations, except for large adrenal tumors (larger than 6 cm) or adrenocortical carcinomas. Perioperative mortality rates range from 0 to 7%, with lower rates in recent reports.[99–106]

Postoperative Care

Careful postoperative metabolic surveillance is essential. Stress doses of glucocorticoids should be started and tapered slowly. Mineralocorticoid replacement may also be necessary after bilateral adrenalectomy. Postoperative complications include wound infection, delayed wound healing, deep vein thrombosis, and gastrointestinal bleeding. After laparoscopic adrenalectomy, patients are usually discharged from the hospital on the first to third postoperative day, but it may be longer in patients with Cushing's syndrome to manage their medical problems and steroid replacement.[99–106]

Patients are encouraged to wear a bracelet to indicate to caregivers that acute adrenocortical insufficiency may occur. Stress can precipitate an acute adrenal insufficiency (addisonian crisis). Patients should be informed about the symptoms of glucocorticoid withdrawal. They may have flu-like symptoms for several months postoperatively. If they have signs of adrenal insufficiency, such as vomiting, electrolyte imbalance, or postural hypotension, they will need additional glucocorticoid treatment.[56,106–108]

Lifelong follow-up after adrenalectomy is necessary. The disease may recur because of incomplete resection, tumor spillage, or ectopic adrenocortical tissue. A known long-term complication of bilateral adrenalectomy is Nelson's syndrome, which results from progressive enlargement of the pituitary gland, with elevated plasma levels of ACTH and melanocyte-stimulating-hormone, causing hyperpigmentation. Currently, one cannot predict whether an individual will develop Nelson's syndrome, but children appear to be at greater risk.[109,110] Nelson's syndrome may develop as long as 20 years after bilateral adrenalectomy, with an incidence as high as 47%. Pituitary radiotherapy at the time of adrenalectomy may prevent Nelson's syndrome or delay its onset.[109,111,112]

MEDICAL THERAPY

Indications for medical therapy are to correct metabolic abnormalities before adrenalectomy and to palliate patients with surgically incurable disease.

SUBCLINICAL CUSHING'S SYNDROME

Preclinical or subclinical Cushing's syndrome is caused by autonomous glucocorticoid secretion in patients who may have no overt, or only minimal, clinical signs and symptoms of full-blown Cushing's syndrome. Subclinical hypercortisolism has been reported in 5 to 20% of patients with adrenal incidentalomas. Depending on the amount of glucocorticoid secreted by the tumor, the clinical spectrum can vary considerably. Diagnostically, patients often have a slightly attenuated diurnal rhythm of cortisol secretion. They may also have a suppressed contralateral adrenal gland. Removing the hypersecreting adrenal gland, even without removing the normal gland, may result in life-threatening acute adrenal insufficiency. The natural history of this condition is unclear because long-term prospective studies are lacking. Subclinical Cushing's syndrome may progress to overt Cushing's syndrome. Some patients with subclinical Cushing's syndrome have subtle biochemical abnormalities that are reversed by adrenalectomy. Therefore, surgery should be considered in young or symptomatic patients and in those who have significant comorbidities, such as diabetes, hypertension, and osteopenia.[113–116] Close follow-up is required for other patients.[80,117,118] This includes 24-hour urinary free cortisol levels, overnight dexamethasone suppression test, and serum electrolyte levels at 6-month intervals to detect progression of endocrine function. Serial imaging studies are also needed to detect tumor growth for the risk of malignancy.

CONCLUSION

In conclusion, there has been much improvement in the management of patients with Cushing's syndrome, including more accurate ACTH testing for diagnosis, better localization studies, and minimally invasive treatment by laparoscopic adrenalectomy. Despite these advances, some problems persist, such as the difficulty in determining whether a patient has a pituitary disease (Cushing's disease) or an ectopic tumor that secretes ACTH and the management of steroid treatment in these patients. A suggested approach to manage

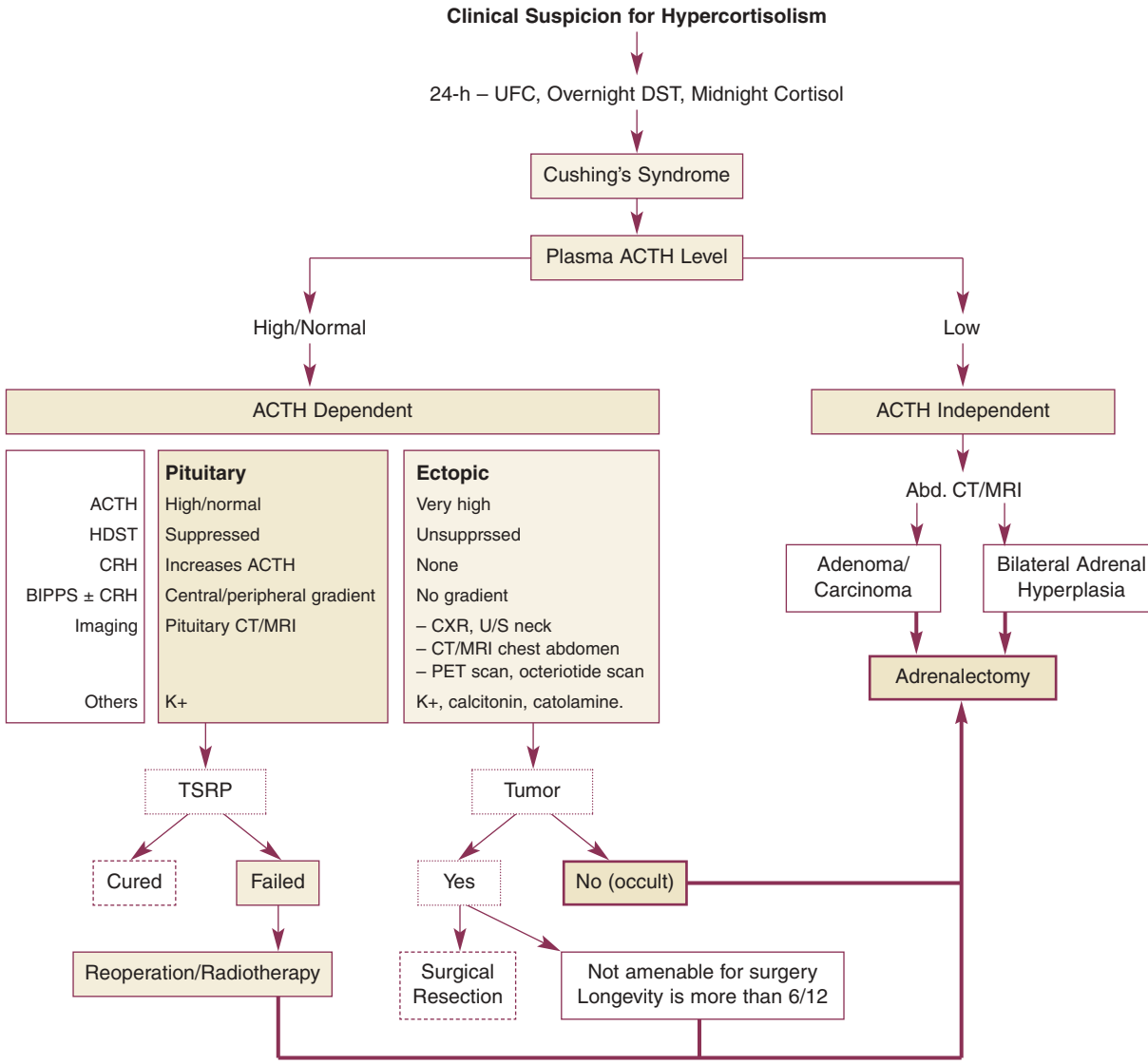


Figure 11–5. Management of Cushing's syndrome. Abd = abdominal; ACTH = adrenocorticotropic hormone; BIPSS = bilateral inferior petrosal sinus sampling; CRH = corticotropin-releasing hormone; CT = computed tomography; CXR = chest radiography; DST = dexamethasone suppression test; HDST = high-dose dexamethasone suppression test; MRI = magnetic resonance imaging; PET = positron emission tomography; TSRP = transsphenoidal resection of pituitary gland; UFC = urinary free cortisol; U/S = ultrasonography.

patients with a clinical suspicion of Cushing's syndrome is shown in Figure 11–5.

REFERENCES

1. Cushing H. The basophil adenoma of the pituitary body and their clinical manifestation (pituitary basophilism). Bull Johns Hopkins Hosp 1932;50:137–95.
2. Magiakou MA, Mastroakos G, Oldfield EH, et al. Cushing's syndrome in children and adolescent: presentation, diagnosis and therapy. N Engl J Med 1994;331:629–36.
3. Plotz CM, Knowltone Al, Ragan C. The natural history of Cushing's syndrome. Am J Med 1952;13:597–614.
4. Abma EM, Blanken R, De Heide LJ. Cushing's syndrome caused by topical steroid therapy for psoriasis. Neth J Med 2002;60:148–50.
5. Young CA, Williams IR, MacFarlane IA. Unrecognised Cushing's syndrome and adrenal suppression due to topical clobetasol propionate. Br J Clin Pract 1991;45:61–2.
6. Le Roux CW, Beckles MA, Besser GM, et al. Cushing's syndrome secondary to inhaled corticosteroids mimicking HIV-associated lipodystrophy. HIV Med 2001;2:133–5.
7. Perry RJ, Findlay CA, Donaldson MD. Cushing's syndrome, growth impairment, and occult adrenal suppression associated with intranasal steroids. Arch Dis Child 2002;87:45–8.
8. Clutter WE. Cushing syndrome: hypercortisolism. In: Doherty GM, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott-Raven; 2001. p. 235–45

9. Aniszewski JP, Young WF Jr, Thompson GB, et al. Cushing syndrome due to ectopic adrenocorticotropic hormone secretion. World J Surg 2001;25:934–40.
10. Findling JW, Tyrrell JB. Occult ectopic secretion of corticotropin. Arch Intern Med 1986;146:929–33.
11. Wajchenberg BL, Mendonca BB, Liberman B, et al. Ectopic adrenocorticotropic hormone syndrome. Endocr Rev 1994;15:752–87.
12. Wajchenberg BL, Mendonca BB, Liberman B, et al. Ectopic ACTH syndrome. J Steroid Biochem Mol Biol 1995;53: 139–51.
13. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 1998;19:647–72.
14. Jeffcoate W. Alcohol-induced pseudo-Cushing's syndrome. Lancet 1993;341:676–7.
15. Koelz A, Girard J. Cushing's syndrome or obesity. Bilateral adrenal hyperplasia in a boy 10 years of age. Eur J Pediatr 1976;121:237–46.
16. Ross EJ, Linch DC. Cushing's syndrome-killing disease: discriminatory value of sign and symptoms aiding early diagnosis. Lancet 1982;2:646–9.
17. Norton JA, Li M, Gillary J, Le HN. Cushing's syndrome. Curr Probl Surg 2001;38:488–545.
18. Weber A, Trainer PJ, Grossman AB, et al. Investigation, management and therapeutic outcome in 12 cases of childhood and adolescent Cushing's syndrome. Clin Endocrinol (Oxf) 1995;43:19–28.
19. Leinung MC, Zimmerman D. Cushing's disease in children. Endocrinol Metab Clin North Am 1994;23:629–39.
20. Chew FS. Radiologic manifestations in the musculoskeletal system of miscellaneous endocrine disorders. Radiol Clin North Am 1991;29:135–47.
21. Greenspan FS, Gardner DG. Basic and clinical endocrinology. In: DeGroot LJ, Jameson JL, editors. Cushing's syndrome. 6th ed. New York: McGraw-Hill; 2001. p. 1691–715.
22. Perry RR, Nieman LK, Cutler GB Jr, et al. Primary adrenal causes of Cushing's syndrome. Diagnosis and surgical management. Ann Surg 1989;210:59–68.
23. Howlett TA, Drury PL, Perry L, et al. Diagnosis and management of ACTH-dependent Cushing's syndrome: comparison of the features in ectopic and pituitary ACTH production. Clin Endocrinol (Oxf) 1986;24:699–713.
24. Nieman LK. Cushing's syndrome. In: DeGroot LJ, Jameson JL, editors. Endocrinology. Vol. 2. Philadelphia: WB Saunders; 2001.
25. Newell-Price J, Grossman A. Biochemical and imaging evaluation of Cushing's syndrome. Minerva Endocrinol 2002; 27:95–118.
26. Findling JW, Raff H. Newer diagnostic techniques and problems in Cushing's syndrome. Endocrinol Metab Clin North Am 1999;28:191–210.
27. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am 2001;30:729–47.
28. Montwill J, Igoe D, McKenna TJ. The overnight dexamethasone test is the procedure of choice in screening for Cushing's syndrome. Steroids 1994;59:296–8.
29. Newell-Price J, Trainer P, Perry L, et al. A single sleeping midnight cortisol has 100% sensitivity for the diagnosis of Cushing's syndrome. Clin Endocrinol (Oxf) 1995;43: 545–50.
30. Papanicolaou DA, Yanovski JA, Cutler GB, et al. A single midnight cortisol measurement distinguishes Cushing's from pseudo-Cushing's state. J Clin Endocrinol Metab 1998;83:1163–7.
31. Castro M, Elias PC, Quidute AR, et al. Out-patient screening for Cushing's syndrome: the sensitivity of the combination of circadian rhythm and overnight dexamethasone suppression salivary cortisol tests. J Clin Endocrinol Metab 1999;84:878–82.
32. Castro M, Elias PC, Martinelli CE Jr, et al. Salivary cortisol as a tool for physiological studies and diagnostic strategies. Braz J Med Biol Res 2000;33:1171–5.
33. Gafni RI, Papanicolaou DA, Nieman LK. Nighttime salivary cortisol measurement as a simple, noninvasive, outpatient screening test for Cushing's syndrome in children and adolescents. J Pediatr 2000;137:30–5.
34. Meier CA, Biller BM. Clinical and biochemical evaluation of Cushing's syndrome. Endocrinol Metab Clin North Am 1997;26:741–62.
35. Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab 2000;85:637–44.
36. Bethga H, Arlt W, Zimmermann U, et al. Cushing's syndrome due to an ectopic ACTH-secreting pituitary tumor mimicking occult paraneoplastic ectopic ACTH production. Clin Endocrinol 1999;51:809–14.
37. Findling JW, Kehoe ME, Shaker JL, Raff H. Routine inferior petrosal sinus sampling in the differential diagnosis of adrenocorticotropin (ACTH)-dependent Cushing's syndrome: early recognition of the occult ectopic ACTH syndrome. J Clin Endocrinol Metab 1991;73:408–13.
38. Newell-Price J, Morris DG, Drake WM, et al. Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab 2002;87:1640–5.
39. Puig J, Wagner A, Caballero A, et al. Cost-effectiveness and accuracy of the tests used in the differential diagnosis of Cushing's syndrome. Pituitary 1999;1:125–32.
40. Padayatty SJ, Orme SM, Nelson M, et al. Bilateral sequential inferior petrosal sinus sapling with corticotrophin-releasing hormone stimulation in the diagnosis of patients with Cushing's disease. Eur J Endocrinol 1998;139:161–6.
41. Hall WA, Luciano MG, Doppman JL, et al. Pituitary magnetic resonance imaging in normal volunteers: occult adenoma in the general population. Ann Intern Med 1994;120:817–20.
42. Kaltsas GA, Giannulis MG, Newell-Price JD, et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. J Clin Endocrinol Metab 1999;84:487–92.
43. Freda PU, Wardlaw SL. Diagnosis and treatment of pituitary tumors. J Clin Endocrinol Metab 1999;84:3859–66.
44. Findling JW, Doppman JL. Biochemical and radiological diagnosis of Cushing syndrome. Endocrinol Metab Clin North 1994;23:511–37.
45. Donovan LE, Corenblum B. The natural history of the pituitary incidentaloma. Arch Intern Med 1995;155:181–3.

46. Selvias P, Donchkier J, Buysschaert M, Maiter D. Cushing's disease: a comparison of pituitary corticotroph microadenoma and macroadenoma. Eur J Endocrinol 1998;138: 153–9.
47. Fahlbusch R, Buchfelder M, Muller OA. Transsphenoidal surgery for Cushing's disease. J R Soc Med 1986;79:262–9.
48. Ram Z, Nieman LK, Cutler GB, et al. Early repeat surgery for persistent Cushing's disease. J Neurosurg 1994;80:37–45.
49. Bochicchoio D, Losa M, Buchfelder M, and the European Cushing Disease Survey Study Group. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery. J Clin Endocrinol Metab 1995;80:3114–20.
50. Mampalam TJ, Tyrrell JB, Wilson CB. Transsphenoidal microsurgery for Cushing's disease: a report of 216 cases. Ann Intern Med 1988;109:487–93.
51. Sonia N, Zielezny M, Fava GA, et al. Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 1996;81:2647–52.
52. Jennings AS, Liddle GW, Orth DN. Result of treating childhood Cushing's disease with pituitary radiation. N Engl J Med 1997;297:957–62.
53. Lunsford LD, Flickinger J, Lindner G, Maitz A. Stereotactic radiosurgery of the brain using the first United States 201 cobalt-60 source gamma knife. Neurosurgery 1989;24: 151–9.
54. Morange Ramos I, Regis J, Dufour H, et al. Gamma-knife surgery for secreting pituitary adenoma. Acta Neurochir (Wien) 1998;140:430–43.
55. Estrada J, Boronat M, Mielgo M, et al. The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med 1997; 336:172–7.
56. Miller JW, Crapo L. The medical treatment of Cushing's syndrome [review]. Endocr Rev 1993;14:443–58.
57. Morris D, Grossman A. The medical management of Cushing's syndrome. Ann N Y Acad Sci 2002;970:119–33.
58. Colao A, Pivonello R, Lombardi G, et al. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab 1999;84:2664–72.
59. Stewart PM, Walker PR, Holder G, et al. 11-Beta-hydroxysteroid dehydrogenase activity in Cushing's syndrome: explaining the mineralocorticoid excess state of ectopic adrenocorticotropin hormone syndrome. J Clin Endocrinol Metab 1995;80:3617–20.
60. Becker M, Aron DC. Ectopic ACTH syndrome and CRH-mediated Cushing's syndrome. Endocrinol Metab Clin North Am 1994;23:585–606.
61. Beuschlein F, Hammer GD. Ectopic pro-opiomelanocortin syndrome. Endocrinol Metab Clin North Am 2002;31: 191–234.
62. Doppman JL, Pass HI, Nieman LK, et al. Detection of ACTH-producing bronchial carcinoid tumors: MR imaging vs CT. AJR Am J Roentgenol 1991;156:39–43.
63. Loh KC, Fitzgerald PA, Miller TR, Tyrrell JB. Perils and pitfalls in the diagnosis of Cushing's syndrome. West J Med 1998;169:46–50.
64. Chen H, Doppman JL, Chrousos GP, et al. Adrenocorticotropic hormone-secreting pheochromocytomas: the exception to the rule. Surgery 1995;118:988–94.
65. White A, Ray DW, Talbot A, et al. Cushing's syndrome due to phaeochromocytoma secreting the precursors of adrenocorticotropin. J Clin Endocrinol Metab 2000;85:4771–5.
66. Zeiger MA, Pass HI, Doppman JD, et al. Surgical strategy in the management of non-small cell ectopic adrenocorticotropic hormone syndrome. Surgery 1992;112:994–1000.
67. Doppman JL, Nieman LK, Miller DL, et al Ectopic ACTH syndrome: localization in 28 patients. Radiology 1989; 172:115–24.
68. Trainer PJ, Besser M. Cushing's syndrome. Therapy directed at the adrenal glands. Endocrinol Metab Clin North Am 1994;23:571–84.
69. Miccoli P, Bernini GP. Adrenocortical carcinoma. In: Surgical endocrinology. Philadelphia: Lippincott-Raven; 2001.
70. Lindholm J, Juul S, Schmidt K, et al. Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab 2001;86:117–23.
71. Norton JA. Adrenal tumors. In: De Vita Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. Philadelphia: Lippincott-Raven; 1997.
72. Skogseid B , Rastad J, Gobl A, et al. Adrenal lesion in multiple endocrine neoplasia type 1. Surgery 1995;118:1077–82.
73. Copeland PM. The incidentally discovered adrenal mass. Ann Intern Med 1983;98:940.
74, Ross NS, Aron DC. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. N Engl J Med 1990;323:1401.
75. Barnett CC Jr, Varma DG, El-Naggar AK, et al. Limitations of size as a criterion in the evaluation of adrenal tumors. Surgery 2000;128:973.
76. Orth DN. Cushing's syndrome. N Engl J Med 1995;332: 791–803.
77. Dackiw AP, Lee JE, Gagel RF, Evans DB. Adrenal cortical carcinoma. World J Surg. 2001;25:914–26.
78. Icard P, Chapuis Y, Andreassian B, et al. Adrenocortical carcinoma in surgically treated patients: a retrospective study on 156 cases by the French Association of Endocrine Surgery. Surgery 1992;112:972.
79. Kendrick ML, Lloyd R, Erickson L, et al. Adrenocortical carcinoma: surgical progress or status quo? Arch Surg 2001;136:543–9.
80. Angeli A, Osella G, Ali A, Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the national Italian study group. Horm Res 1997;47:279.
81. Pommier RF, Brennan MF. An eleven year experience with adrenocortical carcinoma. Surgery 1992;62:963.
82. Proye CAG, Pattou FN. Adrenocortical carcinoma: nonfunctioning and functioning. In: Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 490–6.
83. Kasperlik-Zaluska AA, Migdalska BM, Zgliczynski S, Makowska AM. Adrenocortical carcinoma: a clinical study and treatment results in 52 patients. Cancer 1995;73:2587.
84. Luton JP, Cerdas S, Bricaire H, et al. Clinical features of adrenocortical carcinoma, prognostic factors and the effect of mitotane therapy. N Engl J Med 1990;322:1195.
85. Haak HR, Hermans J, Krans HM, et al. Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. Br J Cancer 1994;69:947.

86. Schulick RD, Brennan MF. Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. Ann Surg Oncol 1999;6:719.
87. Tikkanen MJ, Sivula A, Kahri A, Pelkonen R. Recurrent adrenal cortical carcinoma with Cushing's syndrome: twenty-five-year follow-up of a patient. J Endocrinol Invest 1980;3:425–7.
88. Kwauk S, Burt M. Pulmonary metastases from adrenal cortical carcinoma: results of resection. J Surg Oncol 1993;53: 243–6.
89. Doppman JL, Chrousos GP, Papanicolaou DA, et al. Adrenocorticotropin-independent macronodular adrenal hyperplasia: an uncommon cause of primary adrenal hypercortisolism. Radiology 2000;216:797–802.
90. Swain JM, Grant CS, Schlinkert RT, et al. Corticotropin-independent macronodular adrenal hyperplasia: a clinicopathologic correlation. Arch Surg 1998;133:541–5.
91. Stratakis CA, Kirschner LS. Clinical and genetic analysis of primary bilateral adrenal diseases (micro- and macronodular disease) leading to Cushing syndrome. Horm Metab Res 1998;30:456–63.
92. Stratakis CA, Carney JA, Lin JP, et al. Carney complex, a familial multiple neoplasia and lentiginosis syndrome: analysis of 11 kindreds and linkage to the short arm of chromosome 2. J Clin Invest 1996;97:599–607.
93. Kirschner LS, Carney JA, Pack SD, et al. Mutations of the gene encoding the protein kinase A type L-alpha regulatory subunit in patients with the Carney complex. Nat Genet 2000;26:89–92.
94. Samuels MH, Loriaux DL. Cushing's syndrome and nodular adrenal gland. Endocrinol Metab Clin North Am 1994;23: 555–69.
95. Young WF, Carney JA, Musa BU, et al. Familial Cushing's syndrome due to primary pigmented nodular adrenocortical disease. N Engl J Med 1989;321:1659–64.
96. Lacroix A, Tremblay J, Rousseau G, et al. Propranolol therapy for ectopic beta-adrenergic receptors in adrenal Cushing's syndrome. N Engl J Med 1997;337:1429–34.
97. Lacroix A, Bolte E, Tremblay J, et al. Gastric inhibitory polypeptide-dependent cortisol hypersecretion: a new cause of Cushing's syndrome. N Engl J Med 1992;327: 974–80.
98. de Herder WW, Bonner TI, Bonjer HJ, et al. Food-dependent Cushing's syndrome resulting from abundant expression of gastric inhibitory polypeptide receptors in adrenal adenoma cells. J Clin Endocrinol Metab 1996;81: 3168–72.
99. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. N Engl J Med 1992;327:1033.
100. Fernandez-Cruz L, Saenz A, Benarroch G, et al. Laparoscopic unilateral and bilateral adrenalectomy for Cushing's syndrome—transperitoneal and retroperitoneal approaches. Ann Surg 1996;6:727–36.
101. Sarkar R, Thompson NW, McLeod MK. The role of adrenalectomy in Cushing's syndrome. Surgery 1990;108:1079–84.
102. McLeod MK. Complications following adrenal surgery. J Natl Med Assoc 1991;83:161–4.
103. Chapuis Y, Pitre J, Conti F, et al. Role and operative risk of bilateral adrenalectomy in hypercortisolism. World J Surg 1996;20:775–9.
104. Imai T, Funahashi H, Takagi H, et al. Adrenalectomy for treatment of Cushing syndrome: results in 122 patients and long-term follow-up studies. World J Surg 1996;20:781–6.
105. Favia G, Boscaro M, Lumachi F, D'Amico DF. Role of bilateral adrenalectomy in Cushing's disease. World J Surg 1994;18:462–6.
106. Go H, Takeda M, Imai T, et al. Laparoscopic adrenalectomy for Cushing's syndrome: comparison with primary aldosteronism. Surgery 1995;117:11–7.
107. Byyny RL. Withdrawal from glucocorticoid therapy. N Engl J Med 1976;295:30–2.
108. Howlett TA. An assessment of optimal hydrocortisone replacement therapy. Clin Endocrinol (Oxf) 1997;46:263–8.
109. Pereira MA, Halpern A, Salgado LR, et al. A study of patients with Nelson's syndrome. Clin Endocrinol 1998;49:533–9.
110. Kemink SA, Wesseling P, Pieters GF. Progression of a Nelson's adenoma to pituitary carcinoma: a case report and a review of literature. J Endocrinol Invest 1999;22:70–5.
111. Nagesser SK, van Seters AP, Kievit J, et al. Long-term results of total adrenalectomy for Cushing's disease. World J Surg 2000;24:108–13.
112. Grabner P, Hauer-Jensen M, Jervell J, Flatmark A .Long-term results of treatment of Cushing's disease by adrenalectomy. Eur J Surg 1991;157:461–4.
113. Takumi S, Itoh N, Sato Y, Tsukamoto T. Subclinical Cushing syndrome due to adrenocorticotropic hormone-independent macronodular adreocortical hyperplasia: changes in plasma cortisol levels during long-term follow-up. Urology 2000;55:145x–xii.
114. Morika M, Fujii T, Matsuki T, Kondo K. Preclinical Cushing's syndrome: report of seven cases and review of literature. Int J Urol 2000;7:126–32.
115. Cheitlin RA, Westphal M, Cabrera CM, et al. Cushing's syndrome due to bilateral macronodular hyperplasia with undetectable ACTH: cell culture of adenoma cells on extra cellular matrix. Horm Res 1988;29:162–7.
116. Hensen J, Oelkers W. Endocrine activity of the silent adrenocortical adenoma is uncovered by response to corticotrophin-releasing hormone. Klin Wochenschr 1990;68:608–14.
117. Mantero F, Arnaldi G. Adrenal incidentaloma: an overview of hormonal data from the national Italian Study Group. Horm Res 1997;47:284–9.
118. Bondanelli M, Campo M, Degli Uberto EC, Pansini R. Evaluation of hormonal function in a series of incidentally discovered adrenal masses. Metabolism 1997;46:107–13.

12

Adrenal Incidentaloma

W. KEAT CHEAH, MBBS, FRACS
QUAN-YANG DUH, MD

An incidentaloma of the adrenal gland (or adrenaloma) is defined as an adrenal tumor that is discovered incidentally and unexpectedly on radiologic imaging without prior knowledge that the patient has adrenal disease. The widespread use of imaging studies such as computed tomography (CT) (Figure 12–1), ultrasonography, and magnetic resonance imaging (MRI) (Figure 12–2) has increased the detection of adrenal incidentalomas, which range from 0.4 to 2% of abdominal CT scans.[1–3] This chapter provides a practical approach to managing patients with adrenal incidentalomas.

Incidentalomas comprise a variety of pathologies (Table 12–1). Most incidentalomas are benign cortical adenomas that do not secrete hormones and are termed nonfunctioning tumors. Some tumors, however, are hormonally active and secrete cortisol (Cushing's syndrome), aldosterone (primary hyperaldosteronism), or catecholamines (pheochromocytoma). A third group consists of malignant tumors that are either primary adrenocortical carcinomas or metastatic cancers to the adrenal gland. In the workup of incidentalomas, it then becomes important to determine whether the adrenal mass is (1) a functioning or nonfunctioning tumor, (2) a metastatic tumor, or (3) an adrenal carcinoma.

EVALUATION

The adrenal gland is one of the frequent sites of metastases, and virtually any malignancy may spread to it. A metastatic tumor should be highly suspected in the setting where an imaging study detects an adrenal mass in a patient with a known history of malignant disease. Common cancers that metastasize to the adrenal gland are from the lung, kidney, breast, gastrointestinal tract, and melanoma. Occasionally, an adrenal metastasis is discovered with an undetermined primary origin; thus, a thorough history and physical examination are essential for all patients (Figures 12–3 and 12–4). For example, melanomas can recur many years after previous surgical excision. The clinical assessment suggests what investigations are required to confirm the diagnosis, such as a chest radiograph and bronchoscopy for lung cancer or a mammogram and biopsy for breast cancer.

The next priority is to assess the functional status of the incidentaloma. Because these lesions are dis-

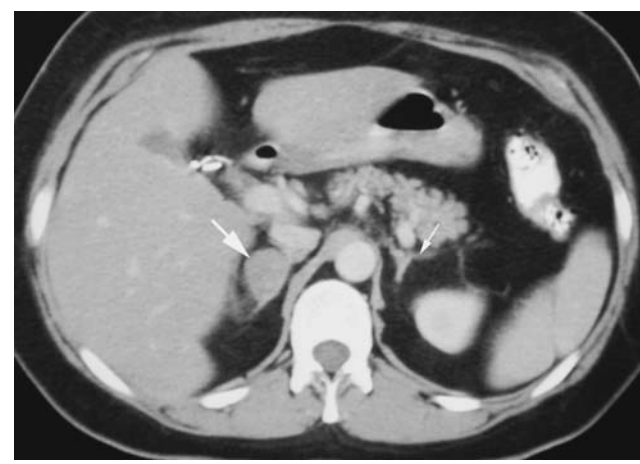


Figure 12–1. A 46-year-old woman had nonspecific right-sided abdominal discomfort and palpitation. An abdominal computed tomographic scan showed a low attenuation 3 cm × 1.8 cm × 1 cm right adrenal tumor (*large white arrow*) and a normal left adrenal gland (*small white arrow*). Biochemical workup showed no hyperfunction. She underwent a laparoscopic right adrenalectomy. Pathology showed a 4 cm adrenocortical adenoma.

covered incidentally, some may secrete hormones without causing overt clinical syndromes. The most common functioning tumors are the adenomas causing Cushing's syndrome, primary hyperaldosteronism, or pheochromocytoma. From an accurate history and physical examination, certain pertinent clinical features such as hypertension—a common feature of all three conditions—or symptoms and signs of glucocorticoid excess in Cushing's syndrome can give clues to the diagnosis. However, biochemical tests, as listed in Table 12–2, remain the hallmark in accurately screening for and diagnosing these conditions.

Table 12–1. PATHOLOGIES OF ADRENAL INCIDENTALOMAS

Nonfunctioning benign tumors
Cortical adenoma
Cyst
Myelolipoma
Ganglioneuroma
Other: angioma, granuloma, lipoma, hamartoma, fibroma, hemangioma
Functioning benign tumors
Pheochromocytoma
Cortical adenoma—Cushing's syndrome, primary hyperaldosteronism
Malignant tumors
Primary adrenocortical carcinoma
Metastatic cancers—melanoma, breast, lung, kidney, stomach, colorectal, pancreas, ovary

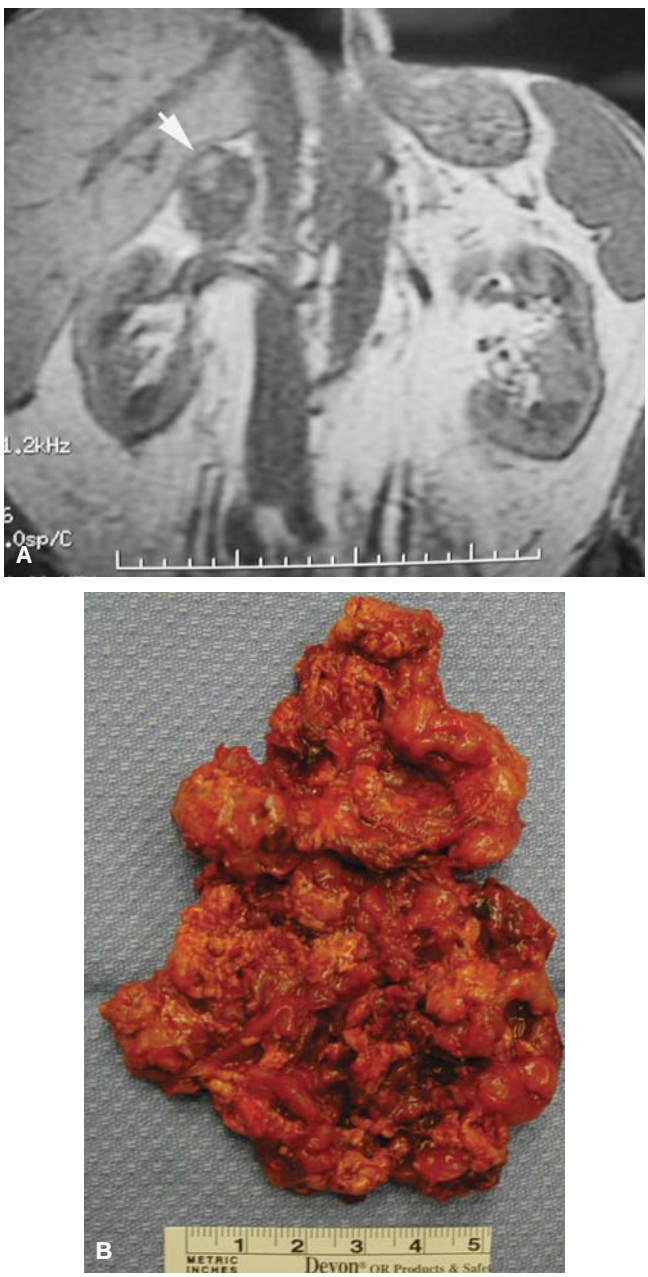


Figure 12–2. A 64-year-old asymptomatic man had routine abdominal magnetic resonance imaging during a routine physical examination. *A*, The right adrenal tumor is heterogeneous and measured 4.3 cm × 4.2 cm × 3.5 cm (*white arrow*). The left adrenal gland is normal. Biochemical workup showed no hyperfunction. He underwent a laparoscopic adrenalectomy. *B*, Pathology showed a 5 cm adrenal cortical adenoma. The tumor was morsellated for removal. The adenoma appears golden-yellow.

Negative results usually indicate that the tumor is nonfunctioning. Most of these masses are cortical adenomas that vary in size, whereas others are adrenal cysts (Figure 12–5), myelolipoma, or adrenal hemorrhages that can be identified from certain CT characteristics and easily monitored on

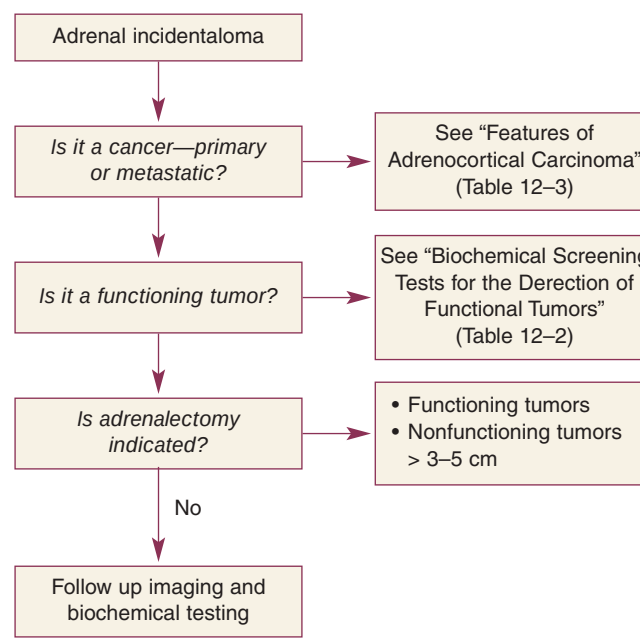


Figure 12–3. Flow diagram for evaluating an incidentaloma.

imaging without removal. As it is unknown at what rate the cortical adenomas grow or whether these tumors can become hormonally active or cancerous, regular follow-up and surveillance are necessary if the adrenal tumor is not resected.

The evaluation process then centers on the likelihood of the adrenal mass being an adrenocortical carcinoma (Table 12–3). These tumors usually grow rapidly and present as large (> 5–6 cm) adrenal masses at the time of diagnosis (Figure 12–6). Clinical findings that support the diagnosis are abdominal or back pain, weakness, and an abdominal mass. Up to 75% of tumors can secrete hormones that cause Cushing's syndrome or virilization or

Table 12–2. BIOCHEMICAL SCREENING TESTS FOR THE DETECTION OF FUNCTIONAL TUMORS

Pheochromocytoma
Elevated urinary (24-hour) metanephrines and catecholamines
Cushing's syndrome
Elevated urinary (24-hour) cortisol
Unsuppressed dexamethasone suppression test
Low serum adrenocorticotropic hormone
Primary hyperaldosteronism
Hypokalemia
High serum aldosterone
High ratio of serum aldosterone/plasma renin activity

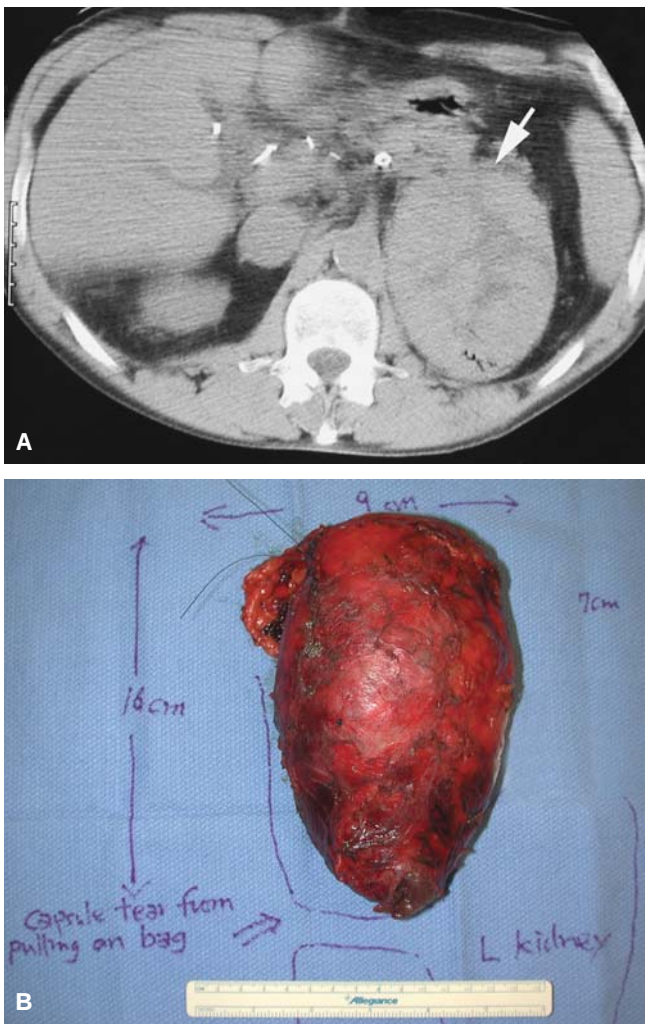


Figure 12–4. A 62-year-old man, who 3 years ago had a liver transplant because of end-stage liver disease owing to hepatitis C, had a computed tomographic (CT) scan because of left flank pain. *A*, An abdominal CT scan showed a 9 cm left adrenal tumor (*white arrow*). Fine-needle biopsy of this lesion was most consistent with a metastatic hepatoma. Other studies, including positron emission tomographic scan, showed no other obvious metastasis. He underwent a diagnostic laparoscopy, which showed no obvious other lesions and had a laparoscopic hand-assisted left adrenalectomy. *B*, The pathology showed a 16 cm × 9 cm × 7 cm metastasis from a hepatoma.

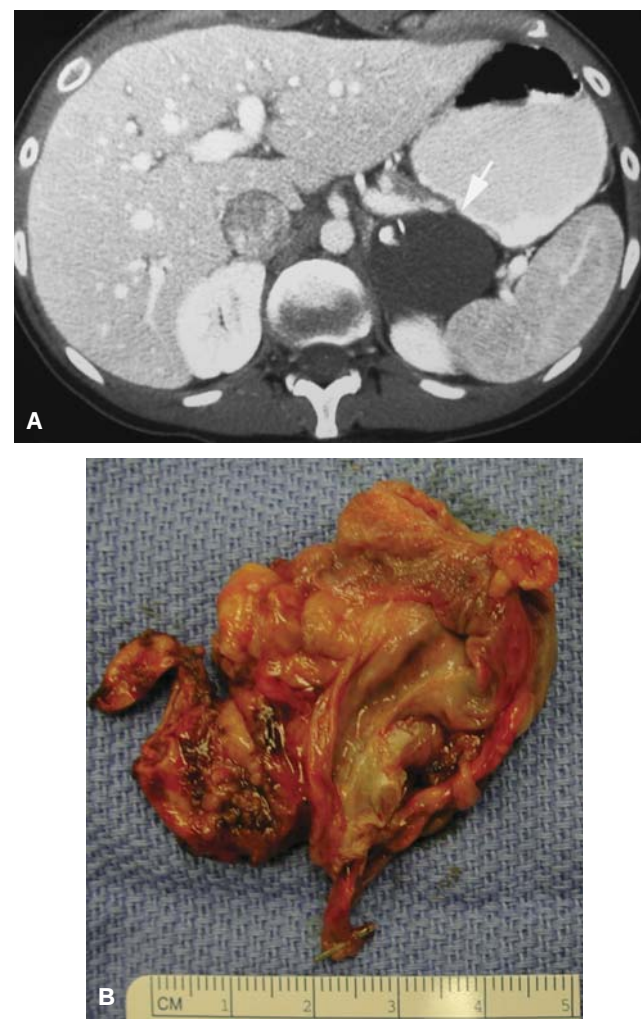


Figure 12–5. A 26-year-old woman had left upper quadrant pain. *A*, An abdominal computed tomographic scan showed a 6 cm × 5 cm × 4 cm left adrenal cyst (*white arrow*) with calcifications in the cystic wall. Biochemical workup showed no hyperfunction. She underwent a laparoscopic left adrenalectomy. *B*, Pathology showed a 6 cm endothelial cyst.

Table 12–3. FEATURES OF ADRENOCORTICAL CARCINOMA

Rapid growth
Abdominal pain, weakness, abdominal mass, anemia
Functional in 75% of cases
Large tumor > 5 cm in diameter
Computed tomography—heterogeneous with central necrosis and hemorrhage
Magnetic resonance imaging—isotense on T_1-weighted and hyperintense on T_2-weighted images
Local invasion of adjacent structures
Invasion of vascular structures—renal vein, inferior vena cava
Metastasis to regional lymph nodes
Metastasis to liver, lung, bone

feminization syndromes from excess sex steroid hormone. In particular, these tumors have a tendency to secrete multiple hormones. Abdominal CT or MRI scans, which often reveal a heterogeneous tumor (with an irregular capsule) invasion to surrounding structures such as kidney, renal vein, or inferior vena cava or metastases to the liver or lungs, give definite evidence of an adrenocortical carcinoma. Cytologic features cannot firmly distinguish between a carcinoma and a benign cortical adenoma. Local invasion, lymphadenopathy, or distant adrenal metastases confirms the diagnosis. For this reason, fine-needle biopsy is inadequate in differentiating between these two tumors on cytologic criteria. However, fine-needle biopsy can be useful in diagnosing a metastatic lesion of unknown primary origin or for the therapeutic aspiration of a large, symptomatic adrenal cyst. A needle biopsy is contraindicated in a patient with pheochromocytoma. All functioning tumors should be excluded by biochemical screening and not by biopsy because of the potential risk of lethal, hypertensive crises.

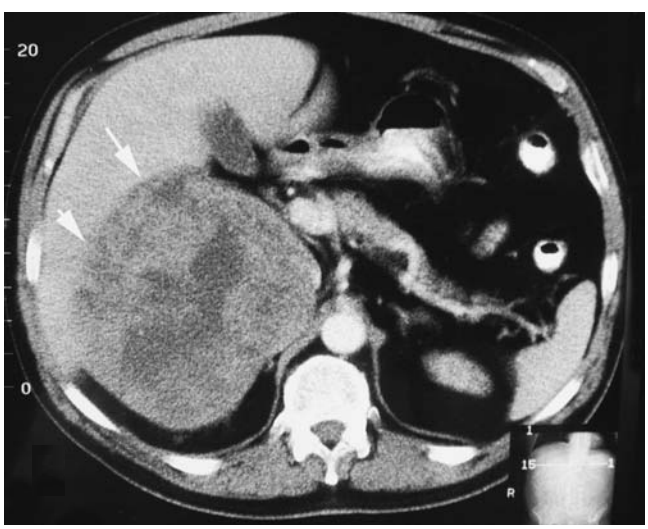


Figure 12–6. A 60-year-old man had recent onset of severe right upper quadrant pain. A computed tomographic scan shows a 10 cm × 9 cm × 8 cm heterogeneous right adrenal tumor (*white arrows*). Biochemical workup showed mild hypercortisolism. He underwent open resection of the right adrenal tumor, with intraoperative findings of invasion into the liver and regional lymphadenopathy.

MANAGEMENT

In general, patients with incidentalomas are managed depending on several factors such as tumor size, functional status, and the likely pathology. The group with malignant adrenal disease poses a challenge to management. Patients with widely disseminated disease and adrenal metastases may receive systemic chemotherapy or immunotherapy, external beam radiation for bone pain from vertebral bone erosions, or just supportive palliative care because of advanced disease. However, some centers advocate a selective approach in resecting solitary adrenal metastasis (without metastasis to other organs) provided that the primary disease is adequately controlled and a reasonable disease-free interval is achieved.[4,5] For patients with primary adrenocortical carcinomas, complete surgical excision combined with chemotherapy offers the best chance for potentially curative therapy against this aggressive and usually fatal tumor. Provided that the patient has no metastatic disease, an en bloc clearance of the adrenal cancer and regional nodes via an abdominal approach is performed.

It is generally agreed that all functioning tumors should be removed to prevent progression of the disease. The specific preoperative, operative, and postoperative care varies depending on the type of tumor being treated.

There has been considerable discussion as to the most effective treatment of patients with a nonfunctioning incidentaloma. As the pathology and natural history of such lesions cannot be predicted with accuracy, the size of the tumor (which correlates with the risk of adrenal carcinoma) is central in deciding which lesions should be removed or observed. A large tumor has a higher chance of being an adrenal carcinoma than a smaller tumor,

and the risk increases with tumors larger than 5 cm. One study of 38 patients showed that the incidence of adrenal cancers larger or smaller than 5 cm was 87% and 13%, respectively.[6] Adrenalectomy is recommended in patients with these large tumors. Such a risk is considerably lower, although not eliminated, in tumors smaller than 3 cm in diameter. These tumors are not removed, unless associated with other characteristics of cancer as mentioned above, but monitored for growth or subsequent function with imaging scans and biochemical testing (Figure 12–7). Regular surveillance is important because cancers that start as small tumors are often misdiagnosed as benign. A lesion that continues to grow or becomes functional should be removed. Nonfunctioning tumors that measure between 3 and 5 cm can be approached in two ways. The first is nonoperative management, such as in the elderly patient with medical conditions that contraindicate surgery, in which the patient undergoes regular surveillance. The second approach is to perform adrenalectomy, especially in the younger patient, who benefits because (1) the lesion is removed, (2) the chance for the tumor to become functional or cancerous is removed, (3) there is a decreased need for regular imaging or biochemical tests that contribute to ongoing costs, and (4) adrenal tumors are more likely to be malignant in young patients. Such a management plan varies among different physicians and institutions and is generally determined by patient selection, surgeon's expertise, and low complication rates of surgery.

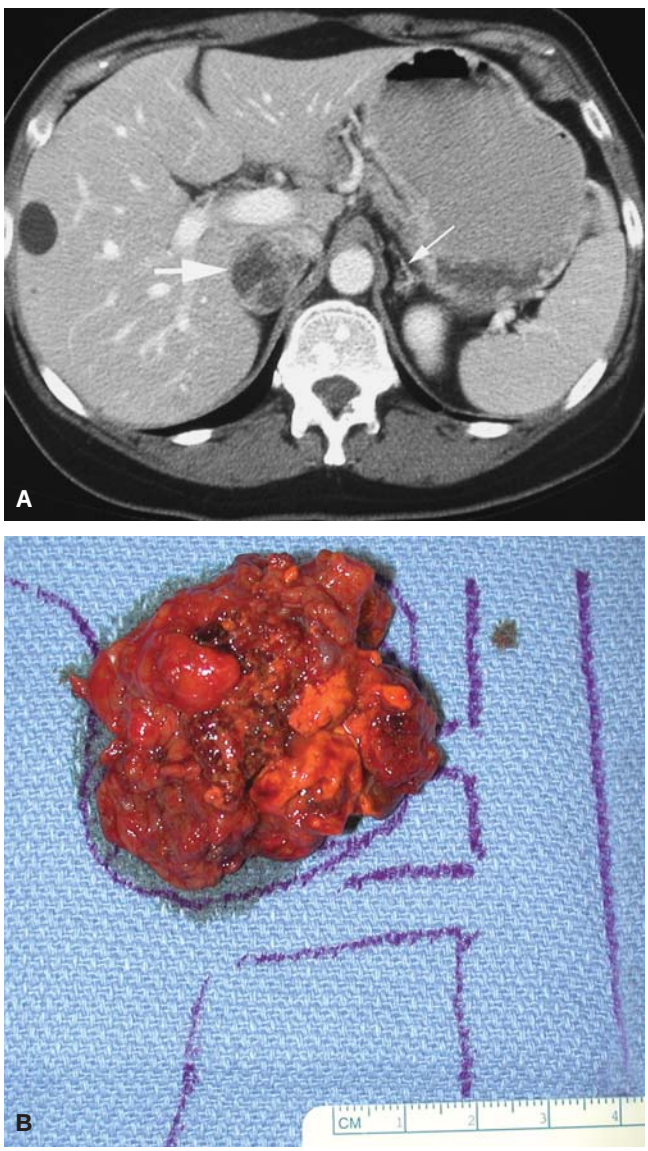


Figure 12–7. A 47-year-old woman had a 2 cm right adrenal tumor discovered incidentally 2 years ago and had a negative biochemical workup. *A*, A follow-up abdominal computed tomographic scan 2 years later showed the right adrenal tumor (*large white arrow*) to have grown to 3.5 cm. The left adrenal gland (*small white arrow*) was normal. Biochemical workup again showed no hyperfunction. She underwent a laparoscopic right adrenalectomy. *B*, Pathology showed it to be a adrenocortical adenoma.

Laparoscopic adrenalectomy achieves complete adrenal resection and is ideal for benign solitary tumors smaller than 8 to 10 cm in diameter (Table 12–4). When compared with open surgery, the laparoscopic approach causes less pain and disability to patients and allows them to leave hospital early to resume work and normal activities.[7,8] The most popular method of laparoscopic adrenalectomy is the transabdominal approach with the patient in the lateral position. During laparoscopic adrenalectomy, care should be taken not to breach the capsule of the tumor to prevent tumor cell seeding. Periadrenal tissue should be resected with all of the adrenal gland. Other surgical approaches are the laparoscopic posterior adrenalectomy and the open posterior retroperitoneal

Table 12–4. BENEFITS OF LAPAROSCOPIC ADRENALECTOMY

Small operative wounds
Minimal postoperative pain
Short hospital stay
Rapid recovery
Early return to normal activities
High rate of success
Low rate of complications

approach. Very large tumors (more than 10 cm) or known adrenal carcinomas should be removed via the anterior or lateral laparotomy or via a thoracoabdominal incision to ensure complete and adequate tumor clearance. Open adrenalectomy is also recommended for small tumors if there is obvious local invasion from preoperative imaging studies. Similarly, the laparoscopic approach may need to be converted to the open approach during adrenalectomy for a more complete resection, especially if adjacent organs are invaded.

REFERENCES

1. Galzer HS, Weymann PJ, Sagel SS, et al. Nonfunctioning adrenal masses incidentally discovered on computed tomography. AJR Am J Roentgenol 1982;139:81–5.
2. Herrera MF, Grant CS, van Heerden JA, et al. Incidentally discovered adrenal tumors: an institutional perspective. Surgery 1991;110:1014.
3. Copeland PM. The incidentally discovered adrenal mass. Ann Surg 1984;199:116–22.
4. Richie JP, Gittes RF. Carcinoma of the adrenal cortex. Cancer 1980;45:1957–64.
5. Kim SH, Brennan MF, Russo P, et al. The role of surgery in the treatment of clinically isolated adrenal metastasis. Cancer 1998;82:389–94.
6. Barnett CC Jr, Varma DG, El-Nagger AK, et al. Limitations of size as a criterion in the evaluation of adrenal tumors. Surgery 2000;128:973–82.
7. Gagner M, Pomp A, Heniford BT, et al. Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. Ann Surg 1997;226:238–46.
8. Duh QY, Siperstein AE, Clark OH, et al. Laparoscopic adrenalectomy. Comparison of the lateral and posterior approaches. Arch Surg 1996;131:870–5.

13

Insulinomas

MILANA B. BOUKHMAN, MD
ORLO H. CLARK, MD

Insulinomas continue to fascinate physicians because of their interesting and often bizarre clinical manifestations. Because of the unusual clinical presentation the diagnosis is often delayed, usually for over a decade from the time of the first clinical symptoms. However, during the past 15 years, these tumors have been diagnosed earlier, owing to better understanding and awareness of the associated clinical syndromes and to improved diagnostic tests and localization procedures. Although rare, insulinoma is the most common tumor of the endocrine pancreas, occurring in about one person per million population per year. The discovery of insulin by Banting and Best in 1922 ultimately led to the hypothesis by Harris in 1924 that overactivity of islet cells might produce hypoglycemia. This tumor was first described by Wilder and colleagues[1] at the Mayo Clinic, who made the diagnosis of endogenous hyperinsulinism in an orthopedic surgeon. Mayo performed an operation on this patient with hypoglycemia and found an islet cell carcinoma with hepatic metastases. The first surgical cure of an islet cell adenoma was reported by Graham in 1929.[2]

PATHOPHYSIOLOGY

The clinical manifestations of insulinomas are based on the excessive secretion of insulin with the resultant hypoglycemia.

An understanding of the physiology of insulin secretion from the beta cells is required for the appreciation of modern diagnostic tests for insulinoma. The beta cells synthesize a large polypeptide molecule, proinsulin, which undergoes proteolytic division into active insulin and a connecting peptide (C peptide) (Figure 13–1). Both C peptide and the double-chain polypeptide insulin are secreted from beta-cell granules and should rise together during pancreatic islet secretion, as occurs during hyperglycemia. Because of neoplastic transformation (insulinoma) or diffuse hyperplasia, the beta islet cells escape from the usual glucose feedback inhibition. Because C-peptide fragments are increased in patients with insulinoma they can be used as a marker of overproduction of the beta islet cells. Thus, C peptide and proinsulin are both usually increased in patients with endogenous insulin oversecretion. In patients with factitious hyperinsulin-

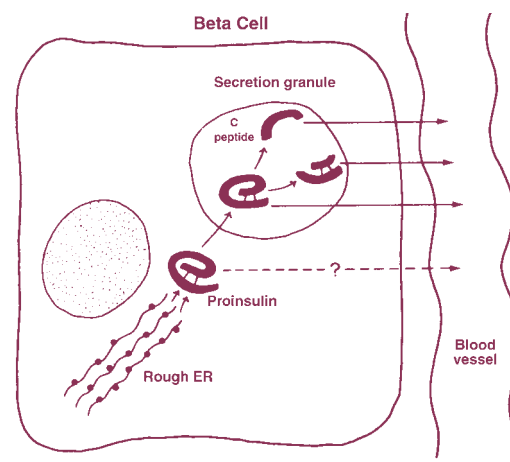


Figure 13–1. Secretion of insulin from the pancreatic islet beta cells. Schema of rough endoplasmic reticulum (ER), where proinsulin is synthesized, and secretion granules, where proinsulin is cleaved into insulin and C peptide. Reproduced with permission from Rubenstein AH, Kuzuva H. Horowitz DL. Clinical significance of circulating C-peptide in diabetes mellitus and hypoglycemia disorders. Arch Intern Med 1977;137:625. Copyright 1977 American Medical Association.

ism, C-peptide levels are usually low and therefore help make the correct diagnosis. In normal individuals, exogenous insulin should suppress beta-cell secretion and C-peptide levels, as should hypoglycemia, whereas in persons with persistent insulin secretion, C-peptide levels will be increased.

Most patients with insulinoma have sporadic disease, but about 10% are associated with other hormone-secreting tumors (parathyroid, other pancreatic, pituitary, adrenal carcinoid, and thyroid) or multiple endocrine neoplasia (MEN) type I. The gene for MEN type I has been identified on chromosome 11. Making the diagnosis of MEN type I is important in patients with insulinoma because the effective surgical therapy is different for patients with MEN type I and for most of those with sporadic islet cell tumors. The primitive APUD (amine precursor uptake and decarboxylation) neural crest cells, as reported by Pearse,[3] were initially thought to migrate to colonize various parts of the developing gut. The cells then differentiated to form the endocrine glands of the APUD series but, at the same time, retained their pluripotential endocrine characteristics, which may be displayed in conditions of neoplasia or hyperplasia. The glands in the APUD series include the thyroid, parathyroids, adrenals, pancreas, pituitary, and others. Pearse[3] and Pearse and Polak[4] defined the cytochemical and ultrastructural characteristics of these cells. Although this theory is no longer entirely valid, it provides a useful concept to understand the tumors involved in patients with MEN type I.

CLINICAL MANIFESTATIONS

The symptoms of hypoglycemia usually occur during fasting, especially in the early morning or if a meal is skipped, and during exercise. Some patients must set their alarms at night in order to eat during the night or they will not awaken in the morning owing to profound hypoglycemia. Because some patients have bizarre symptoms with inappropriate behavior or seizures, they are often misdiagnosed and are evaluated by psychiatrists or neurologists.

As previously mentioned, the diagnosis of insulinoma is often delayed. Among our patients, the duration of symptoms prior to diagnosis ranged from 1 hour to 34 years, with a mean of 3.8 years.[5] The diagnosis of insulinoma was delayed for a variety of reasons, including the infrequency of attacks and the fact that the symptoms could be aborted by the ingestion of food. Delay in diagnosis may result in brain damage, especially in children, or death owing to severe hypoglycemia.

The symptoms in patients with insulinoma are attributable to the actions of two hormones: insulin and catecholamines. Epinephrine and other catecholamines are secreted in response to low blood glucose levels. The signs and symptoms of hypoglycemia depend on the severity and duration of hypoglycemia. If the decrease in blood glucose is rapid, the autonomic nervous system is activated to release epinephrine, which causes sweating, nervousness, tremor, palpitations, hunger, and pallor. The release of epinephrine is a compensatory response, which is used to increase blood glucose levels by enhancing the breakdown of hepatic glycogen to glucose.

If the blood glucose levels fall slowly, the manifestations are primarily cerebral in nature, owing to the direct effect of the hypoglycemia on the functioning of the central nervous system. Symptoms such as confusion, incoherent speech, blurred vision, headache, convulsions, and coma ensue. The relative frequency of the above symptoms is illustrated in Figure 13–2.

If the decrease in blood glucose is rapid, persistent and profound symptoms result from both the increased sympathetic activity and the central nervous system impairment (Figure 13–3). In general, hypoglycemic attacks are usually episodic because of the intermittent secretion of insulin, especially in early cases. Medications such as β-blockers should not be used in diabetic patients or other patients with hypoglycemia as they block the catecholamine-related symptoms and even more profound hypoglycemia may occur.

DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIA

In general, all causes of fasting hypoglycemia are potentially serious owing to the possibility of brain damage. This condition may be attributable to either an underproduction of glucose by the liver or an

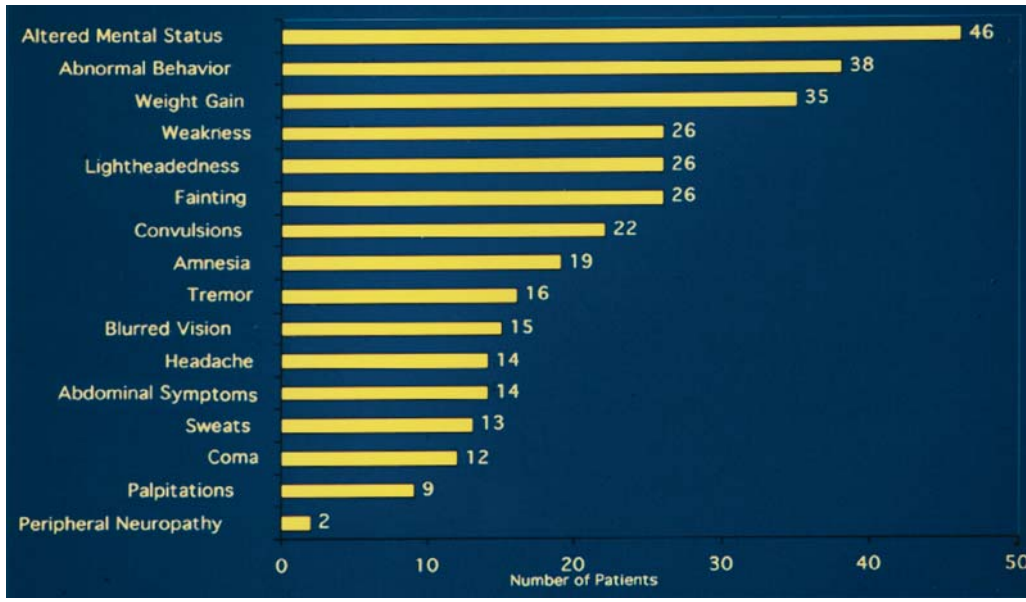


Figure 13–2. Symptoms during hypoglycemic spells in patients at our institution. Adapted from Boukhman MB et al.[5]

overuse of glucose (Table 13–1). Hypoglycemia is a relatively common medical problem and occurs most often in patients with diabetes mellitus. Other conditions causing hypoglycemia include factitious or surreptitious use of insulin in sulfonylurea medications, renal insufficiency, liver failure, adrenocortical failure, heart failure, malnutrition, sepsis, or cancer. When these causes and an insulinoma are not recognizable, a non–islet cell tumor should be considered. The most common tumors are fibrosarcomas, mesotheliomas, leiomyosarcomas, hemangiopericytomas, hepatomas, and lung, gastric, and pancreatic cancer. These tumors are quite large and usually secrete incompletely processed insulin-like growth factor II (IGF-II). The incompletely processed IGF-II interacts with insulin receptors in the liver, muscle, and adipocytes, resulting in inhibition of liver glucose production and increased glucose uptake in the parenchymal tissues. The clinical diagnosis of non–islet cell tumor is made by documenting high or normal IGF-II concentrations and low levels of insulin in a hypoglycemic patient. In patients with insulinomas, proinsulin levels constitute more than 25% of the serum insulin reactivity.

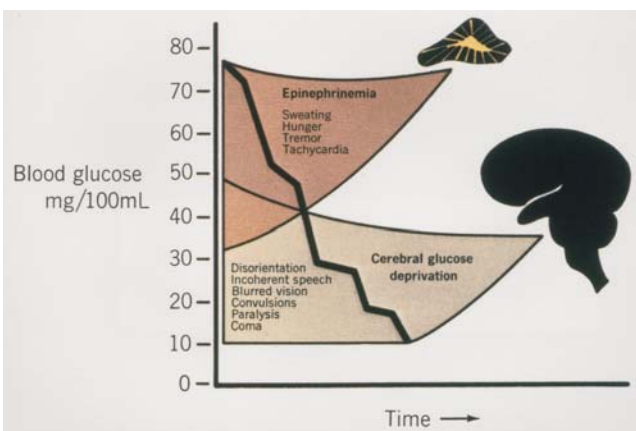


Figure 13–3. Pathophysiology of a hypoglycemic attack. The initial rapid decline in blood glucose stimulates the reflex release of epinephrine by the adrenal gland. As the blood glucose level continues to fall, symptoms caused by epinephrinemia merge with those caused by cerebral glucose deprivation. Reproduced with permission from Edis AJ, Ayala LA. Manual of endocrine surgery. Springer-Verlag; 1975.

When determining the cause of hypoglycemia, it is very important to determine whether the hypoglycemia occurs postprandially or with fasting. Postprandial (reactive) hypoglycemia is much more common than the fasting type. After gastrectomy, patients are prone to "reactive" or postprandial hypoglycemia; these patients may also experience diarrhea and other systemic symptoms associated with catecholamine release. In patients with insulinomas, on the other hand, symptoms almost always occur with fasting and/or after exercise.

Fasting hypoglycemia can occur owing to a variety of causes. Therefore, the low blood sugar levels in a patient with a suspected insulinoma must be dif-

Table 13–1. MAJOR CAUSES OF FASTING HYPOGLYCEMIA

- Postprandial (reactive hypoglycemia)
  - Alimentary hyperinsulinism
  - Hereditary fructose intolerance
  - Galactosemia
  - Leucine sensitivity
  - Idiopathic
- Fasting hypoglycemia
- Conditions primarily owing to underproduction of glucose
  - Hormone deficiencies
    - Hypopituitarism
    - Adrenal insufficiency
    - Catecholamine deficiency
    - Glucagon deficiency
    - Enzyme defects
  - Glucose-6-phosphatase
    - Liver phosphorylase
    - Pyruvate carboxylase
    - Phospho*enol*pyruvate carboxykinase
    - Fructose 1,6-diphosphatase
    - Glycogen synthetase
  - Substrate deficiency
    - Ketotic hypoglycemia of infancy
    - Severe malnutrition, muscle wasting
    - Late pregnancy
  - Acquired liver disease
    - Hepatic congestion
    - Severe hepatitis
    - Cirrhosis
  - Drugs
    - Alcohol
    - Propranolol
    - Salicylates
- Conditions primarily owing to overuse of glucose
  - Hyperinsulinism
    - Insulinoma
    - Exogenous insulin
    - Sulfonylureas
    - Immune disease with insulin antibodies
  - Appropriate insulin levels
    - Extrapancreatic tumors
    - Cachexia with fat depletion
    - Carnitine deficiency
    - Carnitine acyltransferase deficiency

Adapted with permission from Jaspan JB, Polonsky KS, Foster DW, et al. Clinical features and diagnosis of islet-cell tumors. In: Moosa AR, editor. Tumors of the pancreas. Baltimore (MD): Williams and Wilkins, 1980. p. 469.

ferentiated from numerous other causes. Among them is deficient glucose production, as in the patient with cirrhosis of the liver and therefore an inability to mobilize glycogen for a glucose reserve; overuse of glucose in the fasting state (which would include insulinoma); pharmacologic and toxic agents that depress blood sugar; and late starvation when energy reserves may be exhausted. Daily hepatic production of glucose ranges from 100 to 200 g. If more than 200 g of glucose is required to offset hypoglycemic symptoms, then the patient suffers from overuse of glucose, which is consistent with a diagnosis of insulinoma.

DIAGNOSIS

Whipple's triad includes (1) blood sugar < 45 mg/100 mL, (2) symptoms of hypoglycemia, and (3) symptoms relieved with glucose. This constellation of events supports the diagnosis of an insulinoma but is not specific. The diagnosis of insulinoma can now be made with greater certainty owing to the availability of radioimmunoassays measuring insulin, proinsulin, and C peptide. The key test in diagnosing insulinomas is the ratio of fasting insuling to glucose. A ratio of 0.3 or above strongly suggests an insulinoma.

GLUCOSE AND INSULIN LEVELS

The ability to measure plasma insulin levels by radioimmunoassay has greatly aided the diagnosis of insulinoma. The diagnosis is made primarily by the recognition of a circulating insulin level that is inappropriately high for the existing level of blood glucose, especially at the time of hypoglycemia. Two types of measurements can be made: fasting and following provocative testing. By far, fasting values are the most reliable and less dangerous, but an observed 72-hour fast is most helpful in some patients. Symptoms of hypoglycemia generally occur if the serum glucose levels are below 40 mg/mL.

Fasting Test and Insulin-to-Glucose Ratio

The most useful diagnostic test is the demonstration of fasting hypoglycemia in the face of inappropriately high levels of insulin in the serum. The patient is fasted, and blood samples are obtained every 6 hours or when symptoms develop for blood glucose and insulin measurements. The fast is continued until hypoglycemia or symptoms appear, or for a maximum of 72 hours. One-third of insulinoma patients become hypoglycemic within 12 hours of fasting, 80% within 24 hours, 90% within 48 hours, and 98% within 72 hours. Although insulin levels are not always elevated in patients with insulinoma (normal serum insulin levels are less than 30 mU/mL),

they will be inappropriately high relative to the blood glucose concentration. A ratio of plasma insulin to glucose greater than 0.3 is diagnostic, as mentioned above (Figure 13–4).

Proinsulin Measurement

Approximately 85% of patients with insulinomas have elevated plasma levels of proinsulin,[6] which is particularly helpful when the fasting immunoreactive insulin (IRI) is somewhat low or borderline. In addition, in patients with insulinoma, the proportion of proinsulin in relation to total insulin level is elevated. (Normal levels are < 20%.) Very high proinsulin levels (> 50%) suggest that the insulinoma is malignant.

C-Peptide Measurement

A sensitive assay for measuring C-peptide levels is available and is useful for diagnosing insulinoma in the following situations:

1. *Diagnosis of islet cell tumors by C-peptide suppression test.* During this test, commercial insulin is infused into patients to induce hypoglycemia. As expected, with values of serum glucose of 40 mg per 100 mL or less, normal individuals suppress their endogenous secretion of insulin (as measured by serum C peptide) by 50 to 70%.[7]
2. *Diagnosis of islet cell adenomas (or beta cell hyperplasia) in diabetic patients who require insulin.* Many patients who have taken or are currently taking insulin have circulating antibodies to this peptide, which makes reliable measurement of serum insulin difficult. This problem can now be circumvented by the use of the C-peptide assay because this determination is not affected by insulin antibodies. An elevated C-peptide concentration in such cases is a reflection of increased endogenous secretion, as would be expected in patients harboring an insulinoma.
3. *Diagnosis of surreptitious injection of insulin (factitious hypoglycemia).* The availability of testing of C-peptide levels allows a physician to identify patients who are secretly injecting themselves with insulin. Because C peptide is secreted in equimolar amounts as insulin, it also reflects endogenous B-cell secretion. It does not cross-react with insulin antibodies. Thus, failure to detect C peptide during periods of hypoglycemia and hyperinsulinemia indicates that the insulin has been administered and is not endogenous. Therefore, surreptitious insulin use may be suspected. Because the patient may also use sulfonylureas surreptitiously, it is important to measure urine sulfonylureas to exclude this possibility. These studies are especially indicated in patients who are in the medical profession or who have family members with diabetes mellitus.

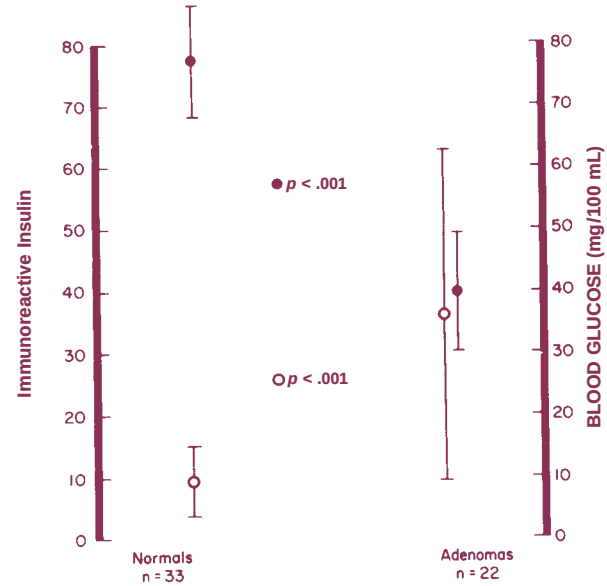


Figure 13–4. Plasma insulin (μU/mL) and blood glucose (mg/100 mL), relationships after overnight fasting in normal subjects and in 22 subjects with solitary beta islet cell adenomas. Both plasma insulin and blood glucose show highly significant differences between the two groups. Reproduced with permission from Harrison TS. Hyperinsulinism and its surgical management. In: Hardy JD, editor. Rhoad's surgery, principles and practice. 5th ed. Philadelphia: JB Lippincott; 1977.

Provocative Tests

Provocative tests to diagnose insulinomas are only rarely necessary and have been used infrequently in our medical center during the past 15 years. The details of each procedure are beyond the scope of this discussion but are clearly outlined by Wayne and associates.[8] These stimulation tests offer the following cumulative positive results: tolbutamide tolerance, 80%; glucagon test, 72%; glucose tolerance test, 60%, and L-leucine test, 50%.[9] The calcium

infusion test described by Kaplan and colleagues and recently modified by Doppman and colleagues is of value in selected patients.[10,11]

MANAGEMENT OF SERUM GLUCOSE

Preoperative Management

After the diagnosis of an insulinoma and prior to surgery, it is important to ensure that the patient is protected from hypoglycemic episodes and the resulting damaging effects on the central nervous system. This can be accomplished in most patients by frequent feedings. Diazoxide can also be used preoperatively to decrease the occurrence of hypoglycemia. One should be aware that diazoxide, the half-life of which is 28 ± 8 hours, has been associated with hypotension on induction of anesthesia.[6] Some clinicians recommend discontinuing diazoxide before surgery to avoid this problem and to be able to monitor blood glucose levels during the operation as an important indicator of the successful removal of the insulinoma.[12] We have not had perioperative problems with diazoxide, but it does cause fluid retention and hirsutism. In patients not receiving diazoxide, intravenous glucose infusion is necessary when fasting in preparation for surgery.

Intraoperative Management

Intraoperative monitoring of serum glucose is essential and useful for determining when the insulinoma has been successfully removed. This practice obviates the risk of severe hypoglycemia occurring undetected during manipulation of the tumor and also helps assure the surgeon that all functioning tumor has been removed. Some surgeons use a continuous-flow, enzymatic system, called an artificial beta cell. This system determines and records serum glucose levels at 1-minute intervals. It maintains serum glucose levels in the desired range by infusing serum glucose or insulin as necessary and also records serum glucose values throughout the operation. Serum glucose levels usually increase within 15 to 60 minutes after removal of an insulinoma.[13] Intraoperative glucose monitoring can sometimes be misleading as false positives because glucose levels sometimes increase during anesthesia induction or initial incision[14] and sometimes false negatives occur when there is a longer delay after the insulinoma removal before the glucose level increases.[15] This occurs most frequently in very thin or underweight patients. Overall, however, careful glucose monitoring is essential, and this technique makes it easier.

Postoperative Management

After a successful insulinoma resection, transient hyperglycemia in the range of 200 to 400 mg/dL for a period of several days to several weeks is the rule and demonstrates a successful outcome. Treatment with small doses of insulin is sometimes necessary to avoid glucosuria and ketoacidosis. Rarely, patients may develop permanent hyperglycemia, especially after a subtotal or near-total pancreatectomy. Persistent hypoglycemia, once as high as 10 to 20% of operative cases, can now be expected in only about 5% of patients with benign insulinomas and for some patients with unresectable malignant disease.[16] After subtotal or near-total pancreatectomies for nesidioblastosis, children are more prone to developing diabetes mellitus later in life (usually in adolescence) than are the adults who have undergone similar operations.[17] Rarely, permanent hyperglycemia develops after a very limited resection or even enucleation of an insulinoma.

TREATMENT

Surgery, resection of one or more insulinomas, is the treatment of choice once the diagnosis of insulinoma is established as it is the most reliable method of preventing recurrent hypoglycemic episodes, which can result in permanent brain damage and coma, and curing the patient. Recurrent insulinoma is uncommon except in patients with functioning islet cell cancers and familial disease with multiple islet cell tumors.

MEDICAL TREATMENT OF INSULINOMAS

Diet

Acute episodes of hypoglycemia are reversed with carbohydrate. Patients frequently learn this practice

for themselves before the diagnosis is made and snack frequently. This often results in weight gain. More severe attacks, including coma, require intravenous glucose administration. Many patients with hyperinsulinism find that they do better on a high-protein diet, as do patients with reactive hypoglycemia. This has added appeal in that the total carbohydrate and fat intake can be decreased, as well as total daily calories.

Diazoxide

The most commonly used and effective drug for the management of hyperinsulinism with hypoglycemia is diazoxide. It is currently primarily used for its diabetogenic action in the treatment of hyperinsulinism. The dose of diazoxide ranges from 300 to 800 mg daily in patients with hyperinsulinism. Diazoxide inhibits insulin secretion by a direct action on beta cells and also by stimulating epinephrine release, which itself further inhibits insulin release.

There are unpleasant effects of diazoxide, the most prominent being fluid retention, gastrointestinal irritation, hypertrichosis, and agranulocytosis. Fluid retention can usually be corrected by thiazide diuretics. Despite these associated conditions, diazoxide is usually tolerated by most patients and has been helpful both for preoperative management of these patients and for long-term therapy in patients with insulinoma who have unresectable tumors or who are unwilling to undergo surgery. In our medical center, a small number of patients with insulinoma have been successfully managed on diazoxide for over 5 years.

Unfortunately, about 40% of patients either fail to respond to diazoxide treatment or have clinical sequelae that compel them to discontinue its use. Seven of 41 patients at our medical center failed to respond to diazoxide.[5] Fourteen of these 41 patients had complications (palpitations [13], edema [5], nausea [2], gastrointestinal discomfort [2], and elevated uric acid [2]). Five of these patients had symptoms or complications that were so severe that they discontinued their diazoxide. Thus, diazoxide was successful in only 29 of our 41 patients.[5] This response to the diazoxide treatment is comparable with that reported by other medical centers.[18]

Somatostatin Analogues

Somatostatin, a naturally occurring peptide widely distributed in the body, inhibits the release of growth hormone. Somatostatin analogues have been used for various types of endocrine tumors with considerable success. Somatostatin has been used effectively to reverse hyperinsulinism in metastatic islet cell carcinoma in some patients.[19] However, the experience with octreotide in the treatment of insulinomas is limited, and many patients fail to respond. In our experience, octreotide scans were positive in fewer than 30% of patients with insulinomas. Rarely, octreotide may exacerbate the hypoglycemia.[20]

Other Therapy

The effectiveness of chemotherapy against malignant insulinomas is limited despite the introduction of several experimental drugs. Regimens using streptozocin in combination with 5-fluorouracil and doxorubicin have been used in the past and continue to be acceptable chemotherapies for unresectable insulinomas despite their side effects. Streptozocin is an antibiotic isolated from *Streptomyces achromogenes*, which is highly toxic to pancreatic beta cells. Streptozocin controls hypoglycemic symptoms in approximately two-thirds of patients with metastatic islet cell carcinoma and also causes a measurable reduction in tumor size in about 50%.[21] It appears to prolong survival.[22] However, these benefits are achieved at the cost of significant toxicity, including liver and renal toxicity, which develops in approximately two-thirds of patients.[22] Other drugs under investigation include calcium channel blockers and interferon-α; these agents are primarily experimental. Hepatic artery chemoembolization, radiofrequency ablation, and debulking have been tried with some success to control the hypoglycemia.

PATHOLOGY

Insulinomas tend to be small tumors equally distributed throughout the pancreas (see Figure 13–5 for distribution data in our patients). In our 50 patients

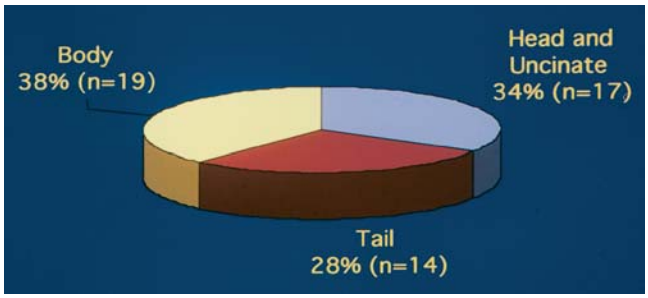


Figure 13–5. Distribution of insulinomas among the patients at our institution. Adapted from Boukhman MB et al.[33]

with solitary tumors, the average size of insulinomas was 1.8 cm in diameter. Thirteen patients had tumors < 1 cm in diameter. The size distribution of the insulinomas is shown in Figure 13–6. Approximately 1% of tumors are ectopic.

Approximately 10% of insulinomas are multiple, 10% are malignant, and 10% occur in patients with MEN type I. These patients usually (approximately 85%) have multiple insulinomas. The presence of multiple insulinomas should alert clinicians to screen for the presence of MEN type I. Early diagnosis of MEN type I is important because of the different surgical management for patients with MEN type I and insulinomas. MEN type I can also be diagnosed preoperatively based on the family history of this condition and on the presence of other endocrine tumors in these patients, especially hyperparathyroidism. In our series of 66 patients, 7 MEN type I patients had hyperparathyroidism, 5 pituitary adenomas, 5 gastrinomas, 1 malignant carcinoid, 1 thyromegaly, 2 papillary carcinomas of the thyroid, 1 hyperaldosteronism, and 1 hypotestosteronism. Among our 8 patients with malignant insulinoma, metastases were located in the lymph nodes (4), lower abdomen (2), brain (1), and lung (1).[5] Luckily, in contrast to gastrinoma, 99% of insulinomas are situated within the pancreas.

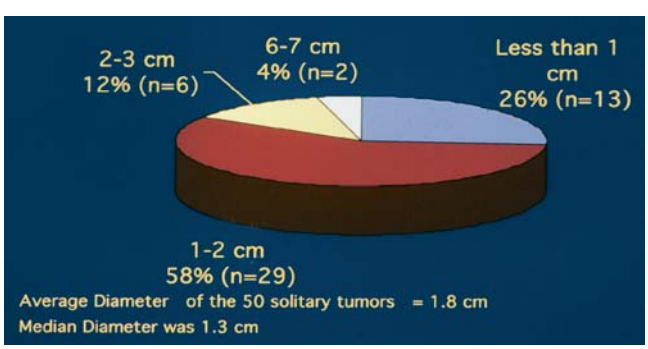


Figure 13–6. Size distribution of insulinomas among the patients at our institution. Adapted from Boukhman MB et al.[33]

Histologically, hyperinsulinism results from either tumors (about 90 to 95% of cases) (Figure 13–7) or hyperplasia or nesidioblastosis (about 5 to 10% of cases) (Figure 13–8). Nesidioblastosis occurs almost exclusively in infants and children. Hyperplasia in this condition is defined as the increased number of pancreatic islet cells usually identifiable as discrete masses, whereas nesidioblastosis is defined as the proliferation of the pancreatic ductal epithelial cells and is diffuse without discrete masses.

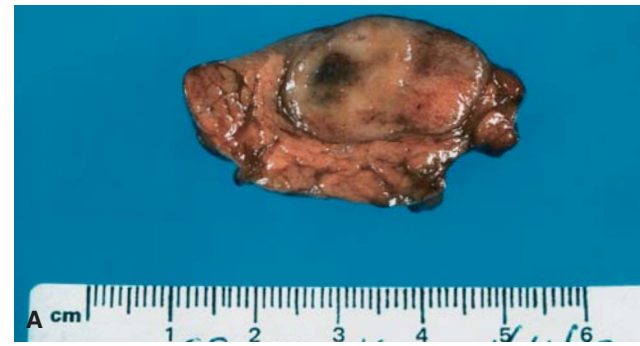
LOCALIZATION OF INSULINOMAS

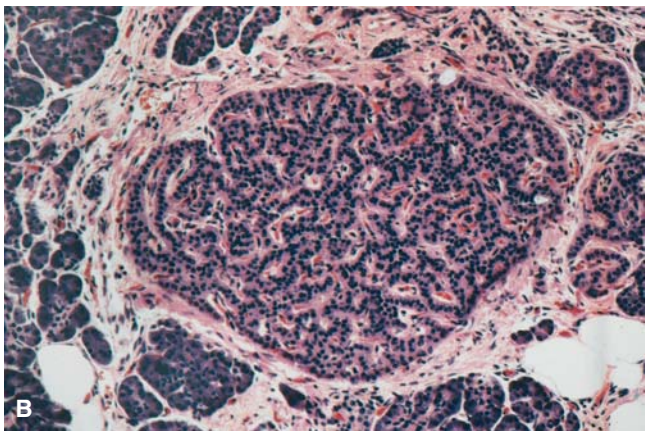
Pancreatic Arteriography

Selective pancreatic angiography, using stereoscopic filming with magnification and subtraction techniques, identifies 50% of tumors with a minimum diameter of 5 mm.[23] Arteriography was formerly the gold standard of insulinoma localization and, in our experience, successfully localized 47% of the tumors. Arteriography in our patients did not demonstrate improved sensitivity with increased tumor size, probably because the hypervascularity of the tumor was equally important for tumor localization. Arteriography is useful in selected patients,[24] especially those with recurrent or persistent disease. Unfortunately, arteriography is invasive and expensive (Figure 13–9).[25] We therefore do not recommend it for most patients.

Percutaneous Transhepatic Portal Venous Sampling

In our patients, transhepatic portal venous sampling (THPVS) detected 66% of the tumors < 1 cm in diameter, with an overall detection rate of 55%. In this procedure, the portal vein is catheterized using a percutaneous transhepatic needle, and the catheter is advanced by fluoroscopic guidance into the multiple small draining veins of the entire pancreas. Blood insulin level is sampled at each site, a record





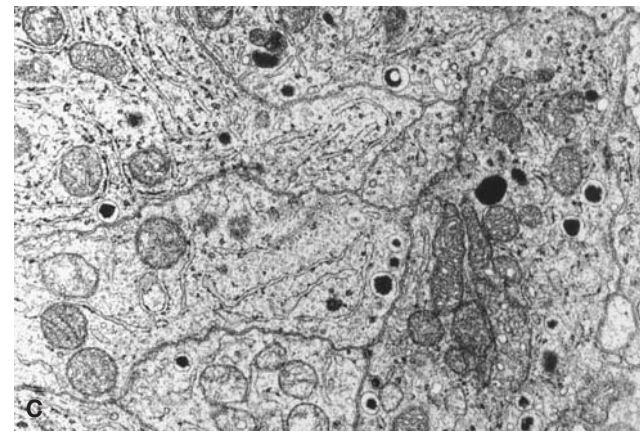
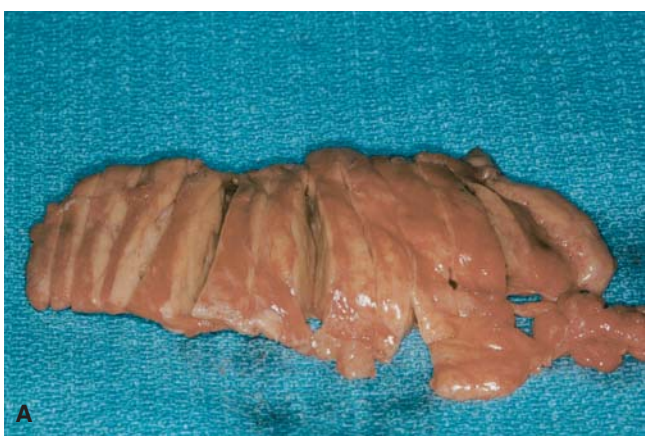


Figure 13–7. *A*, Pathologic specimen from a patient with a large, well-circumscribed, pancreatic neuroendocrine tumor. *B*, Microscopic specimen of this tumor. The appearance of benign and malignant lesions may be very similar. The tumor consists of cells arranged in trabeculae and nests. *C*, Electron micrograph shows abundant dense core neurosecretory granules.

of each sample is graphically noted, and simultaneous peripheral samples are taken as controls.

The drawback to the THPVS is that it is invasive and uncomfortable for the patient and is associated with appreciable complications. In addition, it only regionalizes and does not localize the site of the tumor. The exact location of the tumor still must occur intraoperatively. This procedure has been replaced by a variation of the Imamura procedure, which uses intra-arterial stimulation with calcium.[26] We recommend the Imamura-Doppman procedure for patients with persistent or recurrent insulinoma, although some experts use it for most patients. This procedure has been recommended by some authors to be especially useful in patients with beta-cell hyperplasia or with nesidioblastosis (Figure 13–10).[27]



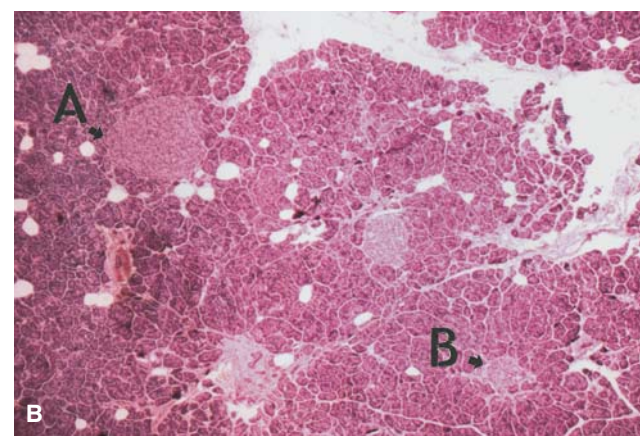


Figure 13–8. *A*, Pathologic specimen from a 72-year-old woman with islet cell hyperplasia. *B*, This microscopic specimen shows a marked focal enlargement of islet A compared with islet B, which suggests islet cell hyperplasia.

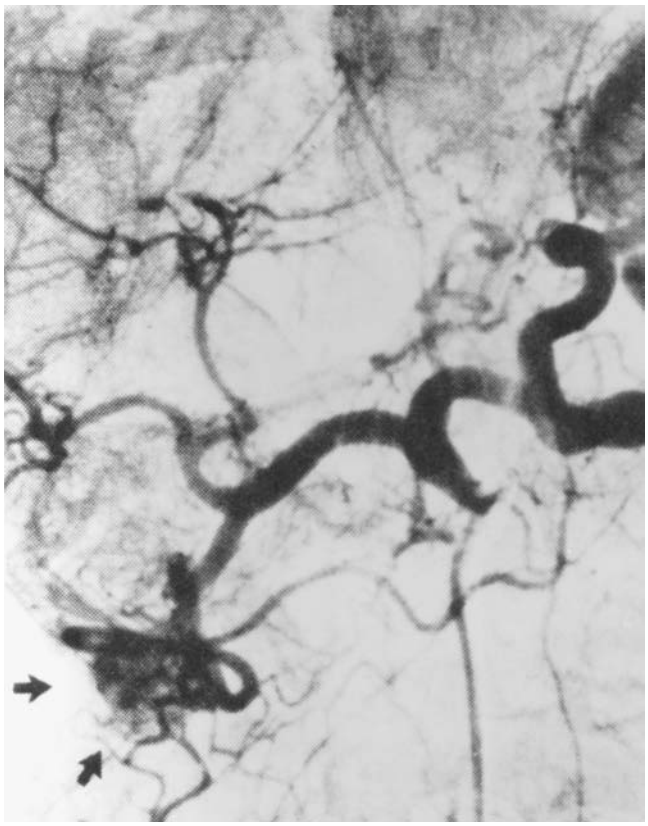


Figure 13–9. Preoperative localization of an insulinoma of the head of the pancreas by celiac artery angiography. Subtraction technique during the arterial phase. The tumor (*arrows*) is clearly seen. Reproduced with permission from Kaplan EL, Lee CH. Recent advances in the diagnosis and treatment of insulinomas. Surg Clin North Am 1979;59:119.

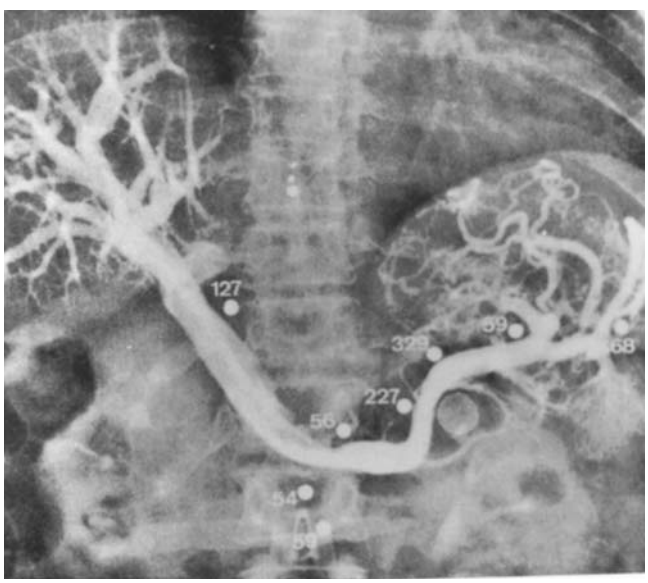


Figure 13–10. Percutaneous transhepatic portal venous sampling. Insulin radioimmunoassay demonstrates peak levels (227 and 329 μU/mL) in the area of the tail of the pancreas. Reproduced with permission from Bottger TC and Junginger T.[31]

Preoperative Endoscopic Ultrasonography

A retrospective analysis from various medical centers showed that endoscopic ultrasonography detected at least 80% of insulinomas that were not visible in transabdominal ultrasonography or computed tomography (CT).[28] In one of the studies, endoscopic ultrasonography correctly identified 32 of the 39 surgically verified tumors, with accurate prediction of its size and site. Twenty-two underwent both endoscopic ultrasonography and angiography, and the former was significantly more sensitive for tumor localization (82% versus 27%). No other tumors were detected in 18 of 19 control patients (specificity of 95%). However, these results are limited for tumors localized to the head of the pancreas, whereas sensitivity achieved for tumors in the body is 78% and for those in the tail of the pancreas only 60%.[29] We believe that this is the preferred preoperative localization study (Figure 13–11). We are using it in most patients as it enables one to laparoscopically remove most of the identified tumors.

There have been several case reports in the literature describing successful use of preoperative intraductal ultrasonography.[30] However, more evidence is

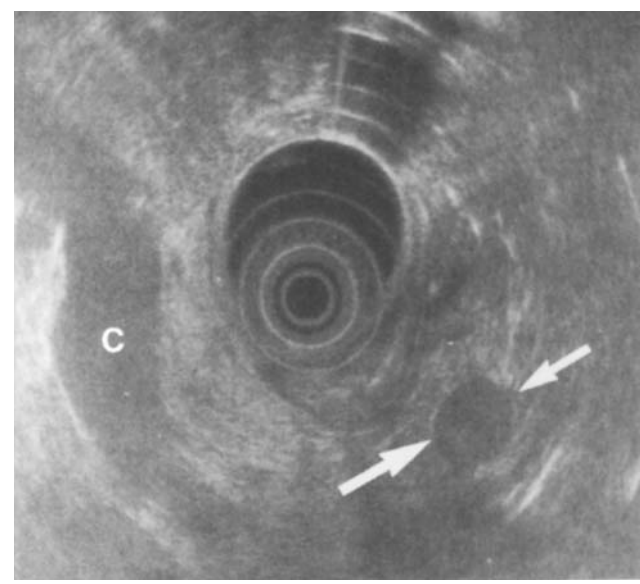


Figure 13–11. Endoscopic ultrasonographic image shows a well-circumscribed, 1 cm hypoechoic mass in the pancreatic head (*arrows*). The probe lies within the second portion of the duodenum. Note the dilated distal common bile duct (C). Reproduced with permission from Buetow P. Islet tumors of the pancreas: clinical, radiologic and pathologic correlation in diagnosis and localization. Radiographics 1997;17:453–72. Copyright 1997 Radiologic Society of North America.

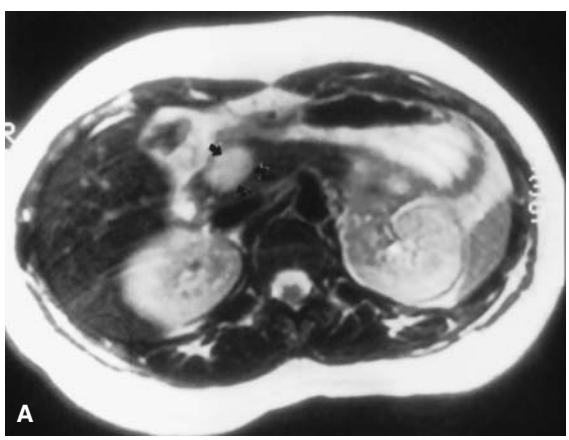
needed before recommending this procedure to be of standard use in insulinoma localization.

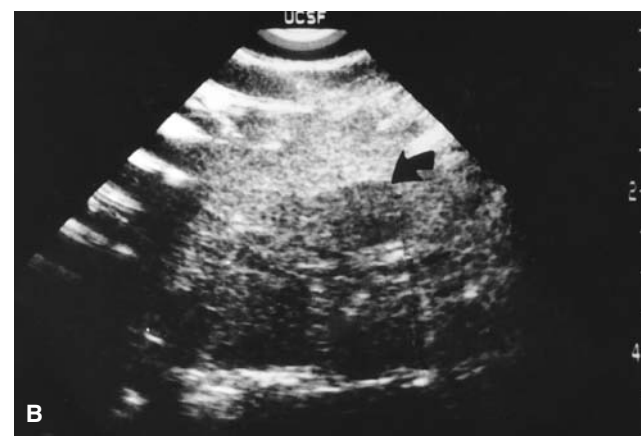
Magnetic Resonance Imaging, Magnetic Resonance Imaging with Gadolinium, CT, and Preoperative Ultrasonography

In our medical center, the accuracy of magnetic resonance imaging (MRI), MRI with gadolinium, CT, and preoperative ultrasonography was 30%, 40%, 24%, and 50%, respectively. These sensitivities are similar to those reported in other medical centers.[31,32] The frequency of use of these studies, as well as arteriography and THPVS, has changed over the years owing to the availability of newer and more sensitive localization procedures. The accuracy of MRI, MRI with gadolinium, CT, and preoperative ultrasonography increased as the size of the tumor increased. Thus, MRI accuracy increased from 0 to 75% as the tumor size increased from < 1 cm to > 2 cm.[33] The accuracy of MRI with gadolinium increased from 0 to 50% and then to 100% as the tumor size increased from 1 cm, 3 cm, and 6 cm, respectively.[33] Because most insulinomas are < 1 cm in diameter, the sensitivities of the above studies for these small tumors do not warrant their use in patients who have not had previous insulinoma operations. Presently, however, CT in our institution is used primarily for screening patients for malignant insulinomas with liver metastases rather than for localization of insulinomas (see Figure 13–12 for illustrations of MRI, preoperative ultrasonography, and CT).

Intraoperative Ultrasonography and Intraoperative Palpation

Intraoperative ultrasonography (IOUS) was introduced in 1985. It identifies insulinomas with 90 to





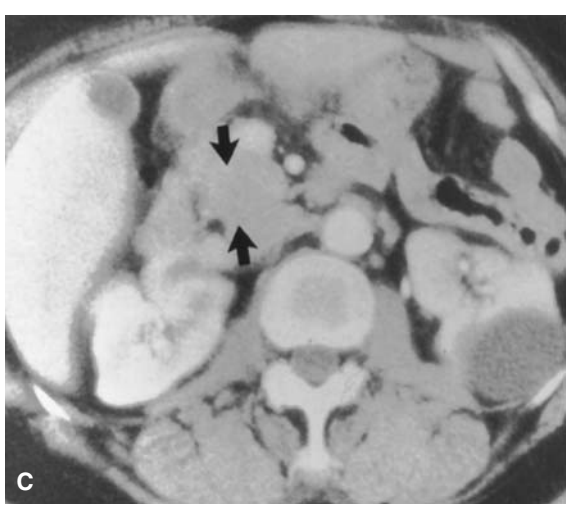


Figure 13–12. *A*, This T_2-weighted magnetic resonance image demonstrates an insulinoma in a region of the pancreatic head (*arrow*). *B*, Preoperative sonogram demonstrates a small insulinoma. *C*, Axial contrast-enhanced computed tomographic scan demonstrates a hypervascular mass within the pancreatic head (*arrows*) that measured approximately 2.5 cm in diameter and produced mass effect on the superior mesenteric vein. Reproduced with permission from Buetow P. Islet tumors of the pancreas: clinical, radiologic and pathologic correlation in diagnosis and localization. Radiographics 1997;17:453–72. Copyright 1997 Radiologic Society of North America.

100% sensitivity,[34] and 91% were identified among our patients.[33] In our medical center, as well as in others, IOUS was significantly more sensitive than intraoperative palpation (91% versus 76% in our medical center).[31–33] Some experts have suggested that this procedure eliminates the need for other preoperative localization procedures.[31,32] In our medical center, as well as in others,[31–33] IOUS before or after a careful mobilization of the pancreas in combination with intraoperative palpation gave the best results. Although it was formerly the only localization technique that we recommended for patients who had not had previous pancreatic operations, we now recommend preoperative transgastric ultrasonography. Among the 20 tumors identified by IOUS in our patients, there were no false-positive diagnoses.[33] The low false-positive rate makes this method more useful because it decreases the false diagnosis of adenoma in a nodular-feeling pancreas, in which nodularity and scarring may lead to unnecessary dissection. IOUS helped to identify 9 of the 11 nonpalpable and nonvisable tumors, thus preventing unsuccessful operations.[33] It also decreases the risk of missing multiple tumors even after one tumor is identified. Additionally, IOUS and preoperative transgastric ultrasonography provide assistance in visualizing anatomic details during the operation, such as the relationship of the insulinoma to the pancreatic duct, thus helping the surgeon to decrease the risk of a postoperative fistula (Figure 13–13 for IOUS illustration).

Recommendation

A variety of procedures have been advocated for detecting insulin-secreting tumors, but there is little consensus about the best method or combination of methods. Most endocrinologists, surgeons, and patients usually prefer preoperative localization if a reliable and cost-effective test is available. Preoperative transgastric ultrasonography appears to be the best localization procedure prior to operation. IOUS in combination with intraoperative palpation usually localizes the tumor and has a combined cure rate of 90 to 100% (94% in our patients).[34] As mentioned, the best preoperative test is transgastric ultrasonography (see Figure 13–14 for the success rates of the various localization techniques at the University of California-San Francisco [UCSF] and Table 13–2 for a summary of the advantages of IOUS).

SURGICAL TREATMENT OF INSULINOMAS

Operative Approach

Operation is the ultimate localization procedure in diagnosis and usually the definitive step to end the treatment of insulinoma. A laparoscopic approach may also be attempted for selected patients whose insulinomas are identified by transgastric ultrasonography preoperatively. A bilateral subcostal incision or an upper midline incision can be used. See Figure 13–15 for an illustration of the relevant anatomy. Initial exploration should involve careful assessment of the liver for metastatic disease.

The pancreas is exposed by dissecting the omentum from the transverse colon throughout its length. The omentum and stomach are retracted superiorly, lysing adhesions between the posterior wall of the stomach and the pancreas. The lesser sac is entered and the retroperitoneum is exposed with careful palpation of the entire surface of the pancreas (Figure 13–16). A Kocher maneuver is performed to mobilize the duodenum anteriorly and to allow bimanual palpation of the head and uncinate process (Figure 13–17). Special attention is paid to any area suspicious for a tumor on preoperative or intraoperative localization studies.

At our medical center, we routinely use IOUS not only to localize the tumor but also to see its rela-

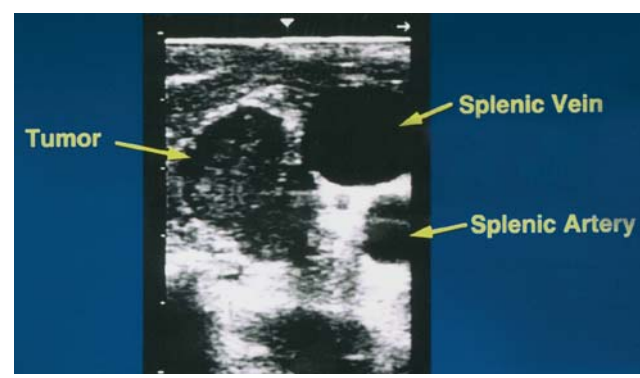


Figure 13–13. Intraoperative sonogram demonstrates the sharply marginated mass, which is predominantly hypoechoic and is situated in close proximity to the splenic vein and artery.

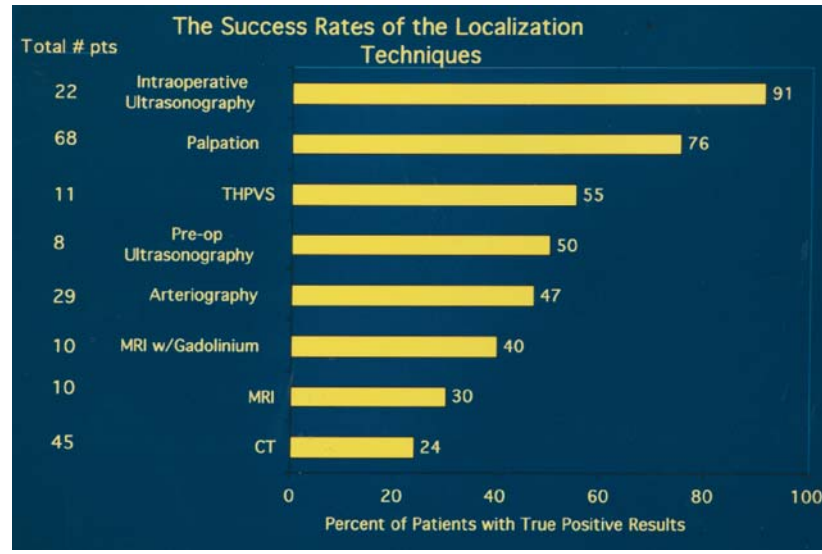


Figure 13–14. Success rates of insulinoma localization at our institution using various localization techniques. CT = computed tomography; MRI = magnetic resonance imaging; THPVS = transhepatic portal venous sampling. Reproduced with permission from Boukhman MB et al.[33]

tionship to the pancreatic ducts, the portal vein, the common bile duct, and the superior mesenteric vessels. This helps in removal of the tumor and decreases the risk of a postoperative fistula. The body and tail of the pancreas are mobilized by incising the peritoneum at the inferior border of the gland and gradually dissecting beneath its entire posterior surface. This is also the approach that is frequently used to expose the left adrenal gland.

If a small pancreatic tumor is found, enucleation is often possible with gentle dissection of the exocrine parenchyma away from the islet cell tumor. Use of the Bovie electrocoagulation unit and clips might lessen the risk of a pancreatic fistula.[35] Before removal of a suspected solitary adenoma, the entire pancreas should be carefully examined because insulinomas are occasionally (approximately 18%) multiple. As mentioned previously, they are only rarely found in extrapancreatic sites.

Pathologists can usually confirm that the removed tumor is an islet cell tumor on frozen section but usually cannot determine whether it is benign or malignant. Following removal, the blood sugar level usually rises and the insulin level falls, indicating a successful operation.

Success

At UCSF medical centers, we have had an 89% success rate at initial pancreatic exploration for insulinomas, including a 96% (46 of 48) success rate in patients with benign solitary tumors.[5] This success rate is similar to the results reported by others.[23,36] Among the patients who had initial pancreatic exploration for insulinoma, 3 of 5 with multiple tumors and 6 of 7 with malignant tumors were successfully treated. Reoperations are not as successful as we and others have reported.[5] The main reasons for failure in our experience[5,37] and that of others were (1) islet cell cancer or metastatic disease, (2) nesidioblastosis/hyperplasia, (3) multiple neoplasms that are especially common in MEN type I patients, and (4) solitary adenomas that are small or soft deeply situated in the pancreas. Some patients have more than one reason for failure. Because of the higher failure rate in patients requiring reoperation, we recommend preoperative localization studies, including transgastric ultrasonography and the Imamura-Doppman procedure in these patients.

Table 13–2. ADVANTAGES OF INTRAOPERATIVE ULTRASONOGRAPHY IN PATIENTS WITH INSULINOMA*

Identified insulinomas with 91% sensitivity
Is more sensitive than intraoperative palpation (91% vs 76% sensitivity)
Identified 9 nonpalpable and nonvisible insulinomas, thus increasing operative success
Decreased the risk of missing multiple tumors
Low false-positive rate; therefore, useful for persistent or recurrent disease
Helped visualize relationship of the tumor to the pancreatic duct; therefore, possibly decreased incidence of postoperative fistula

*From the University of California-San Francisco institutional experience. Adapted from Boukhman MB et al.[33]

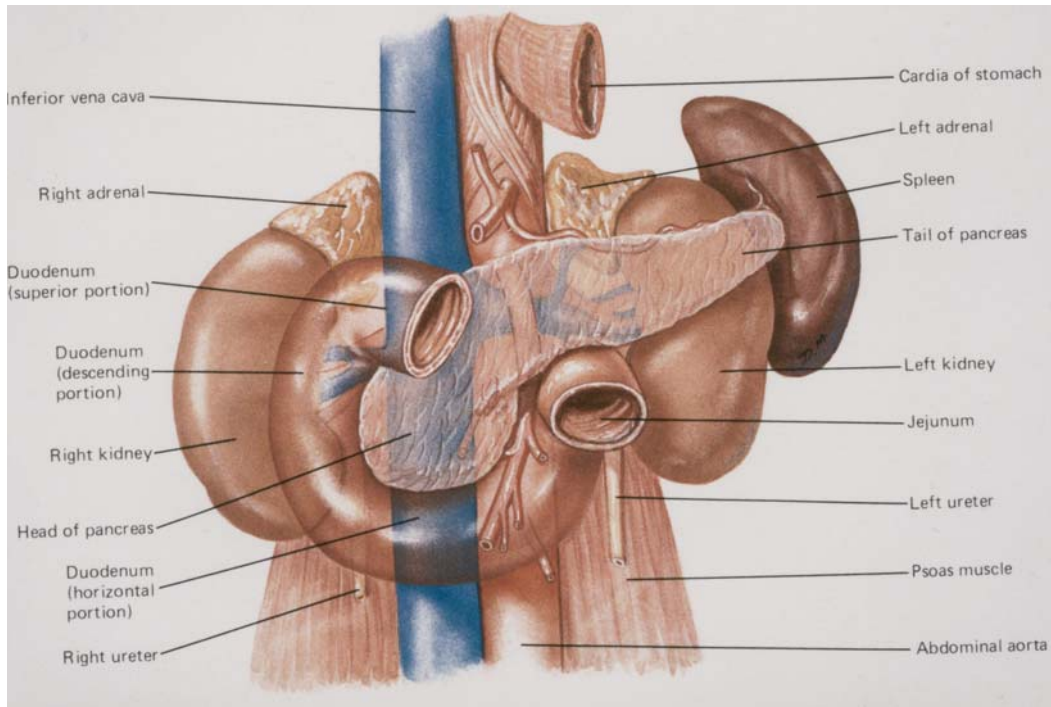


Figure 13–15. Posterior relations of the pancreas. For simplicity, the common bile duct and the components of the portal venous system are not shown. Adapted from Edis AJ, Ayala LA. Manual of endocrine surgery. Springer-Verlag; 1975.

For patients with sporadic insulinoma and solitary tumors, we recommend local incision; for massive tumors in the head of the pancreas, a Whipple procedure is indicated. Patients with MEN should be treated by enucleation of tumors from the head of the pancreas and distal pancreatectomy. For patients with nesidioblastosis, an extensive subtotal or near-total pancreatectomy should be done.

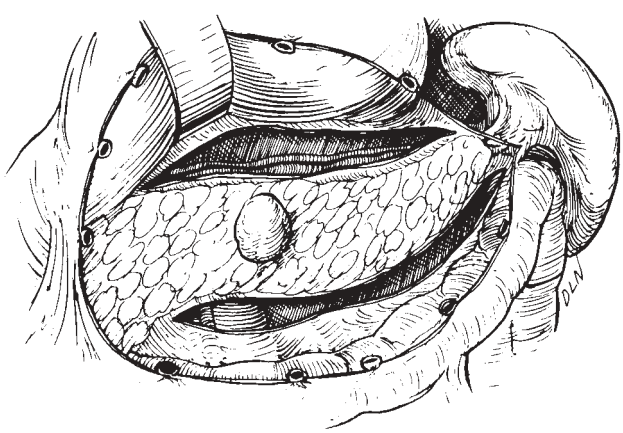


Figure 13–16. Reproduced with permission from Paloyan E, Lawrence AM, editors. Endocrine surgery. Year Book Medical Publishers; 1976.

Complications

Complications are unfortunately relatively common, including fistula, pleural effusion, bleeding, infection, and diabetes mellitus (Figure 13–18). The latter is usually the result of near or total pancreatectomy when doing a distal or near-total pancreatectomy and preserving the spleen when that is possible.

As expected, the complication rate was greater in patients who had more extensive operations, as we and others have reported.[5,38] Enucleation of tumors in the head or uncinate process appears to be associated with more complications, especially fistula formation.[5]

SPECIAL SITUATIONS

MEN Type I Syndrome

MEN type I is a genetically transmitted syndrome and is characterized by endocrinopathies of the parathyroid glands, the anterior pituitary, and the endocrine pancreas. Recently, the gene (*MENI*) has been mapped to chromosome 11.[39] Insulinomas associated with MEN type I syndrome in many

respects differ from insulinomas in patients with sporadic hyperinsulinism. About three-fourths of MEN type I patients with insulinomas have multiple tumors. Malignant insulinomas appear to be somewhat more common in these patients. As mentioned, we recommend a subtotal pancreatic resection with enucleation of tumors from the head of the pancreas (guided by the IOUS for a successful removal) in MEN type I patients.[33,37] Good judgment and experience must be used to avoid recurrence or a failed operation on the one hand and yet prevent endocrine and exocrine pancreatic insufficiency on the other.

Hyperinsulinemic Hypoglycemia in Infants and Children

In infants and children with hypoglycemia owing to organic hyperinsulinism, the pathology patterns are distinctly different from the pathology patterns seen in adults. Because of the different pathology, the localization techniques that are successful for adults are often not effective in infants and children. In addition, different patterns of pathology in the pediatric population necessitate a different surgical approach.

Nesidioblastosis

The term nesidioblastosis was first originated by Laidlaw from the Greek *nesidion* meaning "islet."[40] Vance and colleagues were the first to use this word in its current meaning.[41] This condition is extremely rare in adults, with only a little over 20 cases reported in the literature. In children, nesidioblastosis is more common and can occur either sporadically or in association with MEN type I syndrome. The pathologic appearance of nesidioblastosis is unusual. Ribbons or sheets of islet cells parallel the pancreatic ducts, and discrete islets are usually not seen. The lesions are thought to represent the proliferation of the islet cell–like clusters, including ductulonodular complexes and hypertrophied insulin cells with giant nuclei. The nesidioblastosis can be focal or diffuse.

Beta Islet Cell Hyperplasia

Infants and children with organic hyperinsulinism may also have diffuse islet cell hyperplasia (see Figure 13–8 for a hyperplasia histology slide). In these patients, virtually every islet has abnormal beta cells, which can often demonstrate bizarre nuclear shapes and sizes.

Despite the active debate in the medical community about the best method or combination of methods for treating infants with hyperinsulinism, there is no general agreement regarding the best management. Many authorities favor near-total (95%) pancreatectomy as a procedure of choice when treating infants with persistent hypoglycemia.[42] Unfortunately, even after 95% pancreatectomy, about one-third of the infants remain hypoglycemic, although they may be easier to manage. In addition, over 70% develop diabetes mellitus before adulthood, some immediately postresection, and others usually at adolescence.[43,44]

Among the proponents of the surgical cure, some authors recommend a 95% pancreatectomy,[42] whereas others recommend resecting about 75% of the pancreas to reduce the occurrence of diabetes mellitus postoperatively as well as when the patient reaches adulthood.[43,44] We favor a selective surgical approach

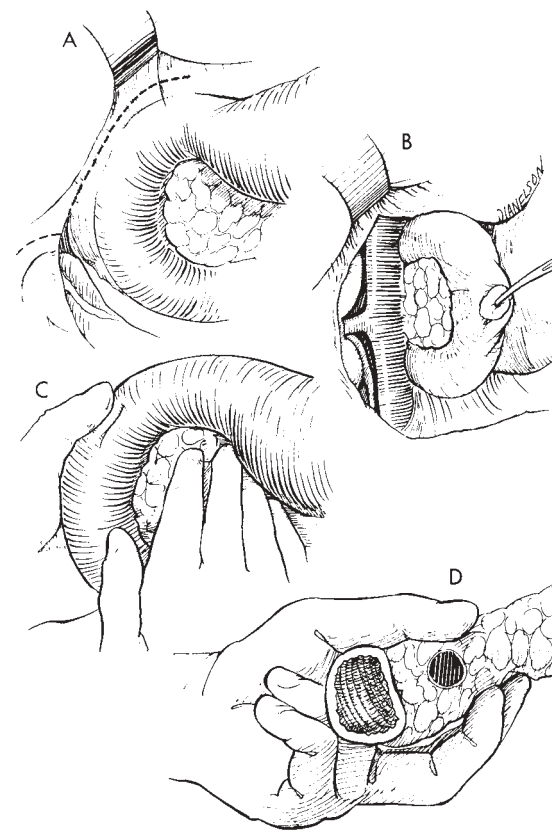


Figure 13–17. Reproduced with permission from Paloyan E, Lawrence AM, editors. Endocrine surgery. Year Book Medical Publishers; 1976.

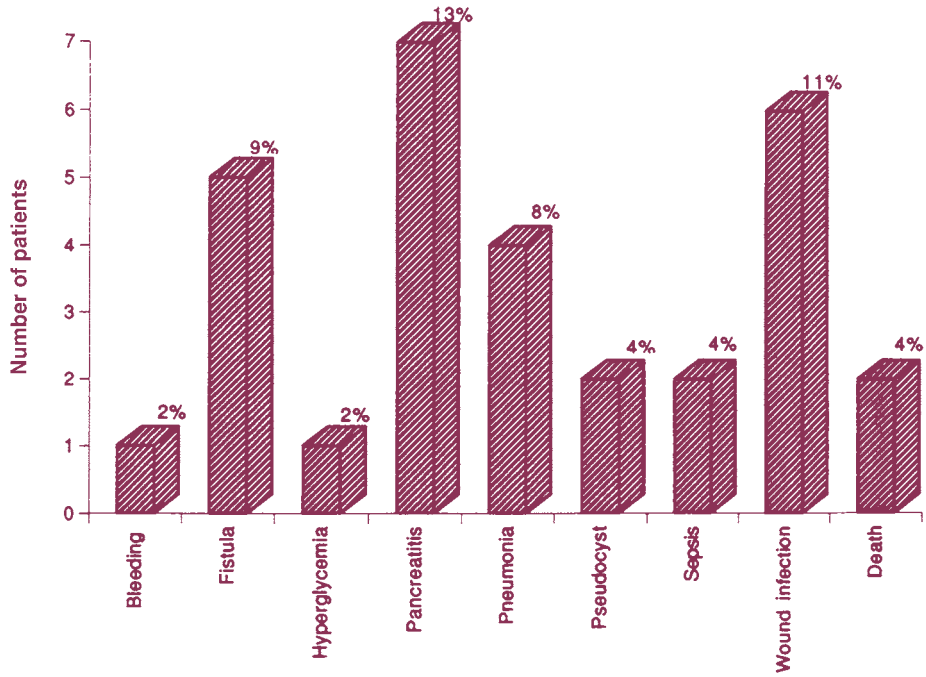


Figure 13–18. Complications from insulinoma operations at our institution. Reproduced with permission from Boukhman MB et al.[5]

depending on the histologic diagnosis at the time of surgery. If nesidioblastosis is focal by frozen-section examination, a 75% pancreatectomy with enucleation of any tumors from the head of the pancreas is recommended. When there is beta cell hyperplasia or a diffuse variant of nesidioblastosis, we and other authors recommend a 95% pancreatectomy despite the higher risk of developing diabetes mellitus later in life.[45] This approach is more aggressive because, according to some authors, diffuse nesidioblastosis is associated with decreased surgery success rates.[46] Thus, in a study by Gauderer and colleagues, among the 12 patients in their study with diffuse nesidioblastosis, 11 patients had a failed 80% primary pancreatectomy and 1 had a failed 90% pancreatectomy.[46] If the frozen section reveals islet cell adenoma with no evidence of hyperplasia or nesidioblastosis, we recommend enucleation with careful inspection for additional tumors. Islet cell cryopreservation may be useful to decrease the long-term risk of diabetes mellitus.

CONCLUSION

Among the causes of hypoglycemia are pancreatic beta islet cell lesions, which release insulin autonomously of the controlling influence of circulating levels of blood glucose. About 90% of these tumors are small, solitary, benign, and sporadic. These pancreatic beta islet cell lesions can now be diagnosed with precision by documenting a glucose-to-insulin ratio > 3, with elevated C peptide and absent sulfonylureas in the urine. The preferred method of treatment is surgery that can be done endoscopically when the tumor is identified preoperatively. The surgical approach differs for patients with sporadic insulinomas, MEN type I syndrome, multiple tumors, extensive involvement, hyperplasia/nesidioblastosis, and age. Preoperative localization testing such as transgastric ultrasonography is useful, and other localization tests are recommended in reoperative cases. Surgical treatment in combination with IOUS carries with it a low mortality and morbidity and a 90 to 95% likelihood of successfully reversing the hyperinsulinism.

REFERENCES

1. Wilder RM, Allan FN, Power MH, Robertson HE. Carcinoma of the islands of the pancreas, hyperinsulinism hypoglycemia. JAMA 1927;89:348.
2. Howland G, Campbell WR, Maltby EJ, Robinson WL. Dysinsulinism: convulsions and coma due to islet cell

tumor of the pancreas, with operation and cure. JAMA 1929;93:674.
3. Pearse AGE. Common cytochemical and ultrastructural characteristics of cells producing hormones (the APUD series) and their relevance to thyroid ultimobranchial C cells and calcitonin. Proc R Soc Lond B Biol Sci 1968;170:71–80.
4. Pearse AG, Polak JM. Neural crest origin of the endocrine polypeptide (APUD) cells of the gastrointestinal tract and pancreas. Gut 1971;12:783–8.
5. Boukhman MB, Karam JH, Shaver J, et al. Insulinoma—experience from 1950-1995. West J Med 1998;169:90.
6. Schwatz, Shires, Spencer. Principles of surgery. Specific considerations. In: Pancreas. 6th ed. Lippincott; 1991. p. 1427.
7. Kaplan E, Fredland A. The diagnosis and treatment of insulinomas. In: Thompson NW, Vinic AI, editors. Endocrine surgery update. New York: Grune and Stratton; 1983. p. 254.
8. Wayne J, Tanaka R, Kaplan E. Insulinomas. In: Clark OH, Duh QY, editors. Endocrine surgery. WB Saunders; 1997. p. 581.
9. Kaplan E, Fredland A. The diagnosis and treatment of insulinomas. In: Thompson NW, Vinic AI, editors. Endocrine surgery update. New York: Grune and Stratton; 1983. p. 259.
10. Kaplan EL, Rubenstein AH, Evans R. Calcium infusion: a new provocative test for insulinomas. Ann Surg 1979;190:501.
11. Doppman JL, Miller DL, Chang R. Intraarterial calcium stimulation test for detection of insulinomas. World J Surg 1993;17:439.
12. Kaplan E, Fredland A. The diagnosis and treatment of insulinomas. In: Thompson NW, Vinic AI, editors. Endocrine surgery update. New York: Grune and Stratton; 1983. p. 261.
13. Grant CS. Insulinoma. Surg Oncol Clin North Am 1998; 7:819–44.
14. Harrison TS, Child GC, Fry WJ. Current surgical management of functioning islet cell tumors of the pancreas. Ann Surg 1973;178:485.
15. dePeyster FA. Planning the appropriate operations for islet cell tumors of the pancreas. Surg Clin North Am 1970; 50:133.
16. Edis AJ, McIllrath DC, van Heerden JA. Insulinoma: current diagnosis and surgical management. Curr Prob Surg 1976; 13:1.
17. Spitz L, Buick RG, Grant DB, et al. Surgical treatment of nesidioblastosis. Pediatr Surg Int 1986;1:26–9.
18. Goode PN, Farndon JR, Anderson J. Diazoxide in the management of patients with insulinoma. World J Surg 1986; 10:586.
19. Curnow RT, Carey RM, Taylor A, et al. Somatostatin inhibition of insulin and gastrin hypersecretion in pancreatic islet cell carcinoma. N Engl J Med 1975;292:1395.
20. Stehouwer CD, Lems WF, Fischer HR. Aggravation of hypoglycemia in insulinoma patients by the long-acting somatostatin analogue octreotide. Acta Endocrinol (Copenh) 1989;121:34.
21. Broder LE, Carter SK. Pancreatic islet cell carcinoma. Ann Intern Med 1973;79:108.
22. Schein P, Kahn R, Gordon P. Streptozocin for malignant insulinomas and carcinoid tumors. Report of eight cases and a review of literature. Arch Intern Med 1973;132:555.
23. Daggett PR, Goodburn EA, Kurts AB, et al. Is preoperative localization of insulinomas necessary? Lancet 1981;i: 483–6.
24. Clouse ME, Costello P, Legg MA. Subselective angiography in localizing insulinomas of the pancreas. AJR Am J Roentgenol 1977;128:741–6.
25. Modlen IM, Tang LH. Approaches to diagnosis of gut neuroendocrine tumors. The last word (today). Gastroenterology 1997;122:583–90.
26. Doppman JL, Chang R, Fraker DL, et al. Localization of insulinomas to the regions of the pancreas by intra-arterial stimulation with calcium. Ann Intern Med 1995;123:269–73.
27. Grant CS. Insulinoma. Baillieres Clin Gastroenterol 1996; 10:645–71.
28. Rosh T, Lightdale CJ, Botet JF, et al. Localization of pancreatic endoscopic tumors by endoscopic ultrasonography. N Engl J Med 1992;326:1721–6.
29. Doppman JL. Pancreatic endocrine tumors—the search goes on. N Engl J Med 1992;326:1770–2.
30. Menzel J, Domschke W. Intraductal ultrasonography may localize islet cell tumors negative on endoscopic ultrasound. Scand J Gastroenterol 1998;33:109–12.
31. Bottger TC, Junginger TH. Is preoperative radiographic localization of islet cell tumors in patients with insulinomas necessary? World J Surg 1993;17:427–32.
32. Doherty GM, Doppman JL, Shawker TH, et al. Results of a prospective strategy to diagnose, localize and resect insulinomas. Surgery 1991;110:989–96.
33. Boukhman MB, Karam JM, Shaver J, et al. Localization of insulinomas. Arch Surg 1999;134:818–22.
34. Vinick AI, Renar IP. Insulin-producing tumors. Adv Endocrinol Metab 1993;4(1):1–27.
35. Geelhoed G. Problem management in endocrine surgery. Chicago: Year Book Medical Publishers; 1983.
36. Grant CS, van Heerden MB, Charboneau WJ, et al. Insulinoma. The value of intraoperative ultrasonography. Arch Surg 1988;123:843–8.
37. Demeure MJ, Klonoff DC, Karam JH, et al. Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. Surgery 1991;110:998–1005.
38. Thompson GB, Service JF, van Heerden JA, et al. Reoperative insulinomas, 1927–1992. An institutional experience. Surgery 1993;114:1196–206.
39. Eubanks PJ, Sawicki MP, Ghassan JS, Gatti R. Putative tumor-suppressor gene on chromosome 11 is important in sporadic endocrine tumor formation. Am J Surg 1994;167:180.
40. Koivunen D, Harrison T. The hypoglycemic syndrome: endogenous hyperinsulinism. In: Friesen SR, Thompson NW, editors. Surgical endocrinology. 2nd ed. Lippincott; 1990. p. 225.
41. Vance JE, Stoll RW, Kitabchi AE. Nesidioblastosis in familial endocrine adenomatosis. JAMA 1979;207:1969.
42. Gough MH. The surgical treatment of hyperinsulinism in infancy and childhood. Br J Surg 1984;71:75–8.
43. Labrune P, Lecherallier S, Rault M, Odievre M. Diabetes mellitus 14 years after a subtotal pancreatectomy for neonatal hyperinsulinism. J Pediatr Surg 1990;25:1246–7.
44. Shilyansky J, Fisher S, Cutz E, et al. Is 95% pancreatectomy the procedure of choice for treatment of persistent hyperinsulinemic hypoglycemia of the neonate? J Pediatr Surg 1990;25:1246–7.
45. Goossens A, Gepts W, Saudubray JM, et al. Diffuse and focal nesidioblastosis. Am J Surg Pathol 1989;13:776–775.
46. Gauderer M, Stanley CA, Baker L, Bishop HC. Pancreatic adenomas in infants and children: current surgical management. J Pediatr Surg 1978;12:591–6.

14

Gastrinoma (Zollinger-Ellison Syndrome)

JAMES P. DOLAN, MD
JEFFREY A. NORTON, MD

ETIOLOGY

Gastrinomas are rare neuroendocrine tumors that elaborate excessive and unregulated amounts of the hormone gastrin. They were first recognized clinically in 1955 by Zollinger and Ellison, who reported the occurrence of unusual peptic ulcerations of the jejunum in association with gastric acid hypersecretion and non–beta islet cell tumors of the pancreas in two patients.[1] Over the course of many years, it was realized that the hypergastrinemic state produced by these tumors contributes to a constellation of symptoms and signs that are called Zollinger-Ellison syndrome (ZES).

EPIDEMIOLOGY AND PATHOLOGY

Although the precise incidence is unknown, it is estimated that one to three persons per million develop gastrinomas each year.[2] Likewise, gastrinomas are the underlying cause in approximately 0.1 to 1% of patients with peptic ulcer disease.[3] They occur in both sporadic and familial or inherited forms, with the former occurring in 80% of cases and the latter in 20%. The familial form is usually associated with multiple endocrine neoplasia (MEN) type I (Table 14–1). In this setting, most associated hormonally functional neuroendocrine tumors of the pancreas or duodenum are gastrinomas. Gastrinomas are the most common malignant hormonally functional neuroendocrine tumor, and approximately 60% are found to have lymph node, regional, or liver metastases at initial surgical exploration.[4] Histologically, these tumors are composed of monotonous sheets of small round cells with a uniform nucleus and cytoplasm and a general lack of mitotic figures. In general, they are well vascularized and tend to metastasize primarily to regional lymph nodes and the liver, although widespread metastases to the lung, bone, and brain can also occur. Grossly, tumors are usually encapsulated, firm, and pale or yellow-brown in color (Figure 14–1). They may be single or multiple and may range in size from < 1 cm to > 3 cm. When associated with MEN type I, studies suggest that gastrinomas are usually multiple and found most commonly within the duodenum.[5] Approximately 80% of gastrinomas are found within the gastrinoma triangle (Figure 14–2), an area that includes the first and second portions of the duodenum and the head of the pancreas. Although rare, primary gastrinomas have also been found in the jejunum, stomach, liver, spleen, mesentery, ovary, and heart.[6] In addition, cure of ZES has been reported after excision of solitary gastrinomas that

Table 14–1. CHARACTERISTICS OF MULTIPLE ENDOCRINE NEOPLASIA TYPE I

Mutation in *MENIN* gene (chromosome 11)
Parathyroid hyperplasia
Pituitary adenoma (rarely, hyperplasia)
Multiple neuroendocrine tumors involving the pancreas and duodenum
Adrenocortical adenoma or carcinoma (rare)
Thyroid adenoma
Carcinoid tumors of foregut or midgut (rare)

appear to have arisen within a lymph node. This has given rise to the idea of a lymph node primary gastrinoma.[4] Gastrinomas of the duodenum and pancreas appear to have a similar incidence of overall metastases. However, pancreatic gastrinomas appear to have a higher incidence of liver metastases, whereas duodenal tumors tend to have a higher incidence of metastases to lymph nodes.

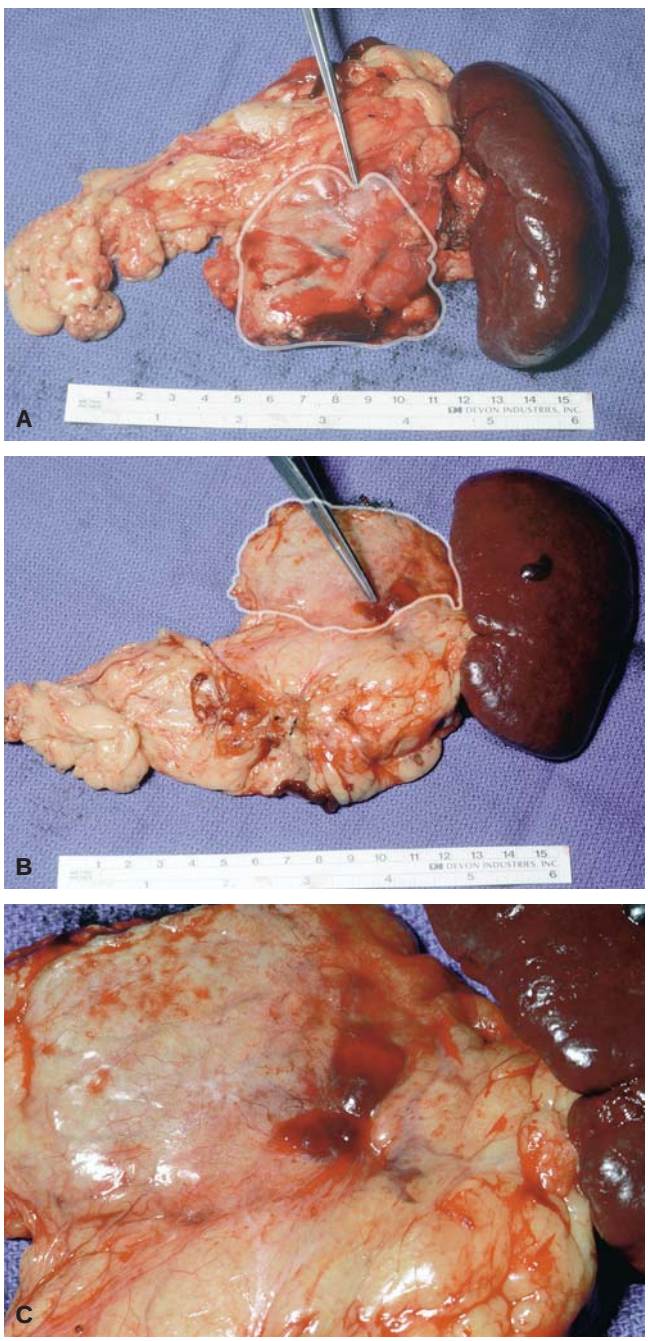


Figure 14–1. *A*, Gross specimen of a distal pancreatectomy showing the anterior view of a gastrinoma (*outlined*). In *B*, the same tumor has been elevated to show a posterior view (*outlined*). *C* shows a magnified view of the image shown in *B*. The dark structure on the right of the specimen in each case is the spleen.

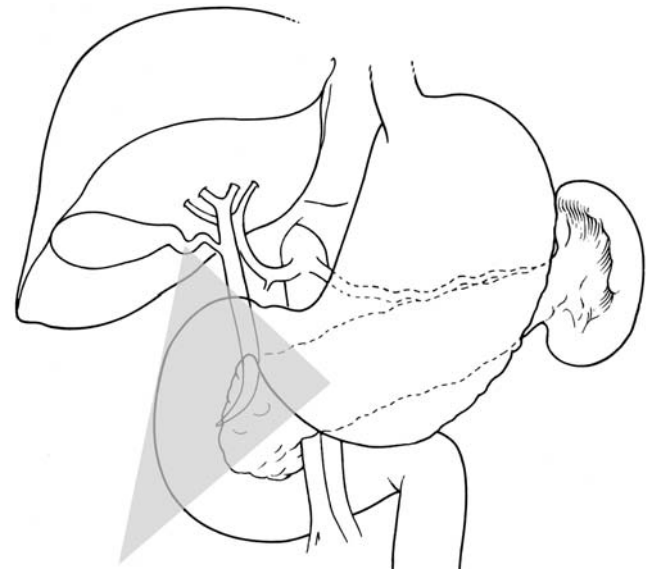


Figure 14–2. The approximate boundaries of the gastrinoma triangle (*shaded area*).

STAGING AND LOCALIZATION OF TUMOR

Overall staging of the extent of disease usually relies on confirmation of the initial diagnosis as well as the integration of evidence from a number of imaging modalities. Conventional noninvasive localization studies may fail to detect tumor in as many as 40% of patients with ZES.[5,7] As a first-line study, abdominal ultrasonography has a sensitivity of 30% and a specificity of 92%.[8] The accuracy of computed tomography (CT) depends on the size of the gastrinoma. Tumors < 1 cm are seldom visualized, 30% of those between 1 and 3 cm are seen, and all > 3 cm are imaged. Overall, CT can identify approximately 80% of pancreatic and 35% of extrahepatic gastrinomas (Figure 14–3).[9] It can also be used as a diagnostic modality by measuring gastrin levels in tissue following fine-needle aspiration (Figure 14–4). Magnetic resonance imaging may be useful in identifying small tumors and liver metastases and in distinguishing metastatic tumors from hemangiomas (Figure 14–5). However, it rarely images primary duodenal gastrinomas, only approximately 25%.[8]

Somatostatin receptor scintigraphy (SRS) is the imaging test of choice for localizing both primary

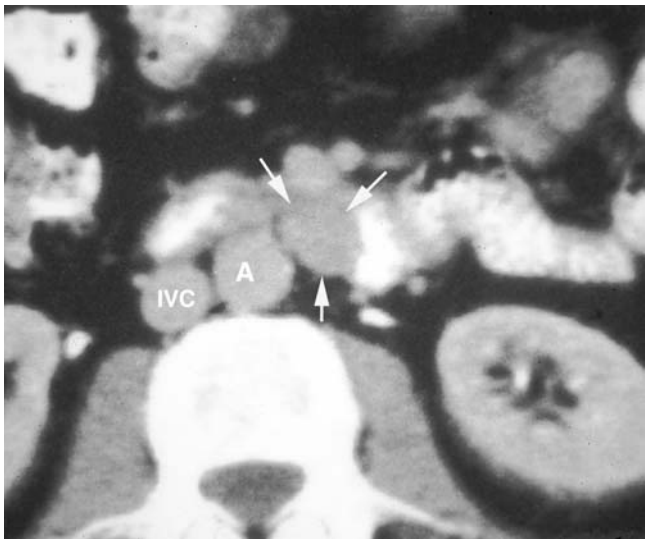


Figure 14–3. Computed tomographic appearance of a gastrinoma (*arrows*). The identification of the tumor is facilitated by the presence of contrast material in the small bowel adjacent to the lesion. No intravenous contrast is seen in the inferior vena cava (IVC) or aorta (A).

(Figure 14–6) and metastatic gastrinomas (Figures 14–7 and 14–8). This radiolabeled somatostatin analogue binds to the type 2 somatostatin receptor that is expressed in most gastrinomas. Ninety percent of tumors can be imaged by this modality with a specificity approaching 100%.[10] However, it still may miss small primary duodenal gastrinomas.

Endoscopic ultrasonography (Figure 14–9) is a fairly new method to localize gastrinoma. It is relatively invasive and can detect small tumors by endoscopically placing a high-frequency ultrasound transducer in the vicinity of the gastrinoma triangle and the liver. The procedure is operator dependent and has not been able to reliably identify small duodenal tumors. One study found the sensitivity of endoscopic ultrasonography to be 50 to 75% for duodenal, 75% for pancreatic, and 63% for lymph node gastrinomas.[10]

Because noninvasive studies may not image the gastrinoma, invasive imaging and regional localization studies have also been used extensively. Previously, selective angiography was the imaging study

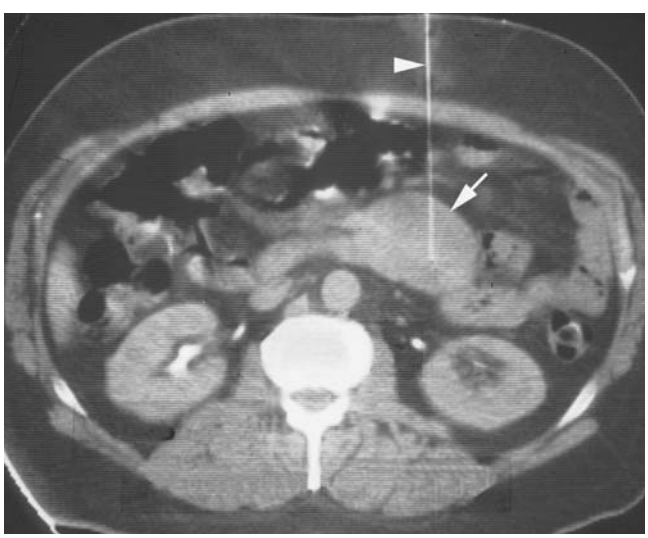


Figure 14–4. Use of computed tomography to guide fine-needle aspiration (*arrowhead*) of a mass lesion in a patient with Zollinger-Ellison syndrome. The gastrin level in the aspirate from the mass was 11,518 pg/mL (the peripheral venous gastrin level was 769 pg/mL), thus confirming it as a gastrinoma (*arrow*).

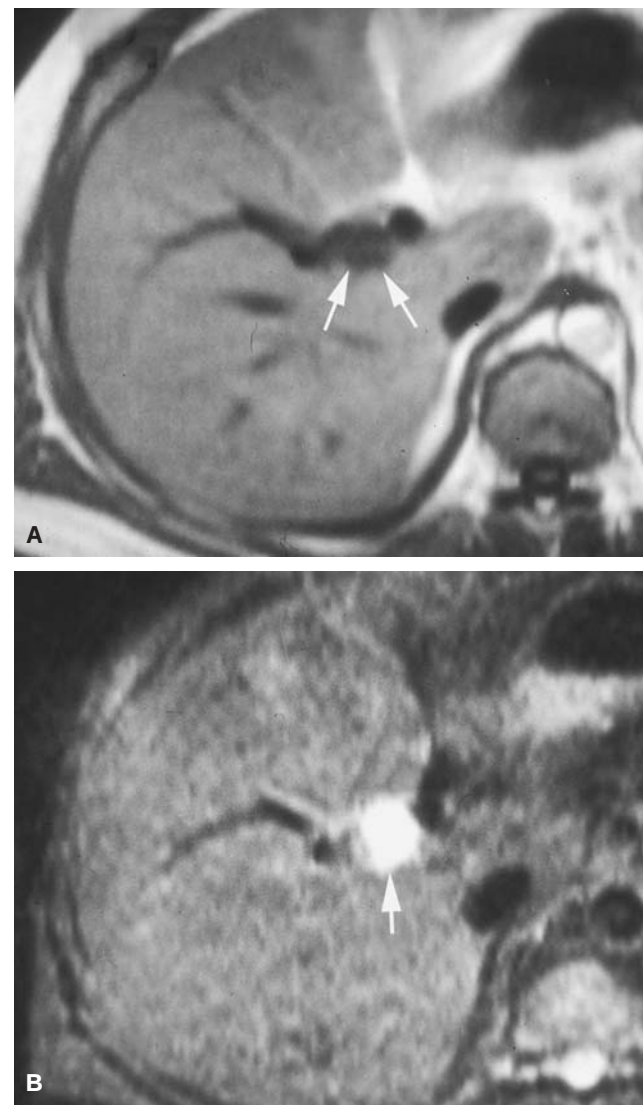


Figure 14–5. *A*, Magnetic resonance visualization of a metastatic gastrinoma in the liver (*white arrows*). In *B*, the same lesion is seen on computed tomographic scan (*white arrow*). The magnetic resonance image was obtained before contrast administration.

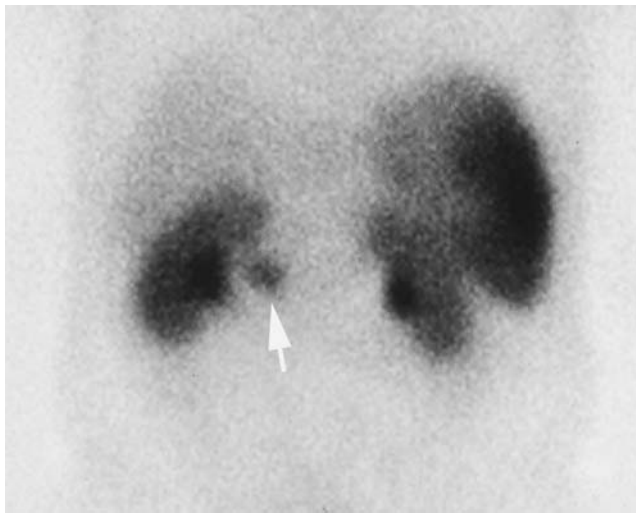


Figure 14–6. Somatostatin receptor scintigram showing isotope uptake by a gastrinoma (*arrow*). On exploration, the tumor was found in the duodenum. The large enhancing area on the right of the figure is the spleen.

of choice and was able to identify 60% of tumors. Primary or metastatic gastrinomas were seen as tumor "blush" within the liver, pancreas, or wall of the duodenum (Figure 14–10). This study has been largely supplanted by SRS. Another invasive localization study that has been used is portal venous sampling for serum levels of gastrin (Figure 14–11, A).[12] This is performed by transhepatic passage of a catheter into the portal vein and its tributaries with sampling of gastrin levels along the portal venous circulation. Alternatively, selective infusion of secretin can be combined with angiography in an attempt to identify the region of the pancreas that contained the gastrinoma (Figure 14–11, B). This approach became popular because it avoided the need for transhepatic portal venous sampling. In this study, secretin is selectively injected into arteries supplying specific regions of the pancreas and liver. Gastrin levels are then measured in

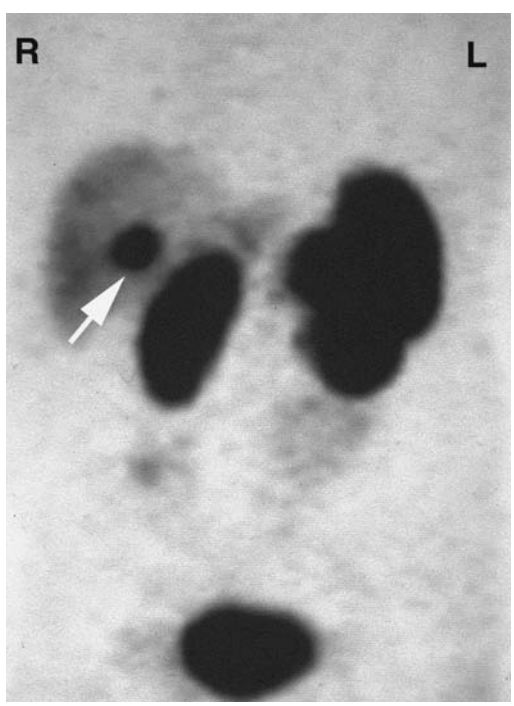


Figure 14–7. Another somatostatin receptor scintigram showing a metastatic gastrinoma in the liver (*white arrow*). Again, the enhancing area on the right of the figure is the spleen.

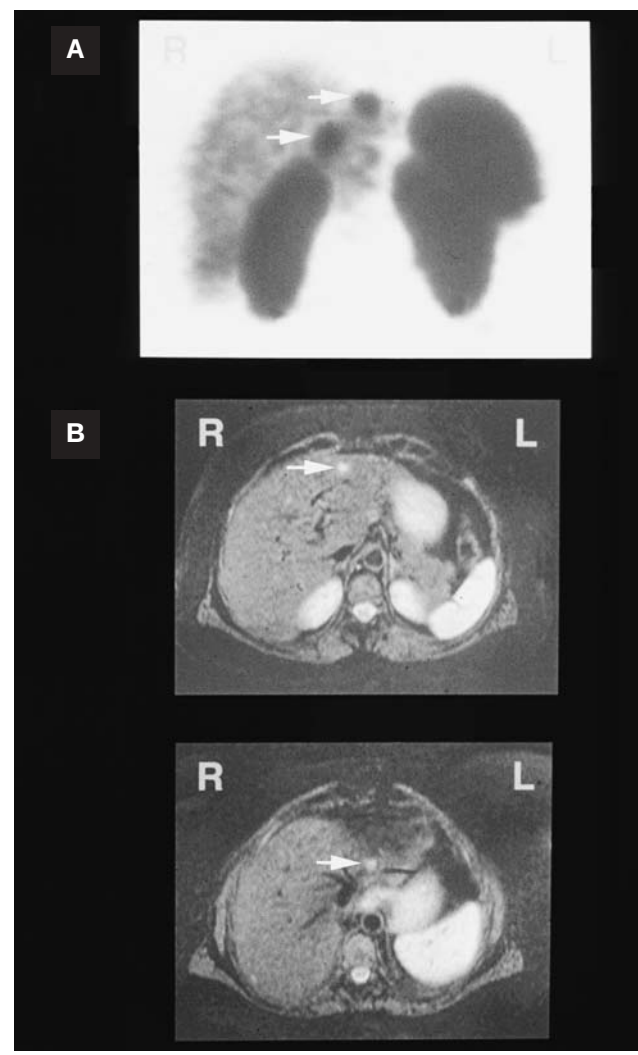


Figure 14–8. Correlation between somatostatin receptor scintigraphy (SRS) and magnetic resonance imaging (MRI) in the detection of metastatic tumors in the liver. In *A*, SRS shows the presence of two distinct liver lesions (*white arrows*). In *B*, the presence of these lesions is confirmed on successive STIR (short tau inversion recovery) sequence MRI displays in the upper and lower panels (*white arrows*).

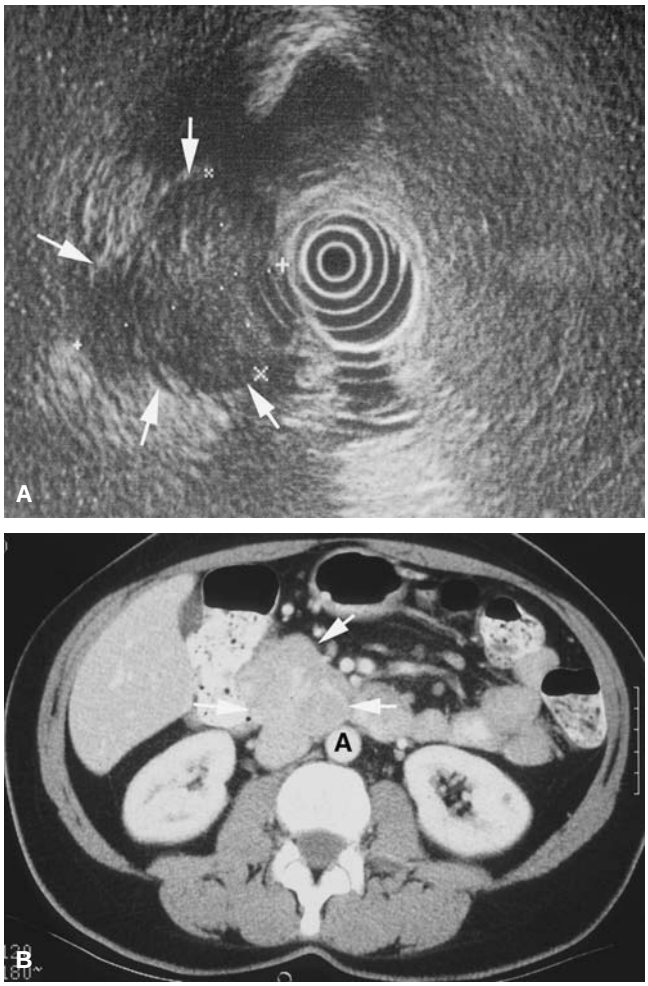


Figure 14–9. In *A*, endoscopic ultrasonography is used to image a large primary gastrinoma (*white arrows*). *B*, In this same patient, the location of the gastrinoma correlates with what is seen on computed tomography (*white arrows*). A = aorta.

the hepatic vein. A substantial increase in hepatic vein gastrin levels localizes the gastrinoma to the area supplied by the injected artery.

Intraoperative studies have been used as a way to localize tumors, particularly those not imaged preoperatively, or to confirm preoperative findings. In this regard, intraoperative ultrasonography (IOUS) and intraoperative endoscopy (IOE) with and without transillumination have proven utility.[13] IOUS images gastrinomas within the pancreas as sonolucent masses (Figure 14–12) and facilitates removal of these tumors by showing the relationship of the tumor to the pancreatic duct and other structures. IOUS has been ineffective at imaging duodenal gastrinomas such that IOE with duodenal transillumination was developed. Using endoscopy, the operator may be able to directly visualize the gastrinoma (Figure 14–13), and, using transillumination, the tumor appears as a photo-opaque mass (Figure 14–14, A). Once identified, the tumor can be marked with a suture and removed with a small margin of normal duodenal tissue (Figure 14–14, B to D). Intraoperative secretin-stimulated gastrin levels have been used to determine when all of the gastrinoma has been removed.[14]

SYMPTOMS AND SIGNS

The mean age at diagnosis of ZES is 50 years, and the male-to-female ratio is approximately 2:1. In patients with MEN type I, ZES is usually diagnosed in the third decade of life.[4] Clinical manifestations are related to the excessive secretion of gastric acid. The most common symptoms are epigastric pain, diarrhea, heartburn, and dysphagia. Almost all patients with ZES will be found to have peptic ulcers, with the proximal duodenum as the most commonly involved site. A minority of patients will have multiple ulcers or ulcers in unusual locations such as the distal duodenum or jejunum.[15] In 7 to 10% of patients, a perforated peptic ulcer may be the initial sign of the disease. Gastric acid hypersecretion also leads to secretory diarrhea, which occurs in up to 40% of patients with ZES and may be the sole presenting complaint in 20% of individuals.[16] In those with diarrhea, malabsorption

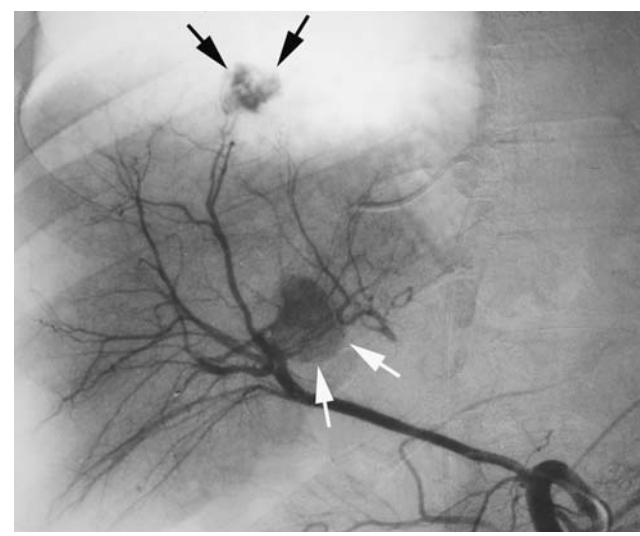


Figure 14–10. A unique situation in which selective angiography images both the primary gastrinoma (*white arrows*) and a metastatic lesion within the liver (*dark arrows*).

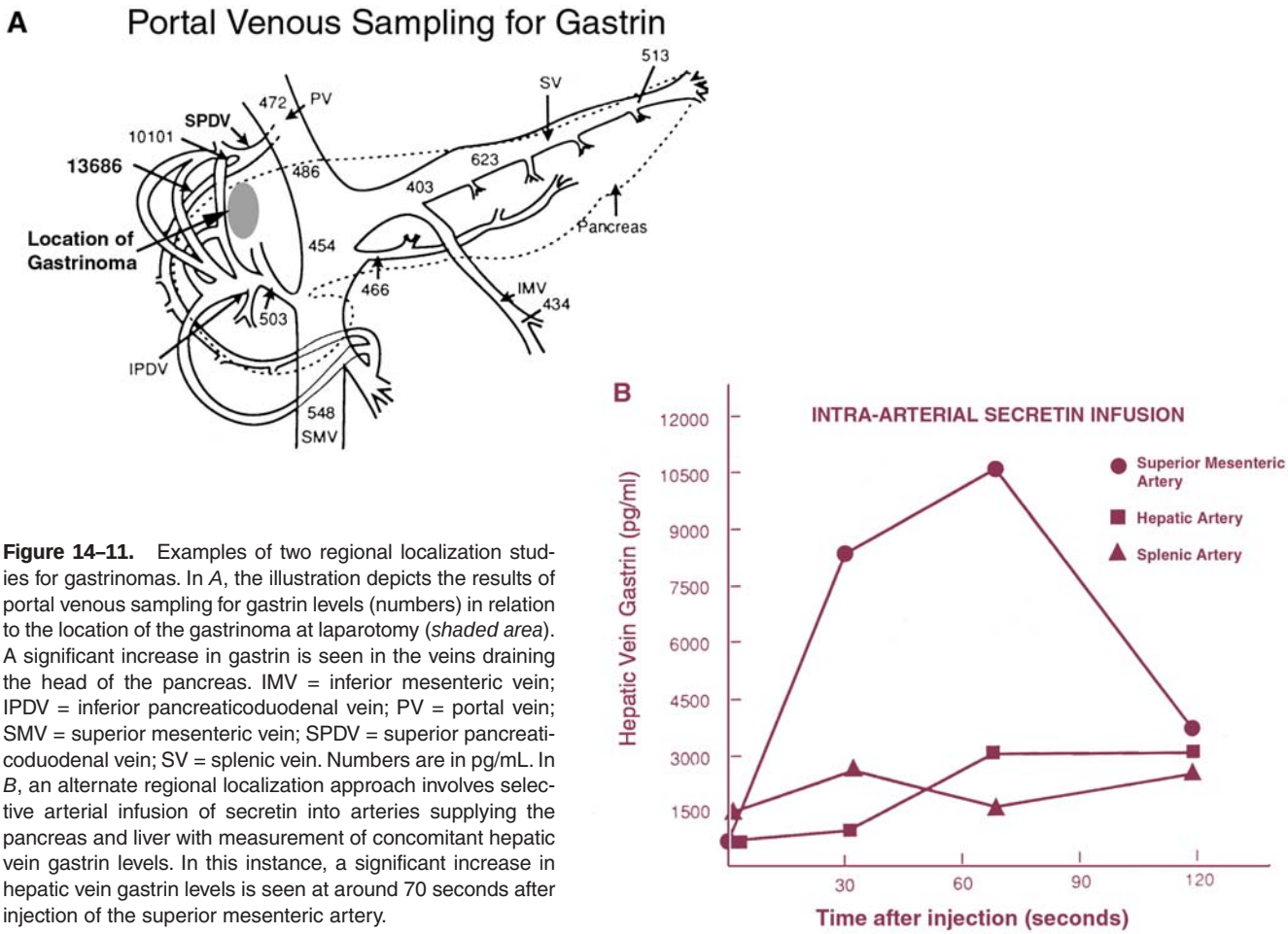


Figure 14–11. Examples of two regional localization studies for gastrinomas. In *A*, the illustration depicts the results of portal venous sampling for gastrin levels (numbers) in relation to the location of the gastrinoma at laparotomy (*shaded area*). A significant increase in gastrin is seen in the veins draining the head of the pancreas. IMV = inferior mesenteric vein; IPDV = inferior pancreaticoduodenal vein; PV = portal vein; SMV = superior mesenteric vein; SPDV = superior pancreaticoduodenal vein; SV = splenic vein. Numbers are in pg/mL. In *B*, an alternate regional localization approach involves selective arterial infusion of secretin into arteries supplying the pancreas and liver with measurement of concomitant hepatic vein gastrin levels. In this instance, a significant increase in hepatic vein gastrin levels is seen at around 70 seconds after injection of the superior mesenteric artery.

may manifest itself as weight loss and malnutrition. In approximately 10% of patients, endoscopy shows evidence of lower esophageal inflammation, ulceration, or stricture if the reflux symptoms are long-standing.

DIAGNOSIS

Evidence suggests that, in most cases, the diagnosis of ZES is not immediately considered. In most series, there is a mean period of 6 years from presentation of symptoms to diagnosis.[2] In general, ZES can be accurately diagnosed in all patients by measurement of an elevated fasting serum level of gastrin in association with an increase in basal acid output (BAO). The diagnosis can be confirmed by addition of a provocative secretin stimulation test. Measurement of the fasting serum level of gastrin is the initial study to diagnose ZES. Patients should be off antisecretory medications for 3 to 7 days prior to the determination because histamine$_2$ (H_2) blockers or omeprazole cause an artificial elevation of serum gastrin levels. All patients with ZES will have a fasting serum gastrin level of > 100 pg/mL. Fasting serum gastrin levels in individuals with renal failure, pernicious anemia, or atrophic gastritis may sometimes exceed 1,000 pg/mL; therefore, concomitant measurement of BAO is necessary to confirm the diagnosis of ZES. In this case, a BAO of > 15 mEq/hour in most patients and > 5 mEq/hour in patients with prior operations to decrease gastric acid secretion unequivocally confirms the diagnosis. Confirmatory provocative testing may also be necessary to confirm the diagnosis. An increase of 200 pg/mL in the gastrin level, following secretin administration, is consistent with a diagnosis of ZES (Figure 14–15). This test has a sensitivity of 85% or greater[17] and may be of particular utility in patients who have undergone prior operations to reduce acid output because these patients may have a minimally or moderately elevated gastrin level and BAO.

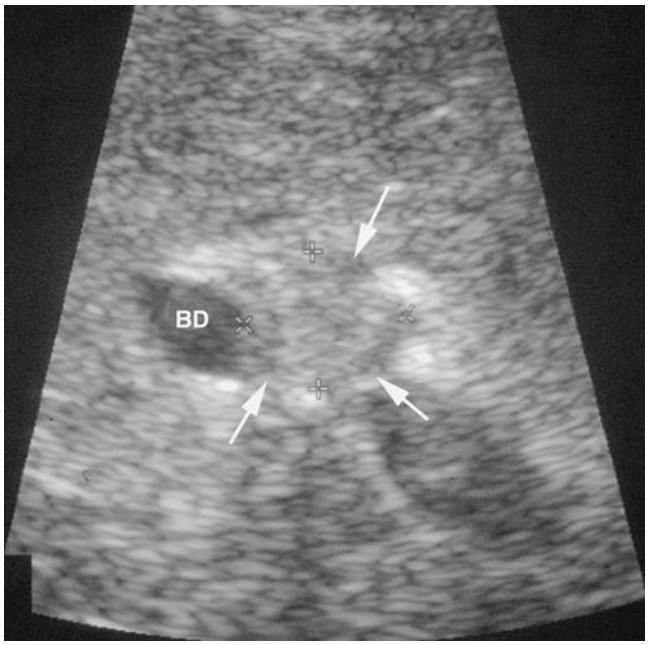


Figure 14–12. Intraoperative ultrasonographic image of a pancreatic gastrinoma (*white arrows*) approximating the common bile duct (BD). Optimally, tumors should be imaged in at least two cross-sections to clearly identify it as a mass lesion.

MEDICAL MANAGEMENT

With current medications, gastric acid hypersecretion can be effectively controlled in all patients with ZES. Total gastrectomy, once the only procedure for control of gastric acid hypersecretion, is no longer necessary. With the introduction of H_2 receptor antagonists and proton pump inhibitors (PPIs), all patients can experience control of acid hypersecretion and

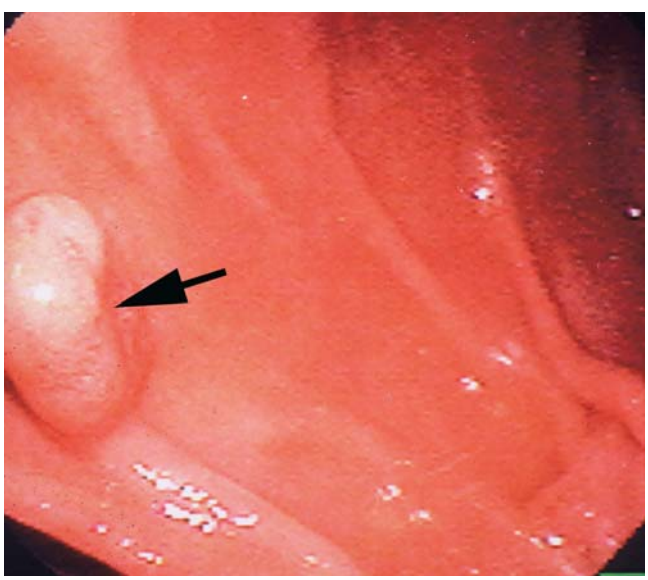


Figure 14–13. Endoscopic view of a gastrinoma. Here the tumor is seen as a submucosal mass on the wall of the duodenum (*black arrow*).

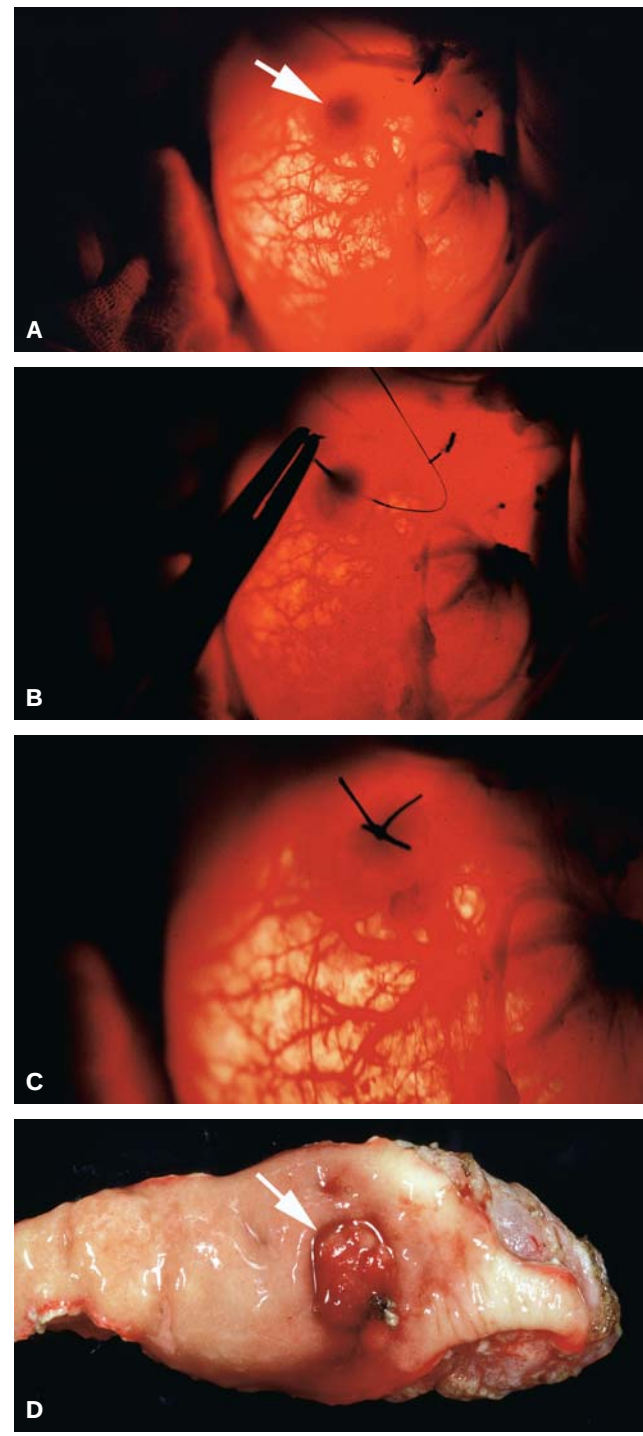


Figure 14–14. *A*, Using intraoperative endoscopy, a transilluminated duodenal gastrinoma appears as an opaque mass (*white arrow*) from the surgeon's perspective. Once identified, the tumor can be marked with a suture (*B* and *C*) and removed. In *D*, the gross specimen is shown (*white arrow*) contained within a margin of normal duodenal tissue.

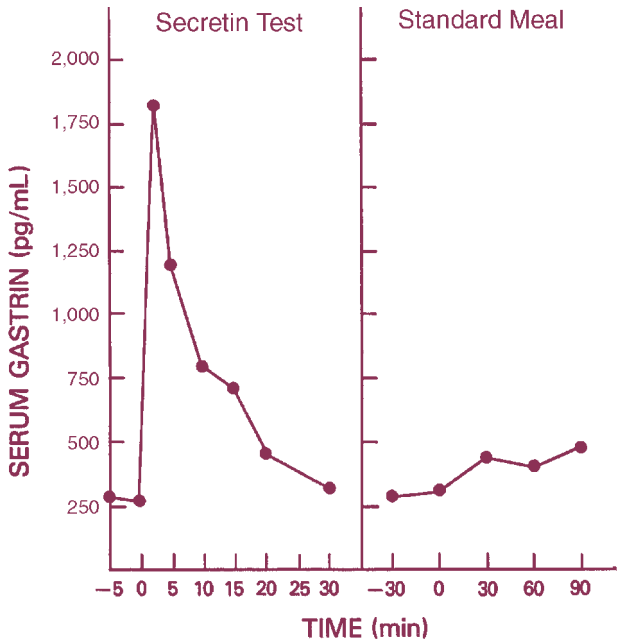


Figure 14–15. An illustration of the response in serum gastrin levels to secretin administration. The secretin bolus was administered at 0 minutes, and a significant elevation in serum gastrin is seen within 5 minutes after administration. The *right panel* shows the serum gastrin response to a standard meal in the same patient.

complete relief of symptoms. Omeprazole, lansoprazole, and pantoprazole are all members of a class of antisecretory drugs that inhibit gastric acid secretion by inhibiting the parietal cell apical H+, K+ adenosine triphosphatase. Recent studies have demonstrated that the intravenous dose of PPI is equal to the oral dose.[18] H_2 receptor antagonists are also effective, but progressively higher doses may be required to control symptoms and may be associated with a long-term failure rate. Relief of symptoms is not a reliable indicator of overall medical control of ZES, and measurement of BAO is necessary to adjust the dose of medication for effective treatment in each individual case. To allow healing of ulceration and prevent recurrences, gastric acid secretion should be maintained below 10 mEq/hour prior to the next dose of medication and should be maintained below 5 mEq/hour if prior ulcer surgery has been performed. It is particularly important to strictly control gastric acid secretion in cases of severe esophageal reflux with strictures because this promotes healing of lesions and reduces the need for esophageal dilation. With long-term medical control of ZES, there are also risks related to sustained achlorhydria. There have been cases reported of MEN type I patients who developed diffuse malignant gastric carcinoid tumors after prolonged treatment with omeprazole.[4] It is therefore necessary to perform periodic gastric surveillance endoscopy on MEN type I patients treated with this agent for long periods.

Chemotherapy has been used in the treatment of gastrinomas but does not prolong survival. The most effective regimen involves a combination of doxorubicin, 5-fluorouracil, and streptozocin and may provide a 40% response.[19] Hepatic artery chemoembolization has also been used but, again, with minimal efficacy. Likewise, the use of long-acting octreotide or interferon-α as antitumor agents has shown minimal effects on the malignant process.

SURGICAL MANAGEMENT

Medical control of symptoms allows time for localization and nonemergent surgical treatment of the gastrinoma. A number of long-term studies have shown that the malignant potential of the tumor itself becomes the main determinant of survival (Figure 14–16).[20] Thus, all patients with sporadic gastrinoma should be considered candidates for tumor localization and surgical exploration for cure. The management of patients with MEN type I and ZES is controversial and complex. In patients with MEN type I and primary hyperparathyroidism (HPT), the usual parathyroid pathology is multigland hyperplasia. It has been shown that successful neck exploration for resection of parathyroid hyperplasia can significantly reduce hypergastrinemia (Figure 14–17) and improve symptoms. Therefore, patients with MEN type I, ZES, and HPT should undergo neck exploration prior to gastrinoma resection.[21,22] Unfortunately, in this population, removal of pancreatic and duodenal tumors seldom cures patients of ZES,[22] but resection of the primary gastrinomas does decrease the likelihood of liver metastases in these patients.[23,24] In addition, the operative management of patients with MEN type I and gastrinoma is complicated by the fact that tumors tend to be multiple and small (4 to 6 mm) and usually involve the duodenum[5] more often than other extrapancreatic sites. In these patients, the controversy centers on the fact that surgery is seldom curative, yet it may be effective to treat the

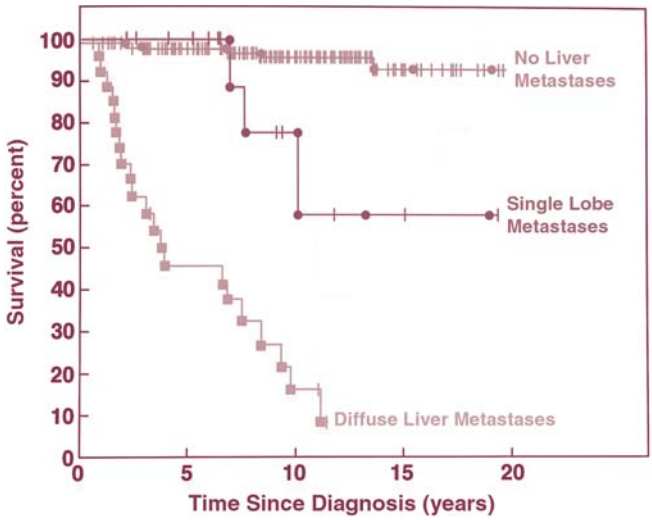


Figure 14–16. Kaplan-Meier survival curves of a large cohort of patients with gastrinomas illustrating the impact of liver metastases on overall survival over a 12- to 20-year period.

potential malignant disease and prevent eventual liver metastases. Although there is a wide range of opinion, we tend to operate on MEN type I patients when the primary tumor is 2 to 3 cm or larger.[22,24] This is based on the fact that the presence of liver metastases correlates with primary tumor size. Four percent of patients with primary gastrinomas < 1 cm develop liver metastases, whereas 28% have liver metastases whose primary tumors are between 1 and 3 cm in diameter and 61% have tumors > 3 cm.[23] After review of current data, it seems more prudent to operate on MEN type I patients with much smaller pancreatic and duodenal gastrinomas because this would tend to decrease the incidence of hepatic metastases.[23,24]

In patients with ZES and MEN type I, the evolution of intraoperative imaging methods has greatly facilitated exploration and resection. This is particularly true for small, multiple duodenal tumors that are difficult to locate. With improvement in intraoperative localization methods such as IOUS, IOE, and the secretin test,[14] as well as increased awareness of duodenal tumors, some studies have reported that gastrinomas can be found and resected in an increasing number of patients with MEN type I and ZES. The experience of the surgeon appears to be another factor in achieving a good surgical outcome.[2]

In patients with ZES who have no clear localized disease, laparotomy is still indicated because recent series suggest that tumor will still be found,[5] usually in the duodenum, and all regional lymph nodes should be removed for pathology review. Enucleation of pancreatic head tumors is usually sufficient, whereas distal or even subtotal pancreatectomy may be necessary for tumors of the body and tail. Studies have demonstrated similar outcomes whether enucleation or resection has been performed.[25] In all patients with ZES, a careful examination of the duodenum is critical.

The conduct of the operation itself relies on a careful exploration of the abdomen and its contents and has been previously described.[13] It is important to explore and palpate the liver, stomach, small bowel and mesentery, pancreas, and pelvis, including the uterus, fallopian tubes, and ovaries in female patients. An extended Kocher maneuver should be performed to mobilize the duodenum and gain access to the pancreatic head. The pancreatic body and tail may be better visualized by opening the gas-

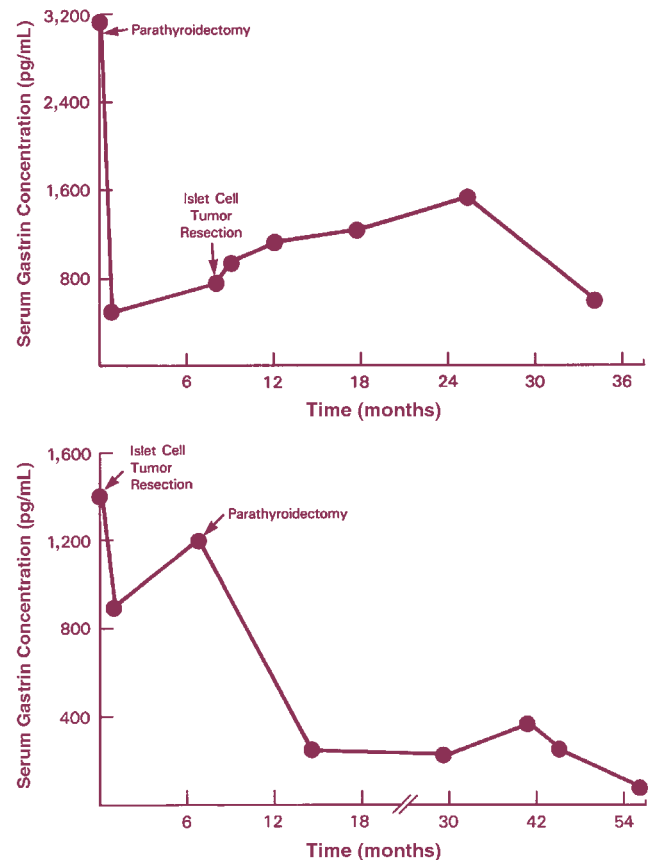


Figure 14–17. Effect of parathyroidectomy on serum gastrin concentrations in two patients with multiple endocrine neoplasia type I and gastrinomas. In each case, parathyroidectomy alone had a significant effect on lowering serum gastrin levels.

trocolic ligament and mobilizing along the inferior border of the pancreas. Once this has been accomplished, the duodenum and pancreas can be fully palpated and examined by IOUS. IOUS may also be used to examine the liver. A 7.5 to 10 mHz near-field transducer is necessary for examining the pancreas, whereas the 2.5 to 5 mHz wide-angle transducer is best for the liver. Tumors appear sonolucent (see Figure 14–12) and should be imaged in three dimensions. The duodenum can then be palpated between thumb and forefinger for the presence of mass lesions. IOE with duodenal transillumination should also be performed. A duodenal gastrinoma appears as a photo-opaque mass lesion within the wall of the duodenum on transillumination (see Figure 14–14, A). The endoscopist may also visualize the tumor as a mucosal defect (see Figure 14–13). Once duodenal lesions are identified, they can be marked with suture and included within the confines of a modest longitudinal duodenotomy. Regardless of the results of IOUS or IOE, a duodenotomy is indicated in nearly all cases. This allows for visualization as well as a more careful palpation of the entire duodenal wall, particularly its medial portion. Suspicious nodules on the medial wall should not be excised until a catheter is passed through the ampulla of Vater to confirm its location. This may have to be accomplished by passing the catheter via the cystic duct into the common bile duct. Finally, the duodenum is preferably closed transversely in two layers to minimize the risk of leakage or obstruction (Figure 14–18, A and B). If a long duodenotomy is necessary, longitudinal closure is indicated (Figure 14–18, C). Regional lymph nodes should also be excised for pathologic examination. Reoperation for recurrent localized gastrinoma is also indicated if the tumor is imageable and results in elimination of all of the tumor in nearly every patient and complete remission in 30%.[26] Further, following reoperation and removal of all identifiable gastrinoma, approximately one-third of patients are cured.[26]

PROGNOSIS AND METASTATIC DISEASE

Currently, approximately 95% of sporadic patients will have gastrinoma found at surgery, and 60 to 68% of patients will be cured.[5,26] The 5-year survival for patients with distant metastatic disease is, on average, no better than 40% (Figure 14–19).[23,27] In addition, a minority of these patients will experience accelerated tumor growth, which ultimately results in a more rapid demise. Although the exact mechanism underlying this more malignant tumor behavior has yet to be elucidated, it correlates with the serum level of gastrin and the presence of bilobar liver or bony metastasis.[20] It appears that surgery is a potentially effective treatment for metastatic gastrinoma. Patients with localized lymph node metastases seem to benefit most from surgery, and up to 30% may be biochemically cured,[4] whereas patients with resected localized metastatic liver disease have an 85% 5-year survival (Figure 14–20).[27] Further resection is not

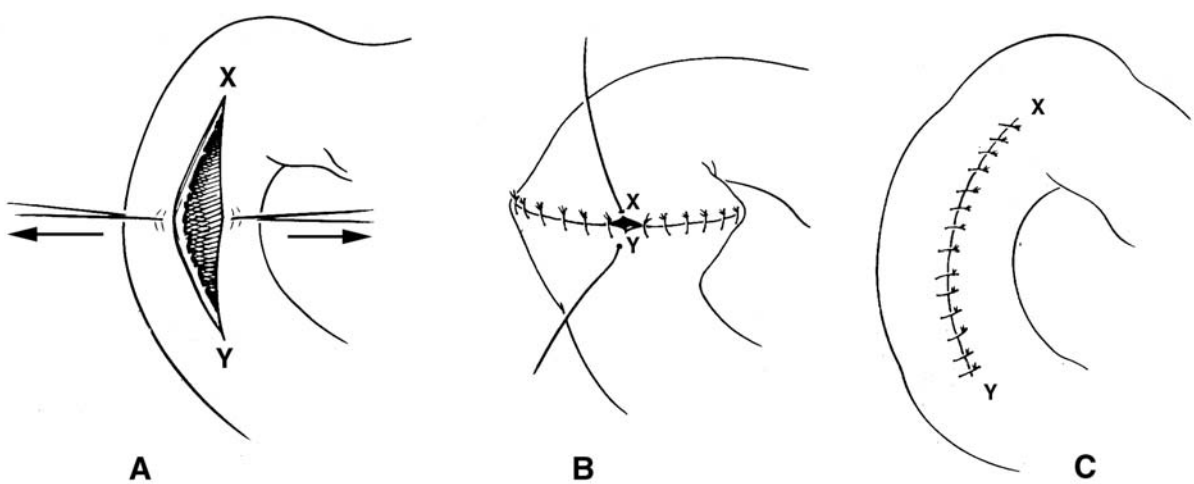


Figure 14–18. Illustration of closure techniques after duodenotomy. Under usual circumstances, the incision is closed transversely (*A* and *B*) to minimize the risk of leakage or duodenal stenosis. However, in cases for which a long duodenotomy is necessary to examine the duodenum for the presence of a small gastrinoma, the incision may be closed longitudinally (*C*).

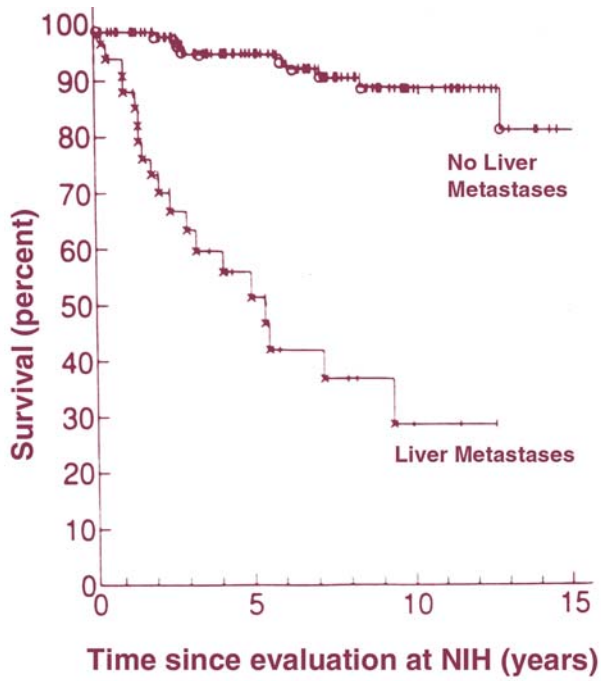


Figure 14–19. Kaplan-Meier survival curves for a group of patients with gastrinomas who were evaluated and treated surgically at the National Institutes of Health (NIH). Again, the impact of metastatic disease is illustrated by the decreased survival of those individuals with metastatic liver disease.

always necessary because patients have had similar benefits from surgical ablative therapy of liver metastases.[28] Currently, aggressive surgery in appropriate patients with hepatic metastases seems to demonstrate a survival advantage.[27]

In patients with MEN type I and gastrinoma, the identification of all tumor foci is problematic, and surgery results in a significantly lower cure rate.[4,22,28–31] With successful control of gastric acid hypersecretion and the indolent growth pattern of the gastrinoma, distant metastatic disease is the most important cause of morbidity and mortality. Although it has been suggested that gastrinomas in patients with MEN type I appear to behave less aggressively than those found in patients with sporadic disease, they do seem to have an equal rate of metastasis to lymph nodes. In fact, in one report, it was found that 86% of tumors had metastasized to lymph nodes at the time of exploration.[29] Duodenal primaries do, however, seem to have a lower rate of metastases to liver. Even in those patients with unresectable disease, hepatic cryosurgery or radiofrequency ablation may reduce symptoms, and the long-term effect of these modalities on survival is similar to resection.

SUMMARY

Gastrinomas are rare neuroendocrine tumors that elaborate excessive amounts of the hormone gastrin. Clinically, this leads to a condition known as ZES. Gastrinomas are usually sporadic, but in 20% of cases, they occur in an inherited fashion, called MEN type I. Sporadic gastrinomas tend to be solitary, with the primary tumor in the duodenum. In the setting of MEN type I, gastrinomas are also small and multiple and commonly involve the duodenum. Indeed, in both circumstances, 80% are found within the gastrinoma triangle (head of the pancreas and duodenum). Diagnosis is based on measurement of fasting serum levels of gastrin and BAO. Secretin stimulation test confirms the diagnosis. Localization of tumor relies on SRS and CT as the best initial studies. The use of intraoperative localization techniques such as IOE or duodenotomy is necessary during surgical exploration to localize small tumors within the wall of the duodenum. Currently, with the use of PPIs, there is excellent medical control of symptoms, and total gastrectomy is no longer indicated. With control of symptoms, the development of metastatic disease has become the major determinant of survival. Although slow growing, up to 60% of gastrinomas are malignant, and surgery remains the only potentially curative treatment for

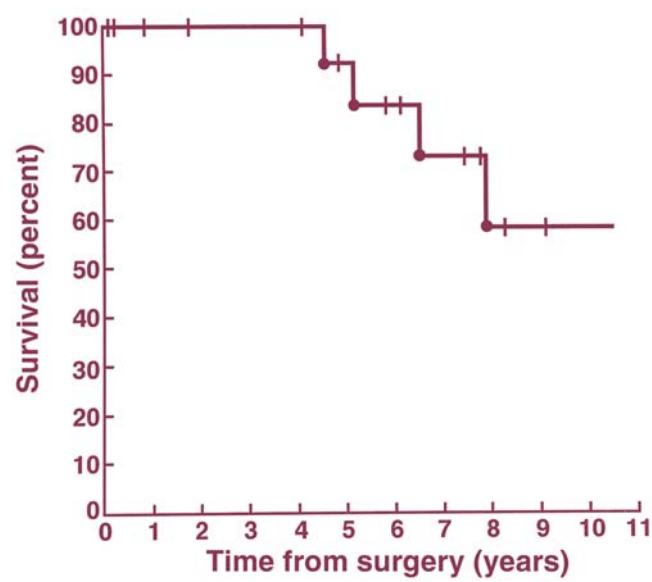


Figure 14–20. Kaplan-Meier survival curves for a group of patients undergoing resection of small, single liver metastases in addition to removal of the primary gastrinoma. Resection of localized (ideally single) metastatic foci has a significant impact on survival in these patients.

these tumors. Current chemotherapy and radiation therapy regimens do not seem to prolong survival. Surgery should be considered in all patients with localized gastrinoma, although in patients with ZES and MEN type I, it is seldom curative. Even in select patients with metastatic liver disease, surgery can cure some patients and enhance survival.

REFERENCES

1. Zollinger RM, Ellison EH. Primary peptic ulceration of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 1955;142:709–28.
2. Meko JB, Norton JA. Management of patients with Zollinger-Ellison syndrome. Annu Rev Med 1995;46:395–411.
3. Isenberg JI, Walsh JH, Grossman MI. Zollinger-Ellison syndrome. Gastroenterology 1973;65:140–65.
4. Norton JA. Gastrinoma: advances in localization and treatment. Surg Oncol Clin North Am 1998;7:845–61.
5. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999;341: 635–44.
6. Abbound P, Bart H, Mansour G, et al. Ovarian gastrinoma in multiple endocrine neoplasia type 1: a case report. Am J Obstet Gynecol 2001;184:237–8.
7. McArthur KE, Richardson CT, Barnett CC, et al. Laparotomy and proximal gastric vagotomy in Zollinger-Ellison syndrome: results of a 16-year prospective study. Am J Gastroenterol 1996;91:1104–11.
8. Frucht H, Doppman JL, Norton JA, et al. Gastrinomas: comparison of MR imaging with CT, angiography, and US. Radiology 1989;171:713–7.
9. Wank SA, Doppman JL, Miller DL, et al. Prospective study of the ability of computed axial tomography to localize gastrinomas in patients with Zollinger-Ellison syndrome. Gastroenterology 1987;92:905–12.
10. Gibril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. Ann Intern Med 1996;125:26–34.
11. Ruszniewski P, Amouyal P, Amouyal G, et al. Localization of gastrinomas by endoscopic ultrasonography in patients with Zollinger-Ellison syndrome. Surgery 1995;117:629–35.
12. Miller DL, Doppman JL, Metz DC, et al. Zollinger-Ellison syndrome: technique, results, and complications of portal venous sampling. Radiology 1992;182:235–41.
13. Sugg SL, Norton JA, Fraker DL, et al. A prospective study of intraoperative methods to diagnose and resect duodenal gastrinomas. Ann Surg 1993;218:138–44.
14. Kato M, Imamura M, Hosotani R, et al. Curative resection of microgastrinomas based on intraoperative secretin test. World J Surg 2000;24:1425–30.
15. Roy PK, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison sydrome. Clinical presentation in 261 patients. Medicine 2000;79:379–411.
16. Roy PK, Venzon DJ, Feigenbaum KM, et al. Gastric secretion in Zollinger-Ellison syndrome. Correlation with clinical expression, tumor extent and role in diagnosis—a prospective NIH study of 235 patients and a review of 984 cases in the literature. Medicine 2001;80:189–222.
17. Slaff JI, Howard JM, Maton PN, et al. Prospective assessment of provocative gastrin tests in 81 consecutive patients with Zollinger-Ellison syndrome. Gastroenterology 1986;90:1637–43.
18. Metz DC, Formarck C, Lew EA, et al. Replacement of oral proton pump inhibitors with intravenous pantoprazole to effectively control gastric acid hypersecretion in patient with Zollinger-Ellison syndrome. Am J Gastroenterol 2001;96:3274–80.
19. von Schrenck T, Howard JM, Doppman JL, et al. Prospective study of chemotherapy in patients with metastatic gastrinoma. Gastroenterology 1988;94:1326–34.
20. Sutliff VE, Doppman JL, Gibril F, et al. Growth of newly diagnosed, untreated metastatic gastrinomas and predictors of growth patterns. J Clin Oncol 1997;15:2420–31.
21. Norton JA, Cornelius MJ, Doppman JL, et al. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome, and multiple endocrine neoplasia type I: a prospective study. Surgery 1987;102:958–66.
22. Norton JA, Alexander HR, Fraker DL, et al. Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 2001;234:495–505; discussion 505–6.
23. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995;108:1637–49.
24. Gibril F, Venzon DJ, Ojeaburu JV, et al. Prospective study of the natural history of gastrinoma in patients with MEN I: definition of an aggressive and a nonaggressive form. J Clin Endrocrinol Metab 2001;86:5282–93.
25. Thodiyil PA, El-Masry NS, Williamson RC. Achieving eugastrinaemia in Zollinger-Ellison syndrome: resection or enucleation? Dig Surg 2001;18:118–23.
26. Jaskowiak NT, Fraker DL, Alexander HR, et al. Is reoperation for gastrinoma excision indicated in Zollinger-Ellison syndrome? Surgery 1996;120:1055–62; discussion 1062–3.
27. Norton JA, Doherty GM, Fraker DL, et al. Surgical treatment of localized gastrinoma within the liver: a prospective study. Surgery 1998;124:1145–52.
28. Hellman P, Ladjevardi S, Skogseid B, et al. Radio frequency tissue ablation using cooled tip for liver metastases of endocrine tumors. World J Surg 2002;26:1052–6.
29. Veldhuis JD, Norton JA, Wells SA Jr, et al. Surgical versus medical management of multiple endocrine neoplasia (MEN) type I. J Clin Endocrinol Metab 1997;82:357–64.
30. MacFarlane MP, Fraker DL, Alexander HR, et al. Prospective study of surgical resection of duodenal and pancreatic gastrinomas in multiple endocrine neoplasia type 1. Surgery 1995;118:973–9; discussion 979–80.
31. McIntyre TP, Stahlfeld KR, Sell HW Jr. Gastrinoma. Am J Surg 2002;183:666–7.

15

Endocrine Tumors of the Pancreas

MICHAEL J. DEMEURE, MD

Neuroendocrine tumors of the pancreas arise from the islet cells within the pancreas. These islands of cells were initially described by Langerhans in 1869 and comprise 1 to 2% of the pancreatic mass.[1] The initial report of an islet cell neoplasm was in 1902 by Nichols.[2] Approximately 95% of islet cell tumors are insulinomas, gastrinomas, or nonfunctional tumors producing no overt clinical syndrome. The remaining small proportion of these tumors may produce glucagon, vasoactive intestinal peptide (VIP), somatostatin, or other pancreatic peptides. The diagnosis of an islet cell tumor is established based on a clinical suspicion of endocrine hormone excess or by a nonsecretory tumor producing symptoms owing to the size or location of the tumor. Once the diagnosis is established by appropriate biochemical tests, judicious use of a variety of available localizing radiologic tests is warranted prior to a decision regarding treatment. These radiologic tests will be discussed in general after a presentation of the clinical features of the various islet cell tumors. Their treatment will also be discussed. The selection of a specific operation depends on a variety of factors including pathophysiology and location of the tumor entity, whether the tumor is benign or malignant, and whether it is a sporadic tumor or is occurring as part of multiple endocrine neoplasia (MEN) type I.

INSULINOMAS

Although insulinomas are the most common of the functional endocrine tumors of the pancreas, they are rare tumors, with an incidence of four per million person-years. A 60-year review including 224 patients provides epidemiologic data.[3] In this series, the median age was 47 years (range 8 to 82 years), and 59% were women. Of these patients, 5.8% had malignant insulinomas and 7.6% had MEN type I. Symptoms include blurred vision, confusion, abnormal behavior, sweating, weakness, hunger, anxiety, and palpitations. The diagnosis may not be made for years in symptomatic patients, many of whom are treated for seizures or psychiatric disturbances before the possibility of an insulinoma is entertained. The mean interval from onset of symptoms to diagnosis is approximately 3 years.[4]

The discovery of insulin as a hormone by Banting and Best in 1922 was followed by a description of the pathophysiology of excess insulin by Harris in 1924.[5] Graham performed the first successful resection of an insulin-secreting tumor in 1929. In 1935, Whipple and Franz wrote the classic description of the clinical manifestations of an insulinoma in what is now known as Whipple's triad[6]:

1. The patient exhibits signs and symptoms of hypoglycemia during fasting.
2. At the time of symptoms, serum glucose is ≤ 45 mg/dL.
3. Symptoms are relieved by oral or intravenous administration of glucose.

The diagnosis, in current times, is generally established by the demonstration of low serum glucose with a simultaneous inappropriately elevated serum insulin level. The ratio of serum insulin to glucose in this setting is greater than 0.4.[7] The gold standard test to establish the diagnosis of an insulinoma is a supervised fast for up to 72 hours. Most patients (80%) will become symptomatic within 24 hours, at which time simultaneous levels of glucose and insulin should be drawn. In unusual or equivocal cases, a provocative test with tolbutamide

or glucagon may be useful to establish the presence of an insulinoma.[8] Adjunctive tests to confirm the diagnosis of insulinoma include an assay for elevated levels of proinsulin and C peptide. Proinsulin is the precursor of insulin.[9,10] Proteolytic cleavage of this protein results in production of C peptide. The differential diagnosis should include other causes of hypoglycemia such as postprandial hypoglycemia, alimentary hyperinsulinism, adrenal insufficiency, hepatitis or cirrhosis, and sulfonylurea overuse (Table 15–1). The presence of circulating insulin-binding antibodies should alert the clinician that the patient is surreptitiously taking insulin.[11]

Once the diagnosis of an insulinoma is established by biochemical means, there exists some debate as to whether localizing studies are necessary before operation. Some authors, myself included, recommend only magnetic resonance imaging (MRI) to evaluate the liver for possible metastatic disease. Of course, a carefully done MRI can demonstrate the primary lesion in about 43% of cases (Figure 15–1). Insulinomas are usually small, with a mean size of 1.5 cm.

Patients usually have initiated treatment prior to seeking medical attention. They find that they can treat their symptoms by eating frequent small meals or waking during the night to have a snack. Many patients report moderate weight gain. The use of pharmacologic agents to control hypoglycemia is usually reserved for patients with unresectable metastatic tumors or in preparation for surgery. Diazoxide suppresses insulin secretion by direct inhibition of the beta islet cells. Control of hypoglycemia is achieved in over 50% of patients, but a significant number suffer adverse effects from the medication, including weight gain from fluid retention, nausea, and hirsutism. A limited number of reports suggest that verapamil may also be effective. Octreotide has been used to control hypoglycemia in patients not well treated by other agents. It requires parenteral dosing and is relatively expensive.

Because approximately 20% of insulinomas cannot be felt or seen by the surgeon at the time of laparotomy, it is essential for any surgeon exploring a patient for an insulinoma to be skillful in the use of high-resolution intraoperative ultrasonography (Figure 15–2). Most common small benign neuroendocrine tumors, including most insulinomas, are amenable to cure by enucleation from the pancreatic parenchyma. Insulinomas arising in the pancreatic head or uncinate process can almost always be removed in this manner. To accomplish this, a thorough Kocher maneuver is needed to allow complete mobilization and bimanual palpation of the pancreatic head. On occasion, to gain access to the uncinate, it is necessary to ligate and divide small branches from the superior mesenteric artery and

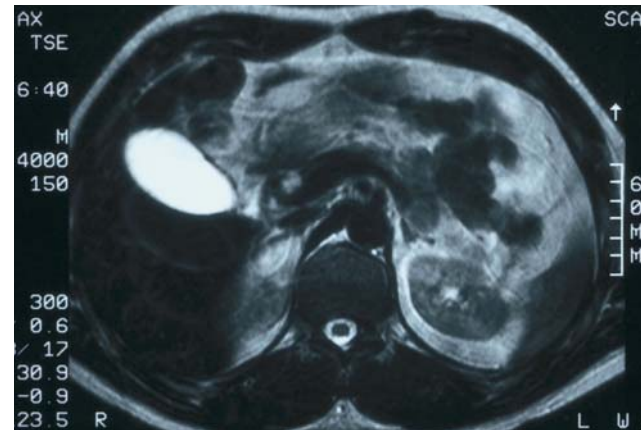


Figure 15–1. An insulinoma is demonstrated in the head of the pancreas by T_2-weighted magnetic resonance imaging.

Table 15–1. CAUSES OF HYPOGLYCEMIA

Insulin excess
Insulinoma
Surreptitious use of insulin
Sulfonylureas
Insulin or insulin receptor autoantibodies
Quinine
Glucose deficiency
Drugs
Ethanol
Propranolol
Salicylates
Haloperidol
Hormone deficiencies
Adrenal insufficiency
Hypopituitarism
Catecholamine deficiency
Enzyme deficiencies
Liver failure
Renal failure
Congestive heart failure
Sepsis and shock
Severe malnutrition or starvation
Intensive exercise
Late pregnancy

Adapted from Cryer PE. Hypoglycemia. In: Braunwald E, Fauci AS, Kosper DL, et al, editors. Harrison's principles of internal medicine. 15th ed. New York: McGraw-Hill; 2001. p. 2138.

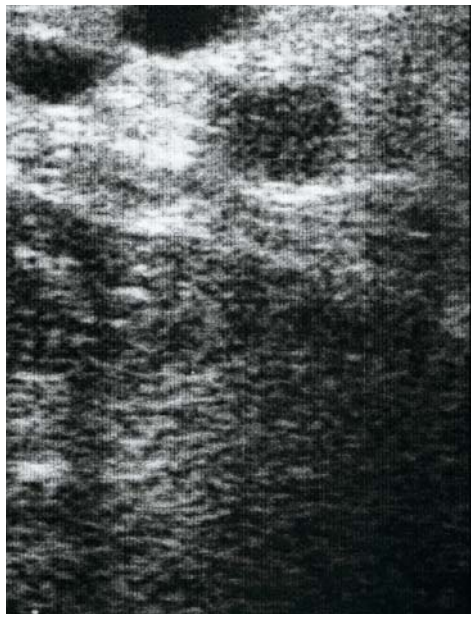


Figure 15–2. This insulinoma is demonstrated in the tail of the pancreas near the splenic artery and vein. The lesion is hypoechoic on intraoperative ultrasonography.

vein. Here high-resolution intraoperative ultrasonography is useful to plan an incision into the pancreatic parenchyma and avoid the major pancreatic duct. The incision may be in either the anterior or posterior surface of the pancreas, but an anterior leak, should it develop after surgery, is easier to repair than a posterior fistula by means of a Roux-en-Y pancreaticojejunostomy. Once the tumor capsule is reached, a fine hemostat is used to develop a plane between the tumor and the surrounding pancreatic parenchyma. At the completion of the procedure, some have suggested administering secretin to assess for leakage of pancreatic juice from the enucleation. No attempt is made to close the site with sutures, but some place an omental pedicle into the pancreatic defect. A closed suction drain should be placed to control a possible pancreatic leak.

Small benign lesions in the body and tail of the pancreas may be treated by either enucleation or resection (Figure 15–3). For large or malignant tumors at the head of the pancreas, a pancreaticoduodenectomy may be required (Figure 15–4). Large or posterior surface neuroendocrine tumors in the pancreas should be removed by means of a distal pancreatectomy with an effort to preserve the spleen. If a lesion is suspected to be malignant, however, the distal pancreas, spleen, and regional lymph nodes along the splenic artery should be resected en bloc. I do not advocate a blind distal pancreatectomy if the insulinoma is not found during intraoperative exploration but prefer to close the patient's incision, reconfirm the diagnosis, and do further investigations to locate the tumor. Recently, a small series was reported consisting of 12 patients undergoing attempted laparoscopic distal pancreatectomy or enucleation for endocrine tumors of the pancreas.[12] Of these patients, 8 had insulinomas. Laparoscopic removal was accomplished in 6 of the 12 patients. The reasons for conversion to open surgery were identification of metastatic disease, inability to find a tumor, and the need to perform a Whipple's operation. The mean operative time for the laparoscopic procedures was 4.5 hours. I have successfully performed a distal pancreatectomy for a benign pancreatic cystic neoplasm using a hand-assisted laparoscopic technique. Although these preliminary efforts suggest great promise for future possibilities, the utility of minimally invasive approaches has yet to be established.

Patients with MEN type I tend to have multiple islet cell tumors of the pancreas that may produce a variety of peptides. One syndrome will, however, predominate. Demeure and colleagues and others have recommended a different operative approach for the MEN type I patient with an insulinoma[13]: a subtotal distal pancreatectomy with enucleation of any tumors seen in the head of the gland.

Intraoperative glucose monitoring with a rapid glucose assay can reassure the surgeon and add a measure of safety by detecting hypoglycemia. A baseline glucose level is obtained soon after induction of anesthesia and at 15- to 20-minute intervals until the insulinoma tumor is removed. Following removal, a rise in serum glucose is indicative of a successful operation. It is common for patients to have mild hyperglycemia for the first 2 to 3 postoperative days, but normal glucose metabolism then returns.

GASTRINOMAS

In 1955, Zollinger and Ellison described two patients with peptic ulcer disease in the jejunum and an islet cell tumor of the pancreas.[14] It is now understood that the predominant feature of the syndrome (Zollinger-

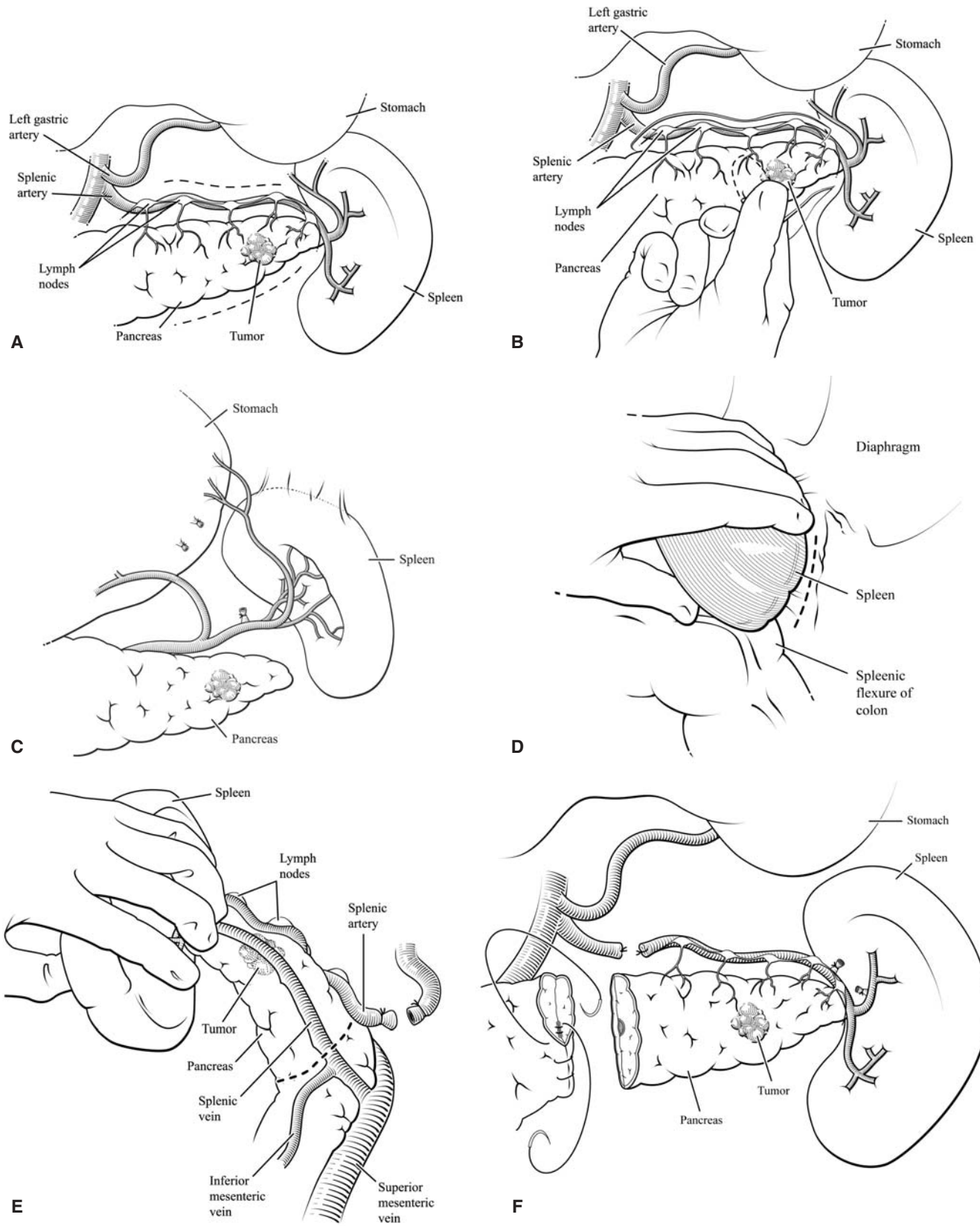


Figure 15–3. Distal pancreatectomy with splenectomy for a potentially malignant lesion. *A*, Incision along the retroperitoneum above and below the pancreatic tail. *B*, Digital palpation for a small tumor in the tail of the pancreas. *C*, Division of short gastric vessels. *D*, Division of splenophrenic attachments. *E*, Resection of the tail of the pancreas to include lymph nodes along the superior border. *F*, Division of the pancreas and oversewing of the pancreatic duct and stump.

Ellison syndrome [ZES]) that now bears their names is an increased serum gastrin level with an increased basal gastric acid production, resulting in peptic ulcers. It was not until 1960 that Gregory and associates first extracted gastrin.[15] Prior to the introduction of radioimmunoassay for gastrin in 1970, the diagnosis was based on clinical presentation and a posi-

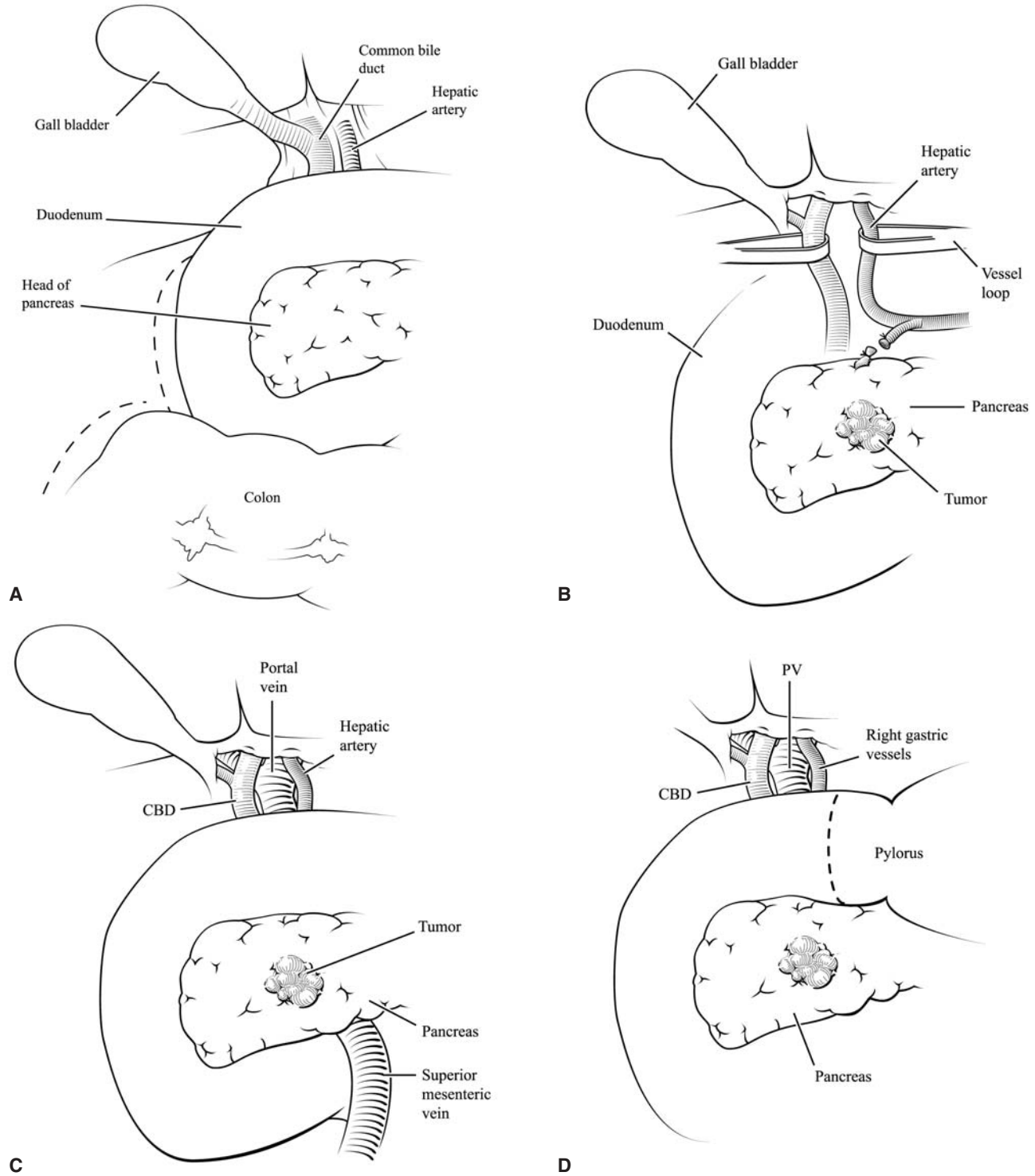
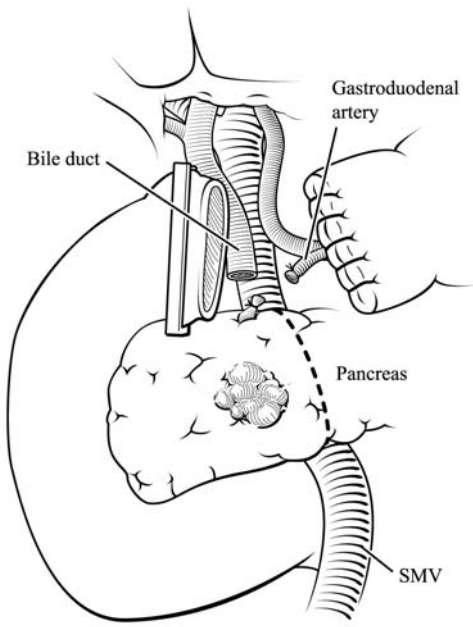
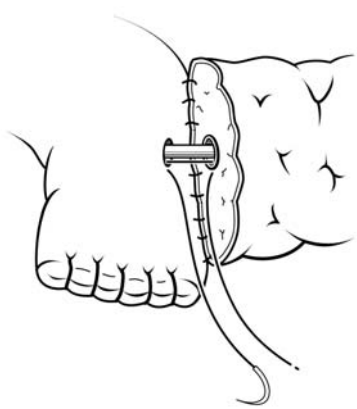


Figure 15–4. Pylorus-preserving pancreaticoduodenectomy for large or potentially malignant islet cell tumors of the head of the pancreas. *A*, (1) Mobilize hepatic flexure of the colon. (2) Duodenum by Kocher maneuver. *B*, Dissection of the common bile duct and hepatic artery with division of the gastroduodenal artery. *C*, The middle colic vein points to the superior mesenteric vein (SMV) at the inferior border of the pancreas. The SMV and portal vein (PV) must be free from the tumor. CBD = common bile duct. *D*, Division of the duodenum just distal to the pylorus. We preserve the right gastric vessels if possible.

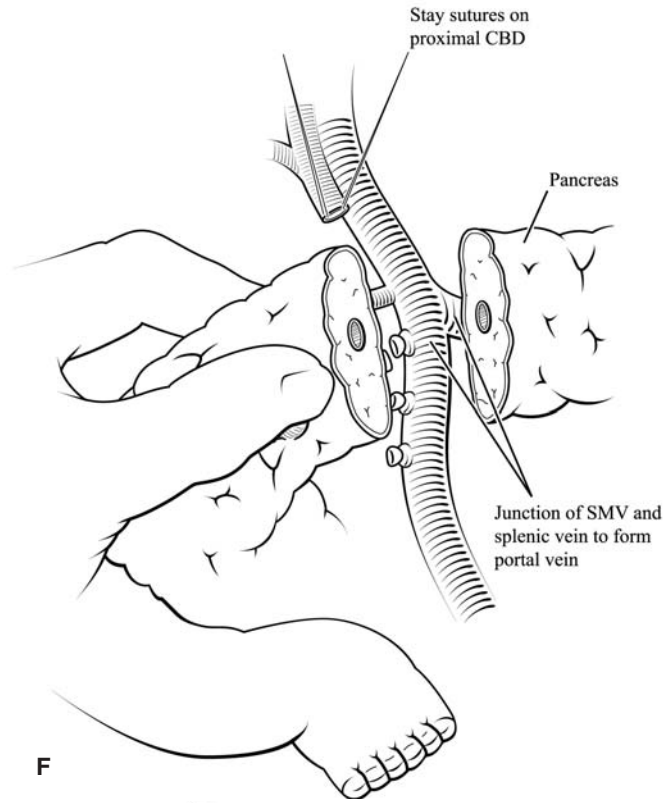
tive bioassay. The usual presenting clinical features are abdominal pain, upper gastrointestinal bleeding, diarrhea, and weight loss. Particularly suggestive of a gastrinoma are peptic ulcers that fail to heal or recur after medical or surgical therapy and ulcers beyond the duodenum. About 15 to 26% of gastrinomas occur as part of MEN type I[16] and about 60% are malignant.[17] Some authors, however, suggest that all



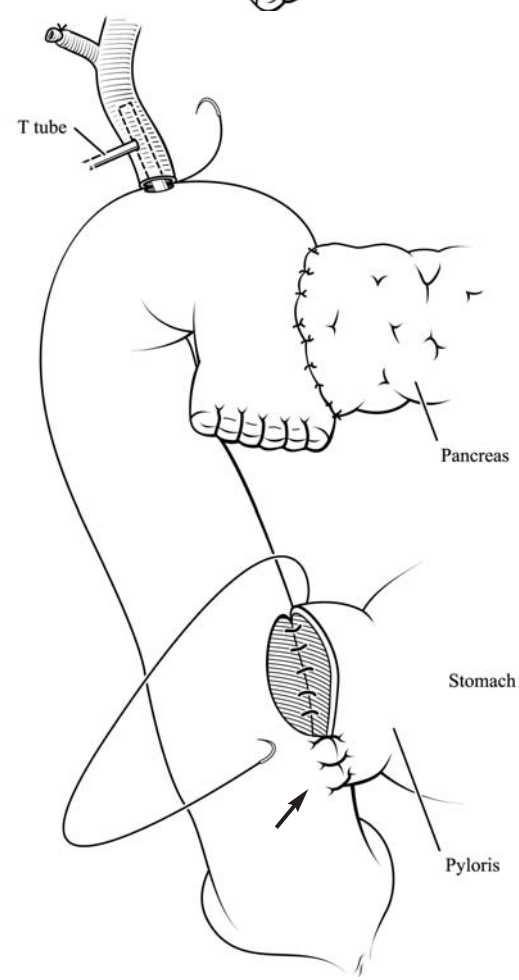
E



G



F



H

Figure 15–4 continued. Pylorus-preserving pancreaticoduodenectomy for large or potentially malignant islet cell tumors of the head of the pancreas. *E*, (1) The gastroduodenal artery is ligated. (2) Division of the distal CBD. (3) Division of the neck of the pancreas. *F*, (1) Small branches from the portal vein to the head of the pancreas are divided between five ligatures. (2) Three branches from the superior mesenteric artery are divided and ligated to free the pancreas and uncinate. *G*, A two-layer anastomosis of the pancreas to the jejunum is made over a small Silastic stent placed in the main pancreatic duct. *H*, A two-layer duodenum to jejunum anastomosis and a single-layer choledocojejunostomy (*arrow*).

gastrinomas are malignant, and those patients who are cured by resection have had their tumors excised before metastases could occur.

The diagnosis of a Zollinger-Ellison tumor must be suspected on clinical grounds and confirmed by the demonstration of increased acid production by gastric analysis and increased serum gastrin levels. A basal acid output (BAO) above 15 mEq/hour is highly suggestive of a gastrinoma, but up to 25% of patients without a gastrinoma may have this level of acid production.[18] A ratio of BAO to pentagastrin-stimulated maximal acid output (MAO) > 0.6 is further confirmation of a gastrinoma. Patients with a gastrinoma who have had a vagotomy or prior gastric resection may fail to achieve these criteria. In these patients, a BAO in excess of 5 mEq/hour is indicative of the diagnosis. The diagnosis can then be confirmed in a patient with increased acid production by assay for a serum gastrin level that is typically above 500 pg/mL (normal is less than 100 pg/mL). Between 25 and 50% of patients with a gastrinoma will have intermediate levels of gastrin between 100 and 500 pg/mL. A secretin stimulation test demonstrating a paradoxical rise in gastrin levels within 2 to 10 minutes confirms the presence of a gastrinoma in this subset of patients. The secretin stimulation test will also effectively rule out antral G-cell hyperplasia that can mimic the picture of ZES.[19]

Prior to the development of potent histamine type 2 (H_2) receptor antagonist agents, control of gastric acid hypersecretion was problematic for patients with ZES. Large amounts of antacids and anticholinergic agents were often inadequate therapy, so total gastrectomy became the treatment of choice for the control of gastric acid overproduction. In the early 1970s, cimetidine was introduced followed by other H_2 receptor antagonists and then later by potent proton pump inhibitors (eg, omeprazole and lansoprazole). With these agents, albeit at doses larger than those used for other diseases such as gastroesophageal reflux, it is now possible to suppress acid secretion in virtually all patients with ZES. Patients may require two to five times the normal dose of cimetidine or ranitidine. The omeprazole doses required generally range from 60 to 200 mg a day, but this drug may be more effective if dosed every 12 hours rather than the usual daily dosing.[20] Recently, concern has been raised that long-term medical therapy with omeprazole may cause hyperplasia of gastric enterochromaffin-like (ECL) cells and gastric carcinoid tumors.

Octreotide acetate is a synthetic analogue of somatostatin that retains the 4–amino acid bioactive moiety and cystine bridge of the native hormone. The result is an agent with a longer half-life than somatostatin that retains the ability to inhibit production of many gut peptides. In ZES patients, a single 1 μg/kg dose of octreotide markedly inhibits gastric acid secretion within 1 hour and continues to suppress BAO for up to 16 hours. Recently, a new long-acting analogue has been introduced. Because it requires parenteral administration and is relatively costly, octreotide remains a second option to omeprazole for acid suppression for patients with ZES. It may, however, be indicated for patients who have developed ECL cell hyperplasia or gastric carcinoid tumors on omeprazole therapy.

Unlike insulinomas, most gastrinomas are malignant. Unless hepatic metastases are already present, the majority of these patients are candidates for an attempt at a curative surgical procedure. Still, only approximately 60% (range 9 to 100) of non–MEN type I or sporadic gastrinoma patients are resected for cure.[21] Evidence now exists to suggest that resection of primary gastrinomas results in a decrease in the incidence of liver metastases.[22] Although a relatively indolent disease, liver metastases are the predominant eventual cause of death of patients who die from ZES. Lung, bone, heart, and adrenal metastases have also been described. For patients who undergo complete resection of their gastrinoma or in whom no tumor is identified at the time of careful exploration, the 10-year survival rate is > 85%. This rate compares favorably with the 25 to 30% 10-year survival rate for those patients whose tumors are metastatic or not completely resected.

Preoperative efforts should be made to locate the gastrinoma, but even if no tumor is identified preoperatively, exploration is warranted. The preponderance of ZES tumors can be found within the "gastrinoma triangle." This area is defined by the junction of the cystic and common bile ducts superiorly, the border of the second and third parts of the duodenum inferiorly, and the junction of the pancreatic neck and

body medially. Accordingly, most gastrinomas will be found in the wall of the duodenum (44%), pancreas, or nearby lymph nodes. Rare ectopic locations include the stomach, proximal jejunum, ovaries, kidney, heart, omentum, and the vicinity of the ligament of Treitz. The exploration for a gastrinoma has been well described.[23,24] Although exploration has been associated with the identification of a gastrinoma in more than 90% of patients, cure rates in non–MEN type I cases remain 30 to 40%[25]:

1. Explore the abdomen thoroughly, including the liver.
2. Open the lesser sac and inspect and perform bimanual palpation of the body and tail of the pancreas.
3. Perform a Kocher maneuver with inspection and palpation of the head of the pancreas. Tumor-bearing lymph nodes may be found behind the uncinate process.
4. Carefully examine the duodenum. A 6 to 8 cm longitudinal duodenotomy may be necessary for inspection and palpation for small submucosal gastrinomas within the duodenal wall (Figure 15–5).
5. Excise multiple paraduodenal and peripancreatic lymph nodes as well as any enlarged nodes or nodules along the surface of the pancreas or along the common bile duct for biopsy.
6. Do not be content with the finding of a single gastrinoma tumor. Continue a thorough exploration.

In selected cases, resection of limited liver metastases is justified, and occasional cures have been reported after resection of a solitary hepatic focus of gastrinoma. Rarely is total gastrectomy needed in the era of effective medical therapy, but it may be justified for the occasional patient who does not comply with medical treatment.

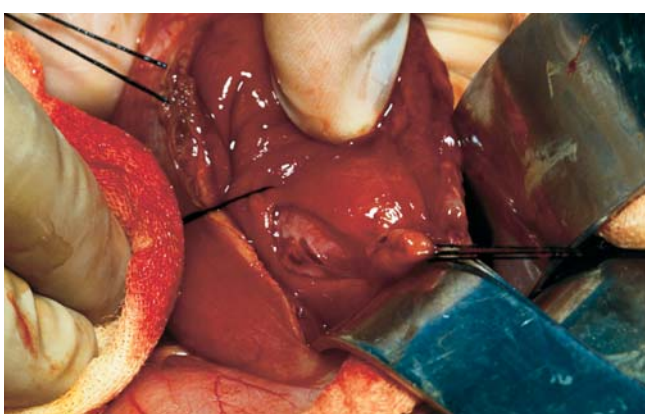


Figure 15–5. A small submucosal duodenal gastrinoma is enucleated.

Perhaps the most controversial topic in the care of patients with gastrinoma is whether and when an operation should be done for the patient with MEN type I–associated ZES. Some have said that these patients all have malignant gastrinomas at presentation and can never be cured by operation.[26–28] More recently, some investigators have recommended that a more aggressive attitude toward exploration be adopted. They reasoned that the prevalence of malignancy among these patients is 47 to 58% (similar to sporadic ZES), and a significant proportion of these patients can be cured by removal of their islet cell tumors.[29] Others, however, counter that complete remission is unlikely because 86% of tumors have metastasized to lymph nodes and 43% have multiple tumors.[30] Norton and colleagues at the National Institutes of Health have advocated a third approach based on their observation that tumors over 2 to 3 cm have a significant potential for metastases.[31,32] Patients with MEN type I and ZES should undergo radiographic studies, and, if visualized, an islet cell tumor should be resected. A subtotal pancreatectomy and enucleation of tumors in the head of the pancreas should be done. Furthermore, the duodenum is explored because multiple tumors may exist there. This approach has not been shown to improve survival but may reduce the development of liver metastases. For MEN type I patients with ZES and hyperparathyroidism, the initial operation should be a neck exploration. A subtotal ($3^1/_2$) parathyroidectomy or total parathyroidectomy with autotransplantation will reduce serum gastrin levels and gastric acid levels.

GLUCAGONOMAS

Glucagonomas are rare tumors originating from the alpha cells of the pancreatic islets. Their incidence is estimated to be approximately 1 per 20 to 30 million person-years. There is a slight female predominance, with a mean age at diagnosis of 55 years. Glucagonomas generally present with a pathognomonic rash called necrolytic migratory erythema. This desquamating pruritic rash usually begins on the extremities and intertriginous regions before

involving the trunk and face (Figure 15–6). These patients may have been treated for psoriasis, pemphigus, zinc deficiency, or eczema for several years before the rash is recognized for what it is, prompting a proper diagnosis. These patients also have mild to moderate diabetes mellitus associated with anemia, weight loss, glossitis, and thrombophlebitis. The diagnosis can be proved by demonstration of an elevated serum glucagon level.

Most (88%) glucagonomas are solitary lesions and occur in the body or tail of the pancreas (Figures 15–7 and 15–8). Computed tomography (CT) or MRI is accurate and sensitive in the search for a primary lesion and evaluation of the liver. Angiography is generally reserved for patients in whom a tumor is not otherwise seen and is accurate in at least 80% of these tumors. There are no known provocative agents for a stimulation test. Complete resection of localized benign tumors is curative and results in rapid resolution of the necrolytic rash (Figure 15–9). Subtotal distal pancreatectomy is recommended for the rare cases caused by hyperplasia of the islets in the pancreatic tail.[33] Seventy percent of these patients will unfortunately present with liver metastases. Surgical debulking can result in symptom improvement and may be indicated if significant reduction of the tumor mass can be achieved.

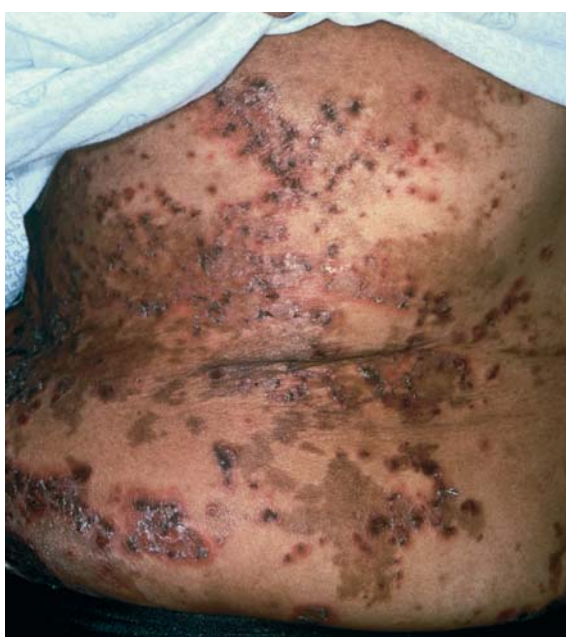


Figure 15–6. The pathognomonic rash for glucagonoma is necrolytic migratory erythema and is depicted here.

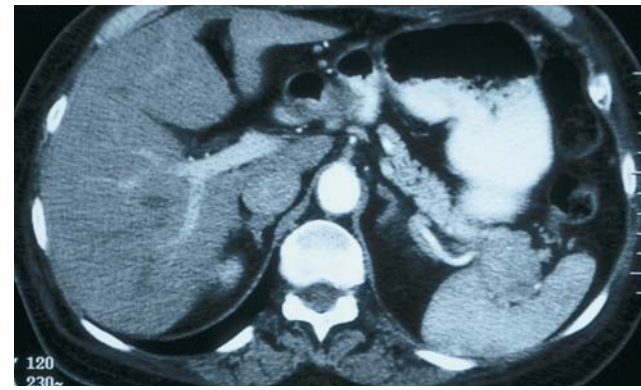


Figure 15–7. This patient's glucagonoma is identified in the tail of the pancreas near the spleen.

SOMATOSTATINOMAS

Somatostatin is a tetradecapeptide gut hormone that inhibits the release or action of almost all other gut hormones, including insulin, glucagon, gastrin, and cholecystokinin. Excessive production of somatostatin by a tumor arising from delta pancreatic islet cells leads to a clinical syndrome featuring steatorrhea, diarrhea, mild diabetes mellitus, cholelithiasis, weight loss, anemia, and hypochlorhydria.[34] These are exceedingly rare tumors. In the largest collected series to date describing 48 patients, 27 patients had pancreatic primary tumors and 21 had intestinal primaries.[35] The mean age at presentation was 51 years (range 26 to 84 years), and 27 (56%) patients were women. Only 26% of patients were free of metastases at the time of presentation.[36]

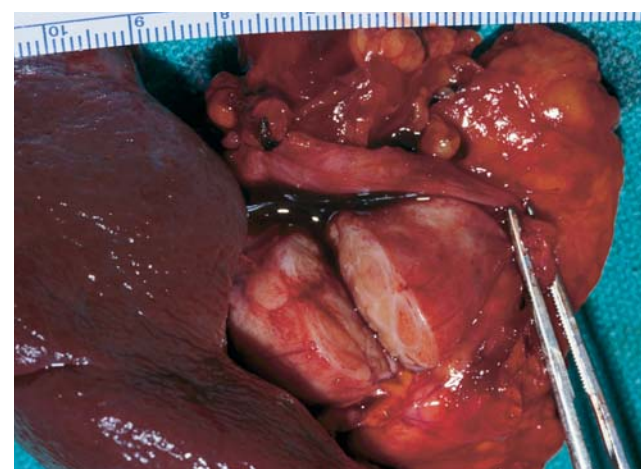


Figure 15–8. This photograph depicts the operative specimen of the en bloc distal pancreatectomy and splenectomy with the cut surface of the glucagonoma tumor.

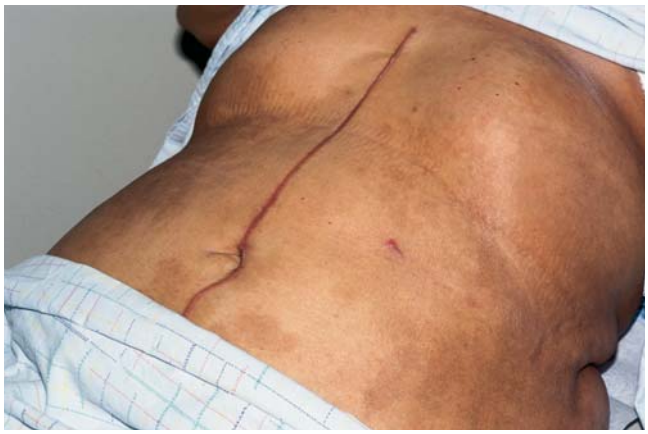


Figure 15–9. There is rapid resolution of the glucagonoma rash on the patient's trunk after removal of her tumor.

Approximately half of the patients have associated endocrine disorders. Duodenal somatostatinomas have carcinoid-like features and have been associated with von Recklinghausen's disease and pheochromocytoma, with or without MEN type IIB.[37]

The diagnosis is established in a patient with suggestive clinical features by demonstration of increased plasma concentration of somatostatin-like immunoreactivity.[38] Tolbutamide or calcium pentagastrin infusion may be useful as a provocative test in the diagnosis of patients with an unclear clinical picture. Because of the rarity of this entity, few patients have been studied, so the reliability of diagnostic tests is not established.

Similarly, optimum surgical approaches have not been established. For small (< 2 cm) localized intestinal somatostatinomas, local wedge resection seems adequate.[39] Pancreatic resection and wedge resection of limited hepatic metastases may be justified for larger tumors as long-term survival has been reported after this operation for metastatic somatostatinomas. No series of metastatic somatostatinomas treated by chemotherapy have been reported. Most treat these as they would other malignant neuroendocrine tumors, with the preferred regimen usually being streptozocin and doxorubicin.

VASOACTIVE INTESTINAL POLYPEPTIDE–PRODUCING TUMORS

Tumors producing VIP (VIPomas) are rare. To date, only about 200 well-documented cases have been reported. The original report of a VIPoma was by Priest and Alexander in 1957, but it remained for Verner and Morrison, a year later, to fully characterize the entity as a distinct syndrome.[40,41] Synonyms for this disease include pancreatic cholera, Verner-Morrison syndrome, and WDHH. The latter term is a reference to the *w*atery *d*iarrhea, *h*ypokalemia, and *h*ypochlorhydria caused by these tumors. Initially, diarrhea is intermittent, and during periods of quiescence, stools are semisolid and relatively few in number. Progressively, however, the diarrhea becomes more severe and unrelenting. Because the diarrhea is secretory and hypermotility is not a feature, crampy abdominal pain is unusual. Characteristically, patients may have 10 to 15 bowel movements and produce up to 10 L of tea-colored liquid stool per day. Approximately 50% of these patients have hyperglycemia caused by the glucagon-like activity of VIP. Hypercalcemia and hypomagnesemia are also common. Twenty percent of patients experience episodic flushing of the skin, characteristically of the face and upper trunk. The etiology is unknown, but the flushing is not attributable to increased levels of serotonin as in the carcinoid syndrome, and these patients do not have elevated urinary levels of 5-hydroxyindoleacetic acid. A large atonic gallbladder is common, but gallstones are an infrequent finding. Approximately 4% of VIPomas occur as part of a MEN type I constellation.

The diagnosis is confirmed by demonstration of an increased serum VIP level by radioimmunoassay. An increased α-chorionic gonadotropin suggests malignancy.[42] The differential diagnosis should include villous adenoma, inflammatory bowel disease, infectious diarrhea, celiac sprue, surreptitious laxative abuse, and other endocrine tumors such as gastrinoma, somatostatinoma, medullary thyroid carcinoma, and carcinoid tumors. At present, there are no known provocative or inhibitory agents to secure an otherwise equivocal diagnosis.

Ninety percent of VIPomas are islet cell tumors of the pancreas. About 10% arise in the adrenal medulla or, rarely, in the kidney, lung, jejunum, or esophagus. Multicentric tumors account for less than 2% of VIPomas. Once a tumor is located by radiography, surgical resection is warranted. Preoperative rehydration and replenishing of depleted potassium stores

are mandatory. Other electrolyte derangements, for example, hypomagnesemia, should also be corrected prior to operation. Preoperative octreotide administration facilitates control of diarrhea. A pancreatic resection (usually distal pancreatectomy) of the tumor is curative for benign tumors, but 50% of these tumors are malignant.[43] Debulking in the face of unresectable or metastatic disease can be palliative by helping to diminish diarrhea. Debulking may also improve the response to chemotherapy. In addition to streptozocin-based combination chemotherapy, indomethacin may be palliative for patients who have symptoms caused by the increased prostaglandin E levels often associated with this tumor.[44] A controversial observation is that octreotide in high doses may have direct antitumor activity. Kraezlin and associates reported regression of hepatic metastases and disappearance of symptoms in a patient with malignant VIPoma after 14 months of treatment.[45] Most patients will, however, achieve initial relief of symptoms without any demonstrable tumor regression.

OTHER ISLET CELL TUMORS

As islet cell tumors are of neuroendocrine origin, it is not surprising that they have been reported to secrete a vast array of hormones. Rare islet cell tumors may produce adrenocorticotropic hormone (ACTH), parathormone, human pancreatic polypeptide (hPP), histamine, or serotonin.[46] No clinical syndrome has been associated with the overproduction of hPP, but screening for elevated serum hPP levels has been used to detect early pancreatic islet tumors among patients with MEN type I. The treatment for these tumors is similar to that for other islet cell tumors. The rare patient with unresectable ACTH-producing tumors may benefit from bilateral adrenalectomy or treatment with metyrapone.

RADIOLOGIC TESTS TO LOCATE ISLET CELL TUMORS

An increasingly wide variety of radiologic tests are becoming available to find small neuroendocrine tumors and to stage malignant lesions. Coupled with the improving sensitivity and resolution of established modalities, such as CT, is an increased concern for judicious economical use of medical resources. Furthermore, many of our patients with these rare tumors live some distance from our hospital, precluding multiple trips to the hospital for preoperative testing. The challenge for the surgeon is to balance these concerns to obtain the maximal information necessary in an efficient, cost-effective manner.

Tumors larger than 3 cm in diameter are readily visualized by a variety of techniques. The most difficult pancreatic endocrine tumors to visualize are the small tumors. These are usually gastrinomas and insulinomas because they are the most common and are, in most cases, less than 2 cm. Nonfunctional and other less common functional tumors are usually easily seen with CT or MRI because they tend to be relatively large. MRI has an advantage over CT because neuroendocrine tumors enhance on T_2-weighted imaging or with gadolinium contrast, making both the primary lesion and a metastastic focus easier to visualize. For small primary lesions (insulinomas and gastrinomas), CT is the most often used noninvasive technique. Even using narrow 5 mm cuts, sensitivity is only 30 to 70%. The sensitivity of MRI is similar to that of CT. Transcutaneous ultrasonography is operator dependent and relatively inexpensive but avoids radiation. Ultrasonography has a sensitivity rate similar to CT or MRI for these tumors and may be quite good at examining the liver for metastatic disease. My own practice is to recommend MRI primarily to examine the liver for possible metastatic disease. If a primary tumor is seen, so much the better. Nuclear scintigraphy with radiolabeled antibodies to the somatostatin receptor has achieved favorable results, particularly for gastrinomas in which sensitivity rates are 58% for the identification of primary lesions and 92% for liver metastases.[47] Some authors believe that somatostatin receptor scintigraphy is the most sensitive noninvasive imaging method of detecting liver metastases, and whole-body imaging allows for visualization of the approximately 9% of gastrinomas that may occur at sites remote from the gastrinoma triangle.[48] Similar results have been reported in small series for insulinomas using somatostatin receptor scintigrams. The utility of positron emission tomography (PET) has yet to be established. Some have suggested that PET may demonstrate primary tumors

with equal sensitivity to MRI or CT but is better at detecting unsuspected distant metastases.[49] Others report that fluorine 18 [^{18}F]fluorodeoxyglucose PET can be used to predict an aggressive tumor behavior and poor prognosis.[50]

Invasive tests may have higher sensitivity rates. Some have adopted endoscopic ultrasonography (EUS) as the best initial test to locate the primary insulinoma or gastrinoma, but sensitivity rates in series vary greatly. Insulinomas will have a distinctive blush on angiography. Initial reports from the 1970s and 1980s using digital subtraction angiography showed excellent sentivity for insulinomas of greater than 90%, but recent series have not duplicated these results.[51,52] The true sensitivity rate is probably in the 50 to 60% range. Transhepatic portal venous sampling (PVS) has a sensitivity rate for gastrinomas of 35 to 90% and for insulinomas of 75 to 90% in experienced hands but is now rarely used, except as part of investigational protocols owing to the invasive nature of this examination. PVS has been replaced at most centers by selective arterial secretagogue injection (SASI), which was initially championed for gastrinomas by Imamura and colleagues.[53] The test is based on the observation that secretin induces a prompt increase in gastrin production by gastrinoma cells. Briefly, an arterial catheter is selectively inserted into one of the three main peripancreatic arteries: the gastroduodenal, superior mesenteric, and splenic arteries. A second catheter is placed in a hepatic vein to collect blood samples (Figure 15–10). Secretin is injected into the selected arteries and then blood samples are collected at 20, 40, 60, 90, and 120 seconds for gastrin level assay. Gastrin levels should rise when the artery supplying the area of the pancreas harboring the gastrinoma is injected (Figure 15–11). In this manner, the tumor is located to within a region in 55 to 100% of patients. The SASI test has been adapted for the localization of insulinomas by using calcium, which is a potent secretagogue for insulin. In a study by investigators at the National Institutes of Health on 25 patients with insulinomas, SASI was better than any other modality used to identify the region harboring the primary tumor in 22 (88%) of the patients. The success rate was 9% for ultrasonography, 17% for CT, 43% for MRI, 36% for angiography, and 67% for PVS.[54] These numbers should be kept in perspective. Operative exploration for an insulinoma by an experienced endocrine surgeon using inspection, bimanual palpation, and intraoperative ultrasonography remains the most sensitive localizing test. Success rates are generally better than 95%.[2] My own policy is to do only an MRI prior to operative exploration for a sporadic insulinoma.

TREATMENT OF METASTATIC ISLET CELL CANCERS

Surgical debulking should be the first consideration for hepatic metastases from functional endocrine tumors when greater than 90% of the tumor mass can be removed.[55] Substantial prolonged palliation and probably prolonged survival can be achieved with low morbidity and mortality rates.[56] Surgical debulking may take the form of resection or ablation by either cryotherapy or radiofrequency probes or a combination of techniques.

When surgical options have been exhausted, medical therapy or hepatic artery chemoembolization may offer benefits. Streptozocin and doxorubicin (Adriamycin) chemotherapy has been associated with a 69% response rate and improved endocrine symptoms

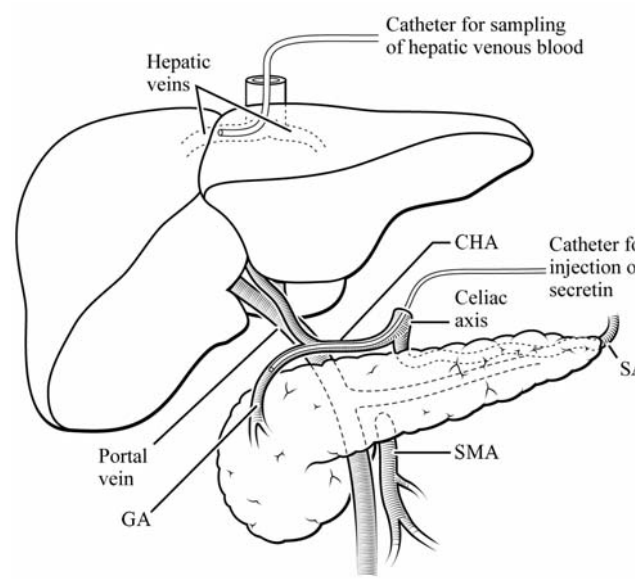


Figure 15–10. Selective arterial secretin injection test. This is a graphical demonstration of the select arterial secretin injection test in which catheters are placed selectively in the mesenteric vessels to inject the secretagogue secretin. Blood samples are obtained from a catheter in the hepatic vein. This test was originally described by Dr. Imamura. CHA = common hepatic artery; GDA = gastroduodenal artery; SA = splenic artery; SMA = superior mesenteric artery.

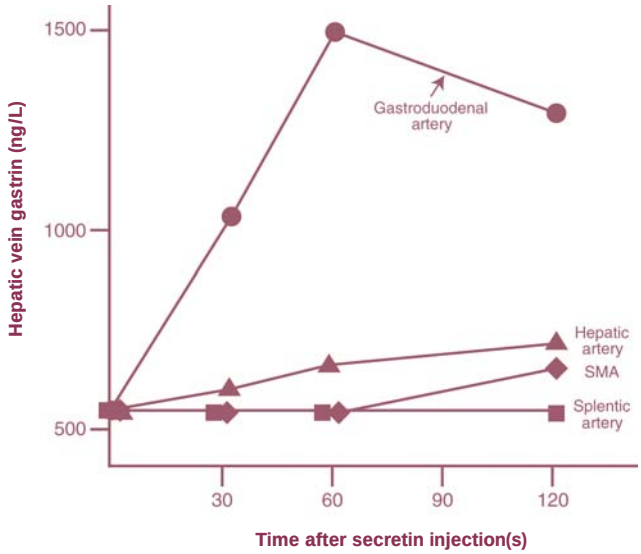


Figure 15–11. Selective intra-arterial secretin test. The results of this particular patient's assay demonstrate a gastrinoma in the distribution of the gastroduodenal artery. An injection of secretin into the gastroduodenal artery resulted in a rapid increase in the gastrin level of the hepatic vein blood. SMA = superior mesenteric artery

for up to 18 months.[57] I have seen encouraging results using hepatic artery chemoembolization in small series of patients with unresectable metastatic disease confined to the liver. This treatment is based on the observation that metastatic foci are predominantly supplied by branches of the hepatic artery. Chemotherapeutic agents injected into the hepatic artery reach the tumor directly and at 20 to 200 times the levels achieved by peripheral venous injection. Embolization of the hepatic artery deprives the tumor of oxygen and slows washout of the injected drugs, thereby enhancing their effect and decreasing systemic adverse reactions. The parenchyma of the liver is spared by virtue of the portal venous inflow. The protocol at our institution uses a three-drug regimen consisting of doxorubicin, mitomycin, and cisplatin. We have treated a small number of patients without apparent toxicity and good palliation of endocrine symptoms.

REFERENCES

1. Morrison H. Contributions to the micoscopic anatomy of the pancreas by Paul Lagerhans (Berlin, 1869). Bull Inst Hist Med 1937;5:259–97.
2. Nichols EH. The relation of blastomycetes to cancer. J Med Res 1902;7:312–59.
3. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma—incidence, recurrence and long-term survival of patients: a 60-year study. Mayo Clin Proc 1991;66:711–9.
4. Grant CS. Insulinoma. Surg Oncol Clin North Am 1998; 7:819–44.
5. Harris S. Hyperinsulinism and dysinsulinism. JAMA 1924; 83:729–33.
6. Whipple AO, Franz VK. Adenoma of islet cells with hyperinsulinism. Am Surg 1935;101:1299–355.
7. Delcore R, Friesen SR. Gastrointestinal neuroendocrine tumors. J Am Coll Surg 1994;178:187–211.
8. Jaspan JB, Polonsky KS, Foster DW, et al. Clinical features and diagnosis of islet-cell tumors. In: Moosa AR, editor. Tumors of the pancreas. Baltimore: Williams & Wilkins; 1980. p. 469–504.
9. Gutman RA, Lazarus NR, Penhos JC, et al. Circulating proinsulin-like material in patients with functioning insulinomas. N Engl J Med 1971;284:1003–8.
10. Rubenstein AH, Kuzuya H, Horwitz DL. Clinical significance of circulating C-peptide in diabetes mellitus and hypoglycemic disorders. Arch Intern Med 1977;137:625–32.
11. Scarlett JA, Mako ME, Rubenstein AH, et al. Factitious hypoglycemia: diagnosis by measurement of serum C-peptide immunoreactivity and insulin-binding antibodies. N Engl J Med 1977;297:1029–32.
12. Gagner M, Pomp A, Herrera MF. Early experience with laparoscopic resections of islet cell tumors. Surgery 1996;120:1051–4.
13. Demeure MJ, Klonoff DC, Karam JH, et al. Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. Surgery 1991;110:998–1004.
14. Zollinger RM, Ellison EH. Primary peptic ulceration of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 1955;142:709.
15. Gregory RA, Tracy HJ, French JM, Sircuo W. Extraction of a gastrin-like substance from a pancreatic tumor in a case of Zollinger-Ellison syndrome. Lancet 1960;i:1045–8.
16. Jensen RT, Gardner JD, Raufman J-P, et al. Zollinger-Ellison syndrome: current concepts and management. Ann Intern Med 1983;98:59.
17. Fox PS, Hoffman JW, Wilson SD, et al. Surgical management of the Zollinger-Ellison syndrome. Surg Clin North Am 1974;54:395.
18. Levin MR, Stagg BH, Clark CG. Gastric acid secretion and diagnosis of Zollinger-Ellison. BMJ 1973;1:139.
19. Deveney CW, Deveney KS, Jaffe BM, et al. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger-Ellison syndrome). Ann Intern Med 1977;87:680.
20. Maton PN, Vinayek R, Frucht H, et al. Long term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a retrospective study. Gastroenterology 1989;97:827–6.
21. Norton JA. Gastrinoma: advances in localization and treatment. Surg Oncol Clin North Am 1998;7:845.
22. Fraker DL, Norton JA, Alexander HR, et al. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. Ann Surg 1994;220:320–30.
23. Thompson NW. Pancreatic surgery for endocrine tumors. In: Clark OH, Duh Q-Y, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 599–606.
24. Wilson SD. Gastrinoma. In: Clark OH, Duh Q-Y, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 607–18.

25. Norton JA, Doppman JL, Collen MJ, et al. Prospective study of gastrinoma localization and resection in patients with Zollinger-Ellison syndrome. Ann Surg 1986;204:468–79.
26. Malagelada JR, Edis AJ, Adson MA, et al. Medical and surgical options in the management of patients with gastrinoma. Gastroenterology 1983;84:1524–32.
27. Mignon M, Ruszniewski P, Haffar S, et al. Current approach to the management of the tumoral process in patients with gastrinoma. World J Surg 1986;10:702–9.
28. Zollinger RM, Ellison EC, O'Dorisio RM, Sparks J. Thirty years' experience with gastrinoma. World J Surg 1984; 8:427–35.
29. Thompson NW. Surgical treatment of the endocrine pancreas and Zollinger-Ellison syndrome in the MEN1 syndrome. Henry Ford Med J 1992;40:195–8.
30. MacFarlane MP, Fraker DL, Alexander HR, et al. Prospective study of surgical resection of duodenal and pancreatic gastrinomas in multiple endocrine neoplasia type 1. Surgery 1995;118:973–80.
31. Weber HC, Venzon DJ, Fishbein VA, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome (ZES): a prospective long-term study. Gastroenterology 1995;108:1637–49.
32. Alexander HR, Bartlett DL, Venzon DJ, et al. Analysis of factors associated with long-term (five or more years) cure in patients undergoing operation for Zollinger-Ellison syndrome. Surgery 1998;124:1160–6.
33. Freisen SR, Hermreck A, Mantz RA Jr. Glucagon, gastrin, and carcinoid tumors of the duodenum, pancreas and stomach: polypeptide "apudomas" of the foregut. Am J Surg 1974;127:90.
34. Krejs GJ, Orci L, Conlon JM, et al. Somatostatinoma syndrome: biochemical, morphologic and clinical features. N Engl J Med 1979;301:285.
35. Vinik AL, Strodel WE, Eckhauser FE, et al. Somatostatinomas, VIPomas and neurotensinomas. Semin Oncol 1987;14:263–81.
36. Konomi K, Chijiwa K, Katsuta T, et al. Pancreatic somatostatinoma: a case report and review of the literature. J Surg Oncol 1990;43:259.
37. Stamm B, Hedinger CE, Saremaslani P. Duodenal and ampullary characteristics, polypeptide content and relation to the MEN I syndrome and von Recklinghausen's disease. Virchows Arch 1986;408:475–89.
38. Eckhauser FE, Colleti LM. Somatostatinoma. In: Beger HG, Warshaw AL, Büchler MW, et al, editors. The pancreas. Oxford: Blackwell Science; 1998. p. 1270–4.
39. O'Brien TD, Chejfec G, Prinz RA. Clinical features of duodenal somatostatinomas. Surgery 1993;114:1144–7.
40. Priest WM, Alexander MK. Islet cell tumor of the pancreas with peptic ulceration diarrhea and hypokalemia. Lancet 1957;ii:1145–7.
41. Verner JV, Morrison AB. Islet-cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med 1958;25:374–80.
42. Freisen SR. Update on the treatment of rare neuroendocrine tumors. Surg Clin North Am 1987;67:2.
43. Zollinger RM. Islet cell tumors of the pancreas and alimentary tract. Am J Surg 1975;129:101.
44. Jaffe BM, Kopen DF, DeSchryver-Kecskemeti K, et al. Indomethacin-responsive pancreatic cholera. N Engl J Med 1977;297:817.
45. Kraezlin ME, Ch'ng JC, Wood SM, et al. Long term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. Gastroenterology 1985;88:185–7.
46. Freisen SR. Tumors of the endocrine pancreas. N Engl J Med 1982;306:580.
47. Gabril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. Ann Intern Med 1996;125:26–34.
48. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999; 341:635–44.
49. Chayvialle JA. A comparison of imaging techniques for the localization of gastroenteropancreatic neuroendocrine tumors. Digestion 1996;57 Suppl 1:54–6.
50. Pasquali C, Rubello D, Sperti C, et al. Neuroendocrine tumor imaging: can 18F-fluorodeoxyglucose positron emission tomography detect tumors with poor prognosis and aggressive behavior? World J Surg 1998;22:588–92.
51. Doherty GM, Doppman JL, Shawker TH, et al. Results of preoperative strategy to diagnose, localize, and resect insulinomas. Surgery 1991;110:989–97
52. Stark DD, Moss AA, Goldberg HI, Deveney CW. CT of pancreatic islet cell tumors. Radiology 1984;150:491–4.
53. Imamura M, Takahashi K, Isobe Y, et al. Curative resection of multiple gastrinomas aided by selective arterial secretin injection test and intraoperative secretin test. Ann Surg 1989;210:710.
54. Doppman JL, Chang R, Fraker DL, et al. Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. Ann Intern Med 1995;123:269.
55. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990;108:1091–6.
56. Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995; 169:36–43.
57. Moertel CG, Lefkopoulo M, Lipsitz S. Streptozocin-doxorubicin, streptozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992;326:519–23.

16

Multiple Endocrine Neoplasia Type I

CHLOE WAGNER, MD
GERARD M. DOHERTY, MD

DEFINITIONS/ETIOLOGY

Multiple endocrine neoplasia (MEN) type I is an autosomal dominant inherited syndrome, with significant variability in its clinical expression. It is characterized by tumors of the parathyroid glands, pancreatic islets, anterior pituitary gland, and certain other tissues. The disease is characterized by near-complete penetrance and variable expressivity. Larson and colleagues in 1988 used genetic linkage to establish the chromosomal region 11q13.[1] Recently, the gene that is mutated in patients with MEN type I has been identified, and several groups now do direct DNA testing to identify carriers.[2,3]

CLINICAL FEATURES

The most common feature of MEN type I is primary hyperparathyroidism. However, depending on the methods used to detect organ involvement, there is a great deal of variability in the penetrance of the different manifestations of MEN type I in different series (Table 16–1).[4–8] Simply put, the more thoroughly one investigates the patient for disease, the more disease is identified.

Primary Hyperparathyroidism

The clinical features of hyperparathyroidism are similar to sporadic cases, with hypercalcemia, low morbidity, and slow progression to signs and symptoms. However, occasional patients have a severe form, with significant renal stone disease, hypercalcemic crisis, osteitis fibrosa cystica, or acute pancreatitis. There is a younger age of onset of hypercalcemia compared with sporadic cases and a similar prevalence in women and men, which contrasts with the female predominance in sporadic hyperparathyroidism.[6,9] The hypercalcemia associated with primary hyperparathyroidism can exacerbate the acid secretion in patients with Zollinger-Ellison syndrome.[10] Hyperparathyroidism associated with MEN type I is characterized by multiple gland involvement, which may be very asymmetric (Figure 16–1). In addition, supernumerary glands frequently occur in locations such as the thymus (Figure 16–2).[11,12]

Pancreatic Islet Cell Tumors

Pancreatic or duodenal neuroendocrine tumors in MEN type I occur most frequently in the fourth or fifth decade. Greater than 95% of those who develop enteropancreatic neuroendocrine tumors already have hyperparathyroidism.[13] However, Zollinger-Ellison syndrome may be the first manifestation in a small population of patients.[14] The clinical presentation usually depends on the increased hormone levels; therefore, patients may present early when tumors are small, for example, with duodenal gastrinomas that are undetectable on preoperative imaging but that cause significant ulcer disease, esophageal reflux symptoms, and diarrhea (Figure 16–3). Symptoms of local enlargement or infiltration including back pain and abdominal mass, left-sided portal hypertension, jaundice, or metastatic disease (cachexia, hepatosplenomegaly) may rarely be present at presentation, but more frequently in older patients with nonfunctional tumors. Nonfunctional neuroendocrine tumors, of which three-

Table 16–1. MULTIPLE ENDOCRINE NEOPLASIA TYPE I CLINICAL DISEASE EXPRESSION

Reference	Parathyroid (%)	Gastrointestinal-Endocrine Axis (%)	Anterior Pituitary (%)
Skogseid et al, 1981–1991, 32 members of 4 affected kindred, extensive testing[8]	90	75	19
Vasen et al, 1974–1989, 52 affected members of 11 families[7]	87	64	27
Marx et al, literature review, 198 members in 21 kindred, up to 1982[6]	97	32	16
Ballard et al, up to 1964, 74 single-case studies, 14 members of one kindred[5]	87	81	65
Majewski and Wilson, 1953–1978, 32 autopsies, subjects > 29 years old[4]	100	100	100

quarters produce pancreatic polypeptide but no syndrome, are the most common tumors overall. These tumors may be quite large or metastatic at presentation (Figure 16–4). Gastrinomas are the most common functional gastrointestinal neuroendocrine tumors, presenting in up to 54% of patients with MEN type I (Table 16–2).[13,15–17] Approximately 20% of patients with Zollinger-Ellison syndrome have MEN type I. Other functional enteropancreatic neuroendocrine tumors occur occasionally; the most frequent of these is insulinoma, whereas glucagonoma, vasoactive intestinal pepide (VIPoma), growth hormone–releasing factor (GRFoma), and somatostatinoma are less common (see Table 16–2).[13,15–17] Patients with MEN type I typically have two or more synchronous enteropancreatic tumors and may have multiple hormonal endocrine syndromes, although, more often, most of the tumors are nonfunctional. Biochemical testing and careful investigation of a symptomatic patient should be the primary methods of the initial diagnosis of a neuroendocrine tumor. Imaging should be used selectively in those patients who have positive pancreatic polypeptide, gastrin, insulin, glucagon, or other enteropancreatic hormone testing or to evaluate symptoms in the absence of biochemical abnormalities.

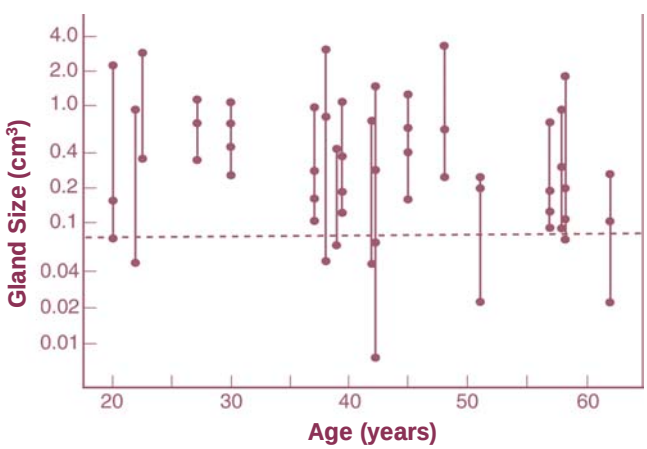


Figure 16–1. Parathyroid gland size plotted versus the patient age. Each set of connected dots represents one patient, and each dot represents one parathyroid gland. The upper limit of the normal size for a parathyroid gland is represented by the horizontal line. The gland size is quite variable even within the same patient, as demonstrated in this graph, and some patients have one or more normal-size glands. Adapted from Marx SJ et al.[12]

Zollinger-Ellison Syndrome/Gastrinomas

Zollinger-Ellison syndrome was initially described as a non–beta islet cell tumor of the pancreas, with gastric acid hypersecretion, and severe peptic ulcer disease (PUD), which is less common now. The

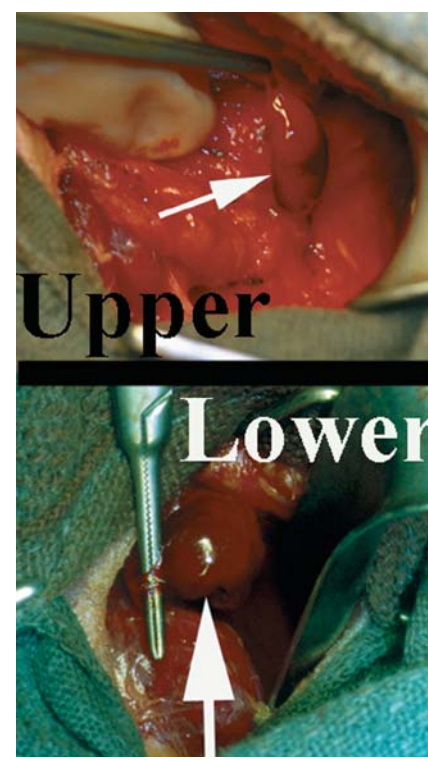


Figure 16–2. Operative photograph of the parathyroid glands in a patient with multiple endocrine neoplasia type I (*arrows* point to parathyroid glands). The glands are dark in color and were hypercellular on microscopic examination.

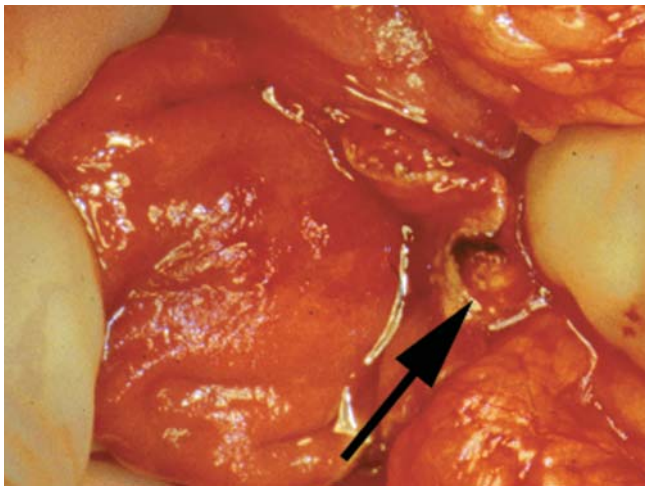


Figure 16–3. Operative photograph of a duodenal gastrinoma. The tumor has been identified and exposed by making a longitudinal duodenotomy and palpating the duodenal wall between thumb and finger. This 3 mm tumor was identified in the submucosal space and is visible only as a "bump" from the mucosal surface shown here. There is no identifiable abnormality on the serosal side of the bowel wall.

majority of tumors occur in the region of the duodenum or head of the pancreas. The "gastrinoma triangle" is defined by the cystic/common bile duct junction superiorly, junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially.[18] Gastrinomas may occur in the pancreas of patients with MEN type I, but, recently, it has become evident that gastrinomas are very frequently in the duodenum, regardless of their presence in the pancreas (see Figure 16–3). In addition, most patients have multiple, small submucosal lesions of the duodenum.[19] Gastrinomas are usually malignant, and regional lymph node metastases are found in 50% of patients at the time of pancreatic surgery.[11] They present in the fourth decade.[13,16] Patients with MEN type I or a family history should be screened for Zollinger-Ellison syndrome with at least one fasting serum gastrin level if they develop either clinical or laboratory features suggestive of the disease. The diagnosis of Zollinger-Ellison syndrome depends on proving autonomous gastrin secretion that does not respond to normal physiologic mechanisms. Therefore, a fasting serum gastrin is typically the initial test. Other helpful tests to establish the diagnosis are the

Table 16–2. PANCREATIC ENDOCRINE NEOPLASM TUMOR SYNDROMES

Tumor	Syndrome	Signs/Symptoms	Major Location	Diagnostic Test
Gastrinoma	Zollinger-Ellison	Abdominal pain, diarrhea, reflux symptoms	Duodenum > 80%	Fasting serum gastrin, secretin test
Insulinoma	Insulinoma	Hypoglycemia, neuroglycopenia	Pancreas	Fasting blood glucose with insulin level, C peptide, and proinsulin fraction
Glucagonoma	Glucagonoma	Rash, anemia, diabetes mellitus, glucose intolerance, weight loss, thromboembolic disease	Pancreas	Serum glucagon
VIPoma	Verner-Morrison, pancreatic cholera	Severe watery diarrhea, hypokalemia	Pancreas 90%, other 10%	Volume of diarrhea and VIP level
GRFoma	GRFoma	Acromegaly	Pancreas	GRF level
Somatostatinoma	Somatostatinoma	Diabetes mellitus, cholelithiasis, diarrhea, steatorrhea	Pancreas, duodenum, or jejunum	Typically by imaging studies, then somatostatin-like immunoreactivity and/or increased number of D cells by stain
PPoma	PPoma	No proven symptoms, weight loss, abdominal mass, hepatosplenomegaly	Pancreas	PP level
Nonfunctional	None	Same as PPoma	Pancreas	None
Carcinoid	Carcinoid	Flushing, palpitations, wheezing, diarrhea, cramping	Pancreas, small bowel, thymus, bronchus	24-hr urinary excretion of 5-HIAA
Gastric ECLoma	Gastric carcinoid	None	Stomach	Usually discovered during endoscopy

ECL = enterochromaffin-like cells; GRF = growth hormone–releasing factor; 5-HIAA = 5-hydroxyindoleacetic acid; PP = pancreatic polypeptide; VIP = vasoactive intestinal peptide.

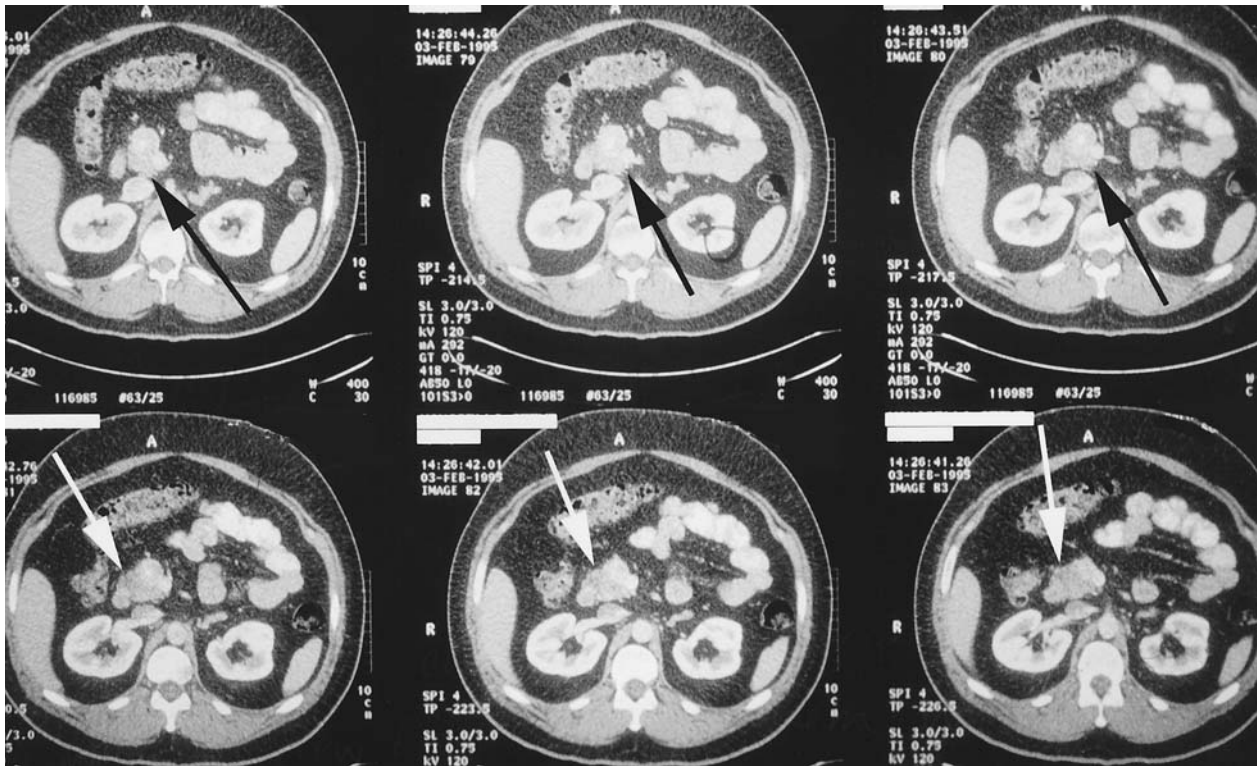


Figure 16–4. Computed tomographic scan of the pancreas in a patient with multiple endocrine neoplasia (MEN) type I and a nonfunctioning tumor of the head of the pancreas. This patient was investigated because of his membership in a kindred with MEN type I and an elevated pancreatic polypeptide level. This otherwise asymptomatic tumor was resected by pancreaticoduodenectomy, and the patient is disease free at 4 years. The *arrow* indicates the neoplasm in the head of the pancreas.

basal acid output (BAO), maximal acid output (MAO), gastric output pH, and provocative tests. A normal BAO is < 5 mEq/hour for women and < 10 mEq/hour for men. The criterion for Zollinger-Ellison syndrome is ≥ 15 mEq for patients who have not previously had any gastric acid reduction surgery.[17] However, the utility of acid output alone is limited because it can vary with the degree of hypercalcemia and can be elevated in patients with idiopathic hypersecretion. Therefore, BAO alone will never make the diagnosis of Zollinger-Ellison syndrome, and other tests are needed. MAO is obtained after a subcutaneous injection of pentagastrin (6 μg/kg). A BAO-to-MAO ratio > 0.6 is indicative of Zollinger-Ellison syndrome but adds little to BAO alone. A gastric output pH > 3.0 in a patient who is not on antisecretory medications rules out Zollinger-Ellison syndrome. Approximately one-third of patients with Zollinger-Ellison syndrome can be diagnosed by a serum gastrin > 1,000 pg/mL with a gastric pH < 3.0.[17] The other two-thirds of the patients require provocative tests[16]:

1. *Secretin.* Two units/kg Kabi secretin is given after two basal values of gastrin have been obtained. Then gastrin levels are measured at 2, 5, 10, 15, and 20 minutes. A positive test is an increase in gastrin > 200 pg/mL. The only cause for a false-positive result is achlorhydria, which can be ruled out with gastric juice pH. Secretin has become difficult to procure recently as it is no longer produced commercially, at least temporarily.
2. *Calcium infusion test.* Fifty-four mg/kg/hour of 10% calcium gluconate is given for 3 hours. Serum gastrin is measured at 120, 160, and 180 minutes with basal values. Fifty-six percent of patients with Zollinger-Ellison syndrome will have an increase > 395 pg/mL in serum gastrin. This test is contraindicated in patients with hypercalcemia or a history of cardiac arrhythmias and is therefore not commonly used in patients with MEN type I.
3. *Standard meal test.* Antral G-cell hyperplasia can mimic Zollinger-Ellison syndrome and should be considered in patients with mildly

elevated gastrin/hyperchlorhydria but with negative secretin and calcium tests. During this test, two basal levels are obtained, and then serum gastrin is measured 30, 60, and 90 minutes after ingestion of a standard meal. A positive test is a serum gastrin increase > 100%, indicating the presence of G-cell hyperplasia. However, 30% of patients with Zollinger-Ellison syndrome also have a positive meal test; therefore, this test cannot exclude Zollinger-Ellison syndrome.

Insulinoma

Less than 10% of patients with MEN type I have an insulinoma, and less than 10% of patients with insulinomas have MEN type I.[20,21] The median age of onset is in the third decade. There is a 1 to 1 male-to-female ratio. In MEN type I, approximately 80% are associated with multifocal islet disease.[22] Although the insulin-producing tumor may be one of several islet cell tumors in the patient, the tumor that is making the insulin is usually solitary and relatively large, on the order of 2 to 4 cm. Patients usually present with symptoms of neuroglycopenia during fasting hypoglycemia (< 40 mg/dL). The diagnosis is made by documenting hypoglycemia in association with inappropriately increased plasma levels of insulin and C peptide during a prolonged fast. Other causes of hypoglycemia include medications (insulin, sulfonylureas), liver dysfunction, renal failure, wasting, and growth hormone (GH) deficiency. Once a diagnosis is made, preparations for surgical approach by preoperative localization are necessary. Computed tomography (CT), ultrasonography, and somatostatin receptor scintigraphy (SRS) are currently our standards for preoperative localization. The studies are designed not only to identify the insulin-producing tumor but also to identify other sites of disease. The imaging studies, however, tend to underestimate the number of lesions in patients with MEN type I. In occasional patients, selective angiography with calcium provocation of insulin production and measurement in the hepatic veins is useful to definitely regionalize the insulin-producing tumor.

Glucagonoma

Glucagonomas result in a migratory necrolytic erythema, weight loss, glucose intolerance, hypoaminoacidemia, and normochromic, normocytic anemia.[23,24] Other less common features include thromboembolic phenomena, neuropsychiatric disturbances, diarrhea, and nonspecific abdominal pain. Glucagonomas occur in 3% of all patients with MEN type I. The age of onset is middle age or later. They typically occur in the tail of the pancreas. They are often large at presentation, 5 to 10 cm, and malignancy is common. Patients present with signs and symptoms of hyperglycemia, and usually diabetes mellitus precedes the diagnosis of glucagonoma. However, Cushing's syndrome is a far more common cause of hyperglycemia in MEN type I. The diagnosis is made by a glucagon level > 1,000 pg/mL often in the presence of the characteristic skin rash.

VIPoma

VIPomas usually (> 80%) originate in the pancreas.[25] The signs and symptoms include severe profuse watery diarrhea (> 700 mL per day and up to 8 L), hypokalemia, and hypochlorhydria. Approximately 1% of VIPomas occur in patients in MEN type I. VIPomas are almost always solitary and are usually > 3 cm in size. Approximately three-quarters occur in the pancreatic tail. More than 60% of VIPomas are malignant, and 37 to 68% of patients have metastases at presentation. Patients typically present in the fourth or fifth decade. The diagnosis depends on a high volume of secretory diarrhea in the presence of a pancreatic endocrine tumor, ideally with documentation of elevated VIP (> 170 pg/mL). The differential diagnosis of secretory diarrhea includes pseudo-VIPoma syndrome, laxative abuse, and Zollinger-Ellison syndrome.

GRFoma

A GRFoma is an endocrine tumor that produces GH-releasing factor, which causes acromegaly.[26] It is a rare tumor, and approximately 30% are associated with MEN type I. These tumors typically occur in the lung (53%), pancreas (30%), or small intestine

(10%). Patients are younger, with a mean age of 38. The tumors are often multiple, large, and metastatic. Sixty-five percent of GRFomas are associated with a tumor causing another hormonal syndrome, such as Zollinger-Ellison or Cushing's syndrome.[27] The diagnosis of a GRFoma is suspected in patients with a pancreatic endocrine tumor and acromegaly, especially in a patient with Zollinger-Ellison syndrome, an adrenocorticotropic hormone (ACTH)-producing pancreatic tumor, or MEN type I. However, it is a rare cause of acromegaly. The diagnosis is confirmed by a GRF level > 300 pg/mL.

Somatostatinoma

Somatostatinomas typically occur in the pancreas or small bowel. The mean age of onset is > 50 years. Most are solitary and large (average size 5 cm) and have metastases to lymph nodes or liver.[28] This hormonal syndrome typically presents with mild diabetes, gallbladder disease, weight loss, anemia, diarrhea, steatorrhea, and hypochlorhydria.[29] The clinical effects are more common in tumors located in the pancreas compared with tumors in the duodenum. These tumors are typically first noticed incidentally during intra-abdominal imaging. The diagnosis is then made by an increase in somatostatin-like immunoreactivity in plasma and/or an increase in the number of D cells defined by immunohistochemical stains of the tumor.

Pancreatic Polypeptide-oma

Pancreatic polypeptide-omas (PPoma) are clinically silent; however, they are the most common neuroendocrine tumor in MEN type I. The true incidence is unknown. They occur throughout the pancreas and may be large at presentation. Malignancy is common and occurs in 64 to 92% of patients.[30] These tumors generally present after 40 years. The diagnosis is made by an increase in the PP level.[31–33] Other causes for an increase in PP levels include old age, inflammatory conditions, bowel resection, alcohol abuse, chronic renal failure, and diabetes mellitus.

Carcinoid

Carcinoid tumors are derived from the embryonic foregut (bronchi, thymus, stomach, pancreas, and duodenum), midgut, and hindgut.[34] Most MEN type I carcinoids are derived from the foregut (69%).[35] They occur in approximately 7% of patients with MEN type I. Foregut tumors produce the carcinoid syndrome less often than midgut tumors. Patients may have an atypical presentation with facial flush, lacrimation, headaches, and/or bronchospasm. Foregut tumors generally do not produce 5-hydroxytryptamine (5-HT), but many secrete histamine and 5-hydroxytrytophen (5-HTP), which is metabolized to 5-hydroxyindoleacetic acid (5-HIAA). Foregut carcinoids in MEN type I are generally bronchial (40%), thymic (35%), duodenal (20%), or gastric (5%).[35] The mean age of diagnosis is approximately 40 years. Mediastinal carcinoid tumors have an increased propensity for malignancy (~ 40% in MEN type I). Carcinoid tumors of the gastrointestinal tract are benign-appearing tumors of neuroendocrine origin and account for 1.5% of all gastrointestinal tract tumors.[36] Overall, 30 to 40% occur in the appendix; however, this is an unusual location when associated with MEN type I. The second most common location is the duodenum, which has been documented in MEN type I. There is no specific relationship documented between hindgut tumors and MEN type I. Midgut carcinoid tumors secrete a variety of vasoactive amines as well as peptide hormones; however, the major substance is 5-HT. Symptoms, which include flushing, diarrhea, abdominal cramping, wheezing, dyspnea, and palpitations, generally develop in midgut or hindgut tumors with metastases to the liver, whereas they can occur with bronchial tumors without liver metastases. The diagnosis is made by a 24-hour urinary excretion of 5-HIAA > 10 mg/24 hour.

There are two types of gastric carcinoid tumors: tumors from enterochromaffin-like cells (ECLoma), which are associated with hypergastrinemia and MEN type I, and non-ECLomas, which are generally sporadic. The pathophysiology of ECLomas is thought to involve a hyperplasia-neoplasia sequence in response to hypergastrinemia.[37] Five to 13% of patients with Zollinger-Ellison syndrome and MEN type I have a gastric carcinoid.[38] They are usually discovered during an endoscopic examination for another indication such as follow-up for Zollinger-Ellison syndrome. They are submucosal lesions and

can be diagnosed histologically by fine-needle aspiratioin using the Sevier-Monger technique to determine ECLoma versus non-ECLoma.[39]

Anterior Pituitary Tumors

The reported incidence in MEN type I syndrome varies from 0 to 100%.[7,16,40] However, pituitary abnormalities may be the first manifestation of MEN type I; therefore, screening with prolactin levels is recommended. There is a 2 to 1 female-to-male ratio. When compared with sporadic pituitary tumors, the overall distribution of tumor types is altered in MEN type I; there are fewer gonadotropin and null cell tumors and more plurihormonal and prolactin-producing tumors.[41] The most common pituitary adenoma associated with MEN type I is a prolactinoma. Other hormones commonly secreted by pituitary tumors associated with MEN type I include GH, GH-prolactin, and ACTH (Figure 16–5). Rarer tumors associated with MEN type I include luteinizing hormone (LH)/follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and nonsecreting adenomas. Patients present with symptoms and signs secondary to mass effect (headache, visual field loss), hypopituitarism, and/or excessive hormone production.

The evaluation for pituitary tumors includes a history of reproductive function (menstrual dates, galactorrhea, fertility, and libido), a history of weight gain, headache, or change in hand size. The physical examination should also include visual field testing. Baseline tests include magnetic resonance imaging (MRI) with gadolinium contrast of sella, basal GH, prolactin, and urine free cortisol. Patients may also be screened for gonadotropin-secreting tumor with basal- and thyrotropin-releasing hormone–stimulated LH, LH-β, LH-α, and FSH. Baseline free thyroxine (T_4) and TSH will identify patients with central hypopituitarism and the rare patient with a TSH-secreting tumor (an increase in T_4 and increased level of TSH).[16]

Galactorrhea, amenorrhea, and/or infertility are common presentations in women with prolactinoma. In men, hypogonadism and mass effect may be the only signs of prolactinoma. Prolactin levels are typically > 300 ng/mL.

The diagnosis of Cushing's syndrome is made by increased glucocorticoid levels (increased 24-hour urine cortisol excretion) or diminished response of glucocorticoid feedback. The feedback is most commonly assessed by the overnight dexamethasone suppression test (dexamethasone 1 mg orally at 11:00 pm should normally suppress cortisol to < 5 μg/dL at 8:00 am). The differential diagnosis includes pituitary-dependent ACTH excess (adenoma or hyperplasia), ectopic ACTH from bronchial carcinoid tumor, or primary neoplasm of the adrenal

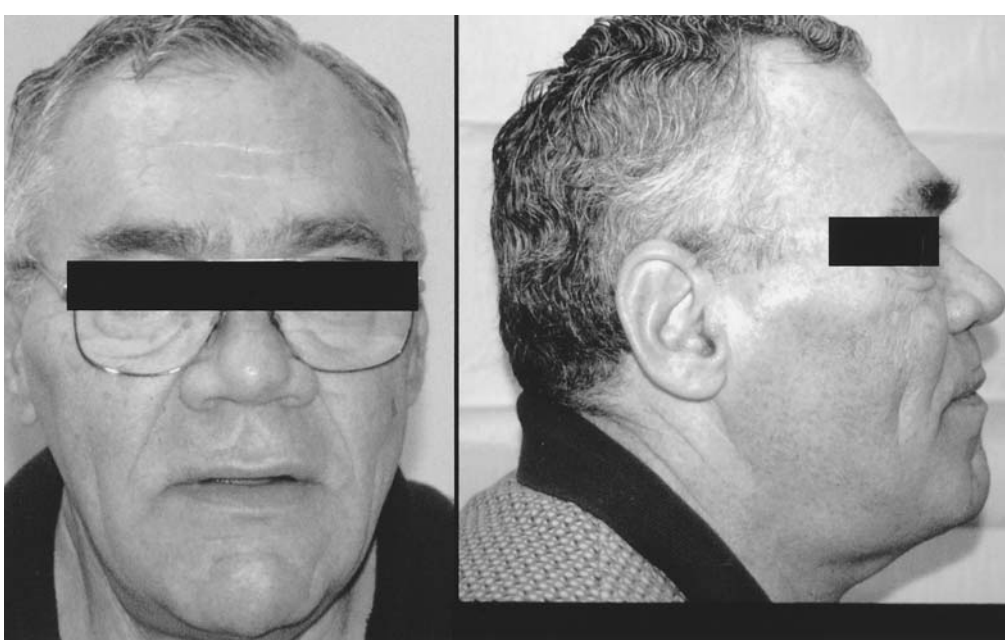


Figure 16–5. Photographs of a typical patient with multiple endocrine neoplasia type I and acromegaly owing to a growth hormone–secreting pituitary adenoma. Note the prominent brow and mandible. He also had gradual enlargement of his hands and feet.

gland. The differential diagnosis begins with checking ACTH. Values < 10 pg/mL identify ACTH-independent Cushing's syndrome, in which case, a CT scan is indicated to evaluate the adrenal glands. If there is more than one lesion, then iodocholesterol scanning may be useful to identify functioning masses. Finally, the response to high-dose dexamethasone can differentiate the ACTH-dependent forms of Cushing's syndrome, either ectopic or pituitary.[42–44]

Other Tumors

Tumors other than parathyroid, gastrointestinal endocrine, and anterior pituitary that may be associated with MEN type I include primary thyroid neoplasms, primary adrenocortical neoplasms, ovarian tumors, and lipomas.

TREATMENT AND RESPONSE

One of the areas of uncertainty in the management of patients with MEN type I is the frequency of significant, life-threatening complications, such as malignant duodenopancreatic islet cell tumors and malignant thymic carcinoids. Previously, primary hyperparathyroidism and Zollinger-Ellison syndrome were potentially lethal complications, but hyperparathyroidism can now be treated to prevent renal stones and insufficiency, and the high gastric acid output can be suppressed by H_2 antagonists or proton pump inhibitors. Some data seem to indicate that the neuroendocrine neoplasms of MEN type I are more indolent than their sporadic counterparts.[45] These data can be used to justify a management strategy that emphasizes palliation of symptomatic disease without more aggressive potentially morbid interventions aimed at prevention or cure of malignancy. A recent retrospective study, however, demonstrated that 46% of patients classified as MEN type I carriers died of MEN type I–related disease at a median age of 47 years (Figure 16–6). Most of these deaths were owing to malignancy, including pancreatic islet cell tumors and malignant carcinoid tumors (Table 16–3).[46] Although carrying the *MEN1* gene did not shorten life span in this study, there was a substantial subset of *MEN1* carriers who died early, often from malignant endocrine neoplasms. Deaths from MEN type I–related disease occurred earlier than unrelated deaths both in *MEN1* carriers and when compared with all non–MEN type I–related deaths in these kindred (see Figure 16–6).[46] Therefore, it is believed that aggressive screening programs to identify and initiate treatment of malignancies in the setting of MEN type I are warranted.

Hyperparathyroidism

The management of hyperparathyroidism associated with MEN type I is complicated by the high incidence of multiple gland disease. In addition, super-

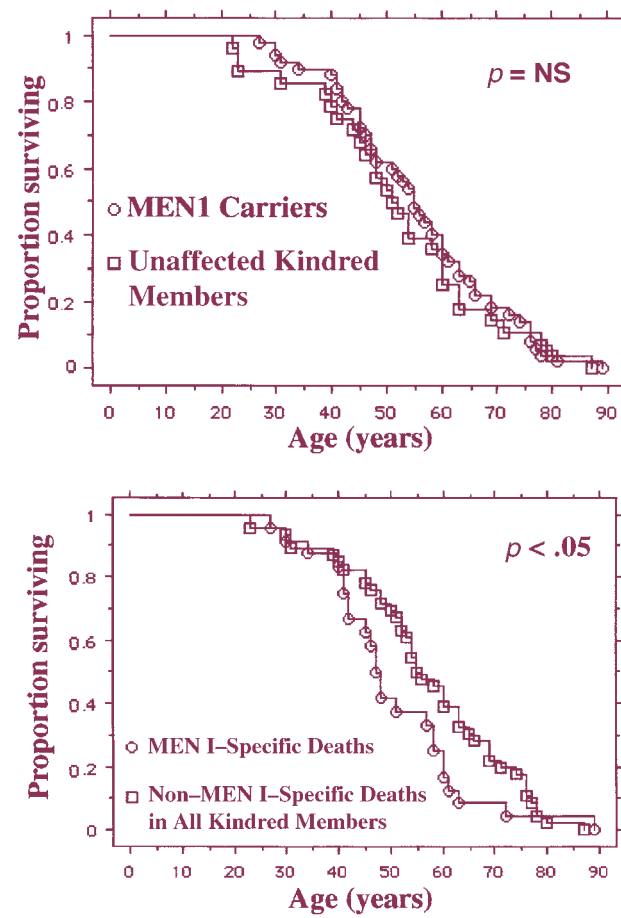


Figure 16–6. Kaplan-Meier survival curves for the multiple endocrine neoplasia (MEN) type I kindreds followed at Washington University. The *upper panel* demonstrated that there was no overall survival difference between the *MEN1* gene carriers, as identified by the clinical characteristics available, compared with their apparently unaffected relatives. However, as demonstrated in the *lower panel*, 46% of the patients who carried *MEN1* died of a cause related to the MEN type I, and those deaths occurred at a younger age than those deaths not attributable to MEN type I. Thus, there appears to be a subset of *MEN1* carriers who develop life-threatening disease at an early age. Adapted from Doherty GM et al.[46] NS = not significant.

Table 16–3. MULTIPLE ENDOCRINE NEOPLASIA TYPE I–RELATED CAUSES OF DEATH IN THE WASHINGTON UNIVERSITY SERIES

Cause	Number of Patients	Age (yr), Median (range)
Malignant islet cell tumor	12	46 (27–89)
Ulcer disease	6	56 (41–72)
Malignant carcinoid tumor	6	53 (42–63)
Hypercalcemia/uremia	3	42 (30–45)
Total	27/59* (46%)	

*Of 59 patients with multiple endocrine neoplasia (MEN) type I who died, 27 died of causes related to MEN type I. Adapted from Doherty GM et al.[46]

numery glands often occur in locations such as the thymus. In general, hyperparathyroidism associated with MEN type I is treated surgically by either subtotal ($3^1/_2$ gland) parathyroidectomy or total parathyroidectomy with heterotropic autotransplantation, either operation including bilateral upper thymectomy. Unfortunately, to date, there has never been a prospective randomized controlled trial comparing the two acceptable surgical procedures for parathyroid hyperplasia. Parathyroid surgery is more frequently unsuccessful in MEN type I compared with sporadic hyperparathyroidism, and recurrent disease is more common because of the multiple gland involvement. The amelioration of primary hyperparathyroidism may slow the progression of some or all MEN type I–associated endocrinopathies.[10]

To optimize the chances for success, it is critical to have an experienced surgeon at the initial operation; it is very helpful if MEN type I is recognized preoperatively. There is no need for noninvasive preoperative imaging. An extensive initial exploration with identification of all four glands with biopsy confirmation is essential, and the resection should include a transcervical thymectomy.[47,48] The thymus may contain parathyroid glands or a MEN type I–associated mediastinal carcinoid tumor. For the subtotal approach, all but 50 mg of the most normal-appearing parathyroid tissue is then resected. To minimize the risk of reoperation in the neck in case of recurrent hypercalcemia, many favor total parathyroidectomy with parathyroid autotransplantation.[49] If autotransplantation is done, an autograft of 50 mg parathyroid tissue is minced into $2 \times 1 \times 1$ mm segments and placed into 20 to 25 pockets in the brachioradialis muscle of the nondominant arm.[49] After successful total parathyroidectomy, there is a period of hypoparathyroidism lasting 6 to 12 weeks; if this does not occur, then there may be residual tissue in the neck or chest. However, the total parathyroidectomy with autotransplantation approach may be associated with a higher incidence of persistent hypoparathyroidism. Cryopreservation of parathyroid tissue is also possible; this can be autotransplanted if the patient does not have complete return of parathyroid function after operation.

The most common reason for reoperation is persistent hyperparathyroidism. In MEN type I, persistent hyperparathyroidism after surgery is most often attributable to failure to identify all abnormal parathyroid glands during initial surgery, and, less frequently, one or more tumors are located in unusual places.[47] In case of reoperation, it is important to review initial operative reports, pathology slides, and pathology reports to understand what parathyroid glands may remain in the neck. Preoperative imaging is important in this context.[50,51] A careful operative plan based on extent of prior surgery and tumor localization studies such as sestamibi, ultrasonography, and MRI is critical, and these procedures should be approached only by an experienced parathyroid surgeon.

Enteropancreatic Neuroendocrine Tumor

The natural history of pancreatic islet cell tumors in patients with MEN type I is different than in sporadic cases. The tumors in patients with MEN type I are multicentric and may have a more indolent course. The role of pancreatic resection in the management of MEN type I with islet cell tumors of the pancreas is not well defined. Currently, operative resection does not appear to be necessary to treat the hormonal syndrome in patients without insulinoma, although it may be helpful with VIPoma. Therefore, the consideration of resection can be focused on the problem of eliminating the risk of death from tumor metastasis. One group has performed careful annual biochemical screening and acted on detected abnormalities with presymptomatic operation in patients with or without imageable tumors.[52] In contrast, others have focused more on identifying imageable disease for intervention based on data indicating that

larger tumors are more likely to develop metastases; the appropriate size criterion for intervention is in question, however. Whereas some data indicate that larger tumors metastasize more frequently,[11,53] other data contradict this (Figure 16–7).[54] In conclusion, it is important to first palliate the endocrine syndrome and then address the tumor as many are malignant.

Zollinger-Ellison Syndrome

The management of patients with MEN type I and gastrinoma is primarily medical. Because of the diffuse nature of the disease, surgical cure is only occasionally achieved. In most patients, management using H_2 receptor antagonists and H+, K+-adenosine triphosphatase inhibitors can effectively control acid hypersecretion. The usual dose of omeprazole is 80 mg per day but can vary between 20 and 120 mg per day. Symptomatic relief only is insufficient to judge the adequacy of the dose of medication. Control of acid secretion must be confirmed using acid output measurements. Once acid output is controlled, the dose can be titrated down using acid output measurements and endoscopic findings as guides.[55] It is important to decrease omeprazole to the lowest effective dose because long-term administration of omeprazole and other antisecretory agents may increase the risk of the development of gastric carcinoid tumors; rats treated with omeprazole had an increased risk of gastric ECLoma owing to achlorhydria-induced hypergastrinemia, which stimulates ECL cells.[56] Security with medical management is based on the notion that this disease is considered relatively indolent compared with sporadic gastrinomas. However, the incidence of malignancy may be higher than previously thought. In a recent report, the incidence of malignancy was 47%, which is similar to that of sporadic gastrinomas.[57] This has raised many questions as to when to intervene surgically. Surgery is usually reserved for patients who are good surgical risks and in whom the gastrin-secreting tumor has been identified. Enucleation or resection in such patients may offer excellent palliation and occasionally cure. Our current practice is to use medical management for patients without imageable tumor (by CT scan or octreoscan) and to explore and resect tumor in patients with imageable tumors. Some are more conservative and limit resection to those patients with larger tumors; for example, patients are medically managed when the tumor is no larger than 3 cm, and resection is employed when the primary gastrinoma is 3 cm or larger. This recommendation is based on data suggesting an increased risk of liver metastases with tumors > 3 cm.[53] The risk in withholding the operative exploration until the tumor is 3 cm or greater is that the tumor will have metastasized to the liver prior to operation, possibly obviating a chance for cure. Furthermore, a recent study from our group has demonstrated a lack of correlation between tumor size and risk of metas-

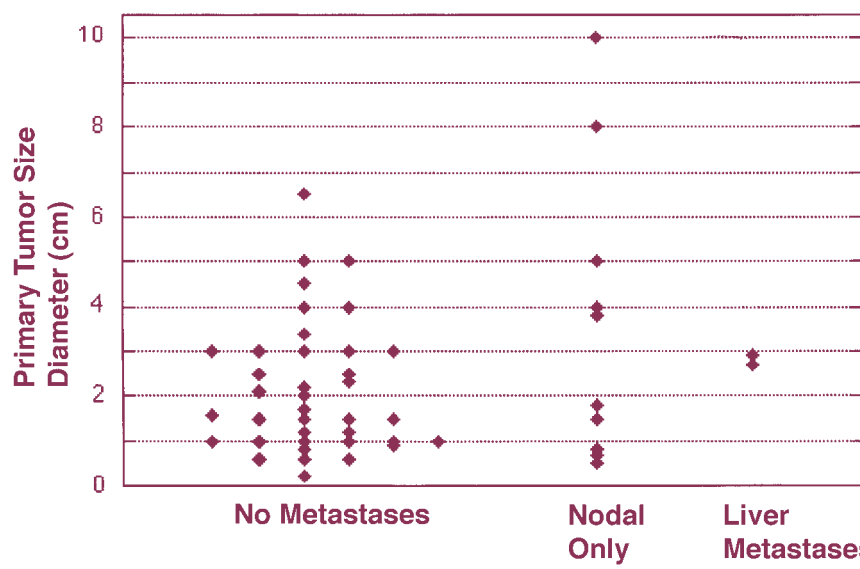


Figure 16–7. Plot of primary enteropancreatic tumor size versus metastases in patients with multiple endocrine neoplasia type I from Washington University. Tumor size did not correlate well with the presence or absence of metastatic disease, particularly with respect to nodal metastasis. Adapted from Lowney JK et al.[54]

tases, pointing out the hazard of a policy of monitoring known tumors.[54] Still others recommend exploratory laparotomy and duodenotomy with resection of all duodenal and pancreatic tumors based on biochemical findings, even in the absence of imageable disease.

Insulinoma

Although many enteropancreatic neuroendocrine tumors in MEN type I can be managed nonoperatively, the exception is insulinoma syndrome, for which resection is generally indicated because (1) the syndrome is difficult to manage nonoperatively and (2) the tumor rarely occurs outside the pancreas and is typically solitary and not associated with lymph node metastasis in MEN type I. Preoperative localization procedures, including abdominal angiography with calcium as a secretagogue, can define the site of an insulinoma in 80% of patients and will identify liver metastases.[11] Transgastric ultrasonography has excellent results in preoperative localization at centers with expertise in this technique. Calcium angiography is not necessary in most patients; however, it may be helpful in selected patients who have multiple tumors and in whom one must be certain to remove the source of the insulin or in patients requiring reoperation. During the exploration for insulinoma, the pancreas is palpated and intraoperative ultrasonography is performed; frequently, other islet cell tumors are also enucleated. Whereas some experts recommend routine subtotal pancreatectomy with enucleation of any pancreatic head tumors, our approach has been to tailor the operation to the individual findings. Our principles are to completely remove all of the tumors while preserving the maximum amount of pancreatic parenchyma. In some patients, this may mean a subtotal pancreatectomy with enucleations from the head, whereas in others, it may mean a pancreaticoduodenectomy with enucleations from the tail of the gland.

Although patients with insulinoma often have many other tumors in the gland, the insulin-producing tumor is usually isolated and curable by limited resection. The postoperative results are excellent with > 90% of patients cured.[58]

Glucagonoma, VIPoma, Somatostatinoma, ECLoma, and Nonfunctional Tumors

The role of surgery for nongastrinoma, noninsulinoma tumors in MEN type I is limited by the availability of safe and effective pharmacologic agents for the palliation of the clinical syndromes. The focus of operative intervention, then, is the management of the potential malignancy. Operatively, the management of patients with glucagonomas, VIPomas, or carcinoid tumors is similar to that of patients with insulinomas. Resection of evident neoplasms appears to be the treatment of choice. However, because many of these tumors are malignant, anatomic resections with regional nodal dissection are more frequently required to completely resect the disease.

The long-acting somatostatin analog ocreotide is now considered to be the drug of choice in the medical palliation of unresectable functional tumors because of improved efficacy over other therapies.[13,59] The treatment for the migratory necrolytic erythema associated with glucagonomas is normalization of amino acid levels, oral zinc therapy, and even glucose or normal saline infusion.[60,61] Octreotide is the drug of choice for glucagonomas. These patients are often poor operative candidates because of poor nutrition from the catabolic state. If surgery is contemplated, then blood transfusions, total parenteral nutrition, and control of hyperglycemia, as well as anticoagulation, have been recommended for the preoperative period.[61]

The initial therapy for VIPomas is directed at replacing volume losses and correcting acid-based and electrolyte abnormalities. The most common cause of death is renal failure and congestive heart failure secondary to hypokalemia. The drug of choice is again octreotide.[59]

Octreotide, the somatostatin receptor agonist, is not useful in the management of the somatostatinoma syndrome. Medical therapy is limited to symptomatic management of diabetes and nutritional deficiencies.[28,62]

Imaging for Neuroendocrine Tumors

Enteropancreatic neuroendocrine tumors spread first locally and to regional lymph nodes and from there generally to the liver. The single most impor-

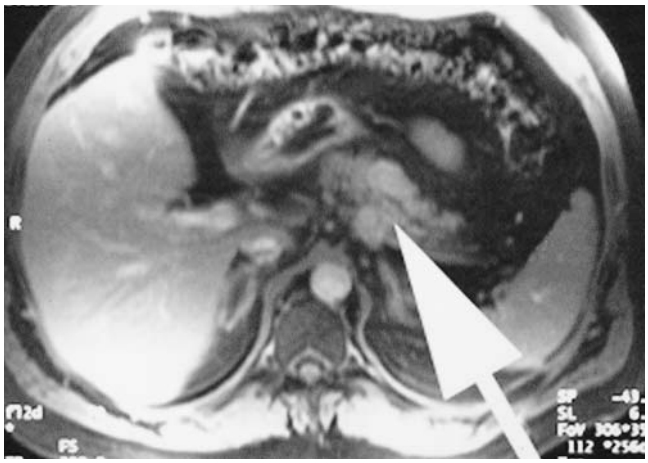


Figure 16–8. Magnetic resonance image from a patient with a multiple endocrine neoplasia type I pancreatic tumor (*arrow*). This was a nonfunctional tumor in the body of the pancreas.

tant factor affecting prognosis is liver metastases. Bone metastases occur late, and other distant metastases are rare. A cross-sectional study (CT or MRI) is the most useful initial test to identify tumors. The localizing rate of MRI is similar to that of ultrasonography and CT for pancreatic lesions (Figure 16–8) but has an increased sensitivity for diagnosis of liver metastases. There are almost always liver metastases before bone metastases, but bone scanning is useful if there are symptoms or biochemical abnormalities that suggest the presence of bone metastases. Angiography can be useful prior to surgery to localize disease and can be combined with stimulatory infusions to provide functional as well as anatomic data (Figure 16–9). The limiting factor in localizing tumors using ultrasonography, CT, angiography, or MRI is tumor size, with < 10% of tumors < 1 cm, 30 to 40% of 1 to 3 cm, and 70 to 80% of > 3 cm detected. Current provocative hormonal testing includes angiography with selective intra-arterial secretin injection and gastrin determination in hepatic venous samples, which permits selective provocation for gastrinoma during localization with a standard angiogram. Similarly, calcium can be used to stimulate insulin from insulinoma.

SRS is critical in the imaging of patients with MEN type I (Figure 16–10). In addition to demonstrating the extent of enteropancreatic tumors, SRS can identify previously unsuspected disease in the chest or abdomen.[63] Although SRS is useful in identifying otherwise occult neuroendocrine tumors in patients with MEN type I, and this can alter management substantially, it also has significant false-positive and false-negative rates, thus necessitating correlation with conventional imaging studies.

Finally, intraoperative ultrasonography and transillumination of the duodenum are extremely helpful to a experienced surgeon in localizing duodenal and pancreatic islet tumors.

Management of Resectable Disease

Patients with imageable, resectable disease should have the option of resection carefully explained and considered. It is critical to have a fully informed patient to reach a decision that addresses not only the risk of the tumor but also the risk of the operation in light of the patient's general health.

Our approach has been to resect all identifiable disease, without being overly aggressive, to keep

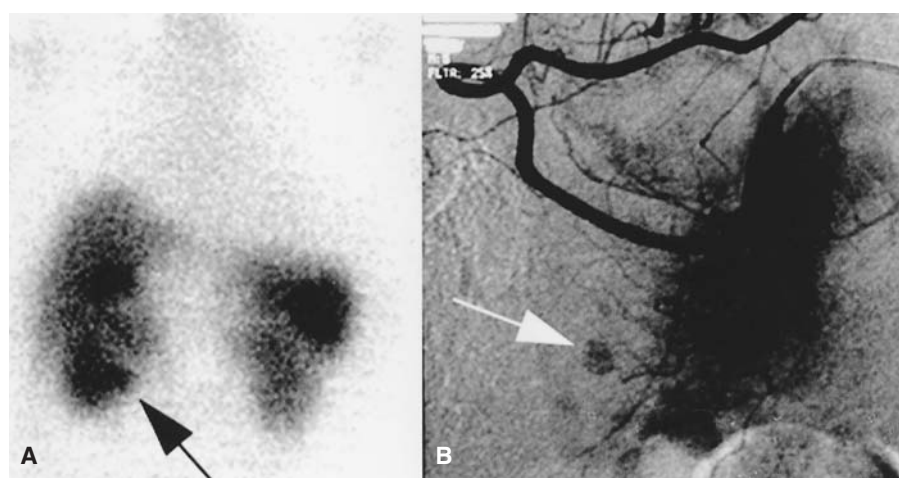


Figure 16–9. Somatostatin receptor scintigraphy (*A*) and angiography (*B*) demonstrating a periduodenal gastrinoma lymph node metastasis (*arrows*) in a patient with multiple endocrine neoplasia type I. The nodal metastases are frequently larger than the primary tumor and are more frequently imageable than primary duodenal gastrinomas.

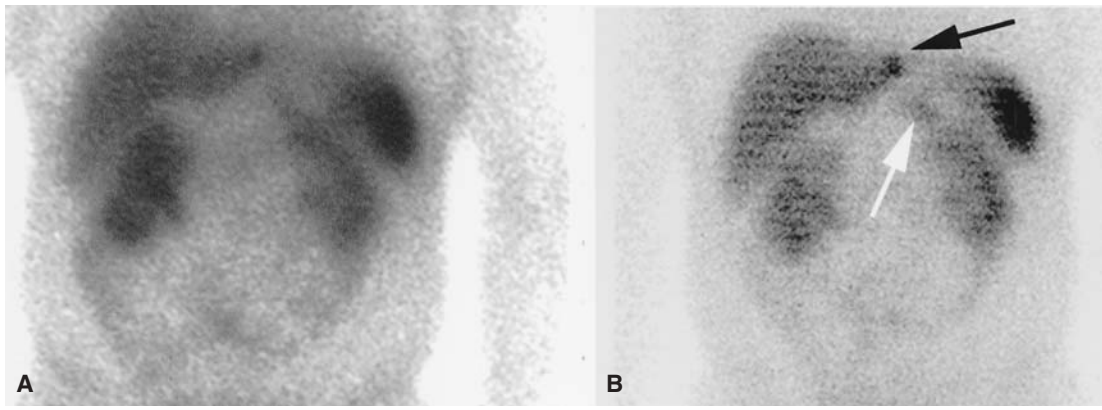


Figure 16–10. Somatostatin receptor scintigraphy in one patient in consecutive annual examinations, demonstrating the development of a left lateral segment liver metastasis from a known pancreatic body tumor. *A*, On the initial study, a focus of uptake was noted in the body of the pancreas, but no increased activity was appreciated in the liver, including evaluation with single-photon emission computed tomography (SPECT). The pancreatic lesion (*light arrow in B*) was confirmed on abdominal computed tomographic (CT) scan but measured only about 1 cm, and after discussion with the patient, it was elected to follow this abnormality. *B*, One year later, repeat imaging showed a clear left lateral segment liver lesion (*dark arrow*), which was clearly visible on SPECT and not appreciable on the earlier study, even in retrospect. This lesion was confirmed on CT scan. At subsequent laparotomy, a single focus of liver disease was identified by ultrasonography and resected. He remains disease free at 3-year follow-up.

morbidity as low as possible and to preserve pancreatic function. For that reason, we tend to use enucleation for lesions in the head of the pancreas, avoiding pancreaticoduodenectomy when possible. Duodenal lesions are resected through a longitudinal duodenotomy, which is then closed transversely (see Figures 16–3 and 16–11). In the classic operation, often called the "Thompson operation," tumors are removed from the wall of the duodenum, a peripancreatic lymph dissection is performed, and a subtotal pancreatectomy is performed leaving only a small portion of the pancreatic head (Figure 16–12).

Management of Metastatic Disease

Patients with widely metastatic disease require lifelong medical management. The role of debulking operations is controversial, and, in general, patients with metastatic disease should not be subjected to surgery unless the tumor can be completely resected for potential cure. Palliative operations may be appropriate for carefully selected patients.

Various chemotherapy regimens have been used in the treatment of metastatic enteropancreatic neuroendocrine tumors. Streptozocin plus 5-fluorouracil, with

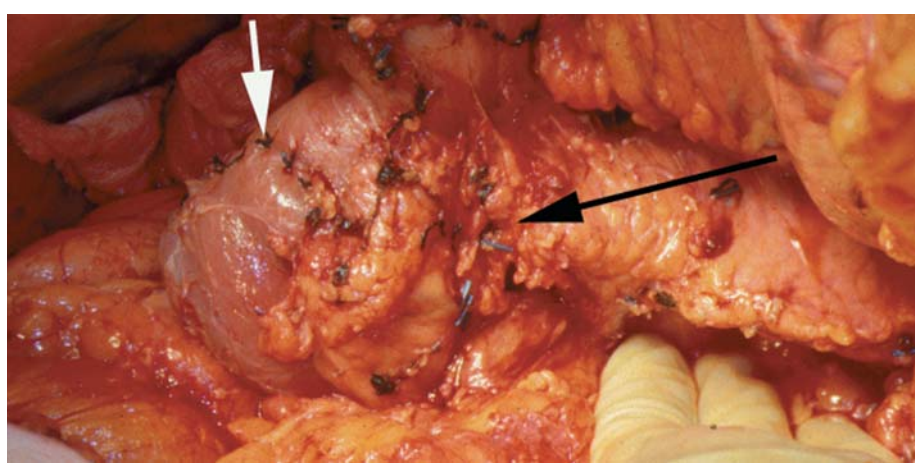


Figure 16–11. Operative photograph after resection of duodenal gastrinomas, with the duodenotomy closed transversely (*white arrow*) and the tumor bed in the head of the pancreas after enucleation of a tumor there (*black arrow*).

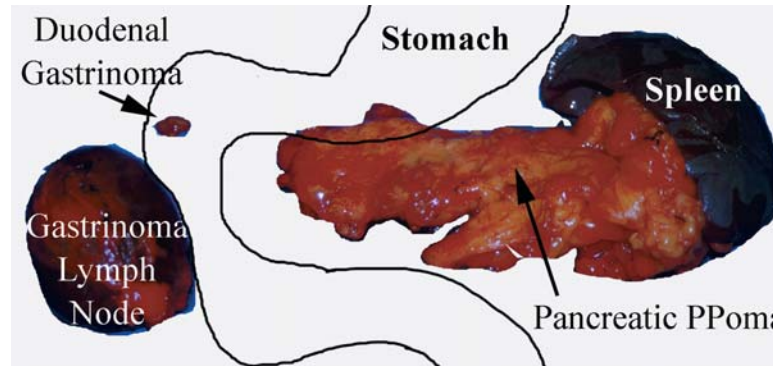


Figure 16–12. Specimen photograph after the "Thompson operation." This 36-year-old man had a single small duodenal wall tumor that was removed through a duodenotomy (as in the patient in Figure 16–11). Adjacent to the duodenum was a large lymph node (6 cm) containing a neuroendocrine tumor that stained strongly for gastrin. Separately in the body of the pancreas, he had a very infiltrative tumor that stained only weakly for gastrin but strongly for pancreatic polypeptide and was adjacent to four involved lymph nodes with similar staining characteristics. He is disease free 1 year after operation.

or without doxorubicin, is the current therapy of choice for metastatic enteropancreatic neuroendocrine tumors.[64,65] Because of the toxicity and generally poor response rates to chemotherapy, most clinicians believe that routine chemotherapy should be reserved for symptomatic patients or those with clear evidence of tumor progression on imaging studies.

The use of interferon has been investigated for patients with various pancreatic tumors, many of whom have failed chemotherapy. In one study, the overall response rate, defined as a decrease of > 50% in tumor size, was 77%, and patients with VIPoma appeared to respond the best.[66] Octreotide is probably not useful as an antitumor agent.

Regional therapies include hepatic artery embolization or ligation and selective administration of streptozocin via the hepatic artery.[67,68] It is important to recognize that these therapies are invasive and only palliative, and the side effects may be severe. On the other hand, because these tumors grow slowly, regional palliation may provide significant long-lasting symptomatic relief in carefully selected patients. Regional therapy is considered only after other options have been exhausted and is of limited value in controlling metastatic spread. However, hepatic artery embolization with or without interferon or chemotherapy may be very helpful in decreasing hormone levels, making controlling symptoms easier in patients with severe symptoms who are no longer responsive to octreotide.

The role of debulking surgery, as briefly mentioned, is controversial. Debulking surgery has been recommended in patients with VIPomas, glucagonomas, somatostatinomas, and intestinal carcinoid tumors and may lead to a marked improvement in symptoms. Recently, nonoperative debulking has been used by radiofrequency ablation of liver tumors under ultrasonographic guidance. In general, debulking laparoscopic and open surgery should be considered in patients with uncontrolled hormonal syndromes who have exhausted the other treatment modalities.

Bronchial/Thymic Carcinoid Tumors

Surgery remains the mainstay of treatment of bronchial and thymic carcinoid tumors. Because of the malignant nature of thymic carcinoid tumors, resection with careful lymph node dissection is recommended. The treatment of metastatic foregut carcinoid tumors has included streptozotocin, interferon-α, histamine antagonists, and somatostatin analogs. However, each has been of limited utility in decreasing tumor growth or symptoms.[69]

Pituitary Tumor Therapies

The current recommendations for management of patients with MEN type I and pituitary tumors are largely the same as for those with sporadic tumors. For example, dopamine-2 receptor agonists are used to suppress hyperprolactinemia, especially in patients with drug-responsive, surgically bulky tumors and in patients who desire to preserve fertility and pituitary function.[40] However, transsphenoidal pituitary microadrenectomy remains the recommendation for most acromegalic patients. Transsphenoidal resection is also the preferred treatment of corticotropinomas with minimal suprasellar extension. Follow-up is important in these patients, namely monitoring tumoral hormone oversecretion, evaluating associated endocrine deficits, and following the patient for mass effects.

FOLLOW-UP IN PATIENTS WITH MEN TYPE I

Monitoring Untreated or Partially Treated Disease

Monitoring untreated hyperparathyroidism requires annual serum calcium, creatinine, alkaline phosphatase, parathyroid hormone, urine calcium, and urine analysis. Bone mass density is obtained less frequently. Monitoring Zollinger-Ellison syndrome requires acid testing to verify correct dosage of antisecretory drug, with a goal of keeping the acid output < 10 mEq/L before the next dose. Endoscopy is necessary if acid control is not satisfactory, confirmed either by acid testing, poor compliance, or gastrointestinal symptoms. Serum prolactin levels annually are necessary when monitoring prolactinomas. For microprolactinoma, the pituitary imaging recommendations follow the same guidelines as in patients with MEN type I without prolactinoma. For macroprolactinoma, pituitary imaging and visual field testing should be performed annually.[11]

Monitoring for New Disease or Recurrence

Monitoring patients with MEN type I is complicated by the pleomorphic expression of the disease. The guidelines for patients who are gene carriers include ionized calcium annually and serum intact parathyroid hormone every 5 years. For the pituitary axis, prolactin levels should be checked every 3 years, with pituitary imaging initially and then every 10 years (preferably MRI). The methods for monitoring the gastrointestinal-endocrine axis are currently controversial.[70] Serum gastrin levels should be obtained annually. High gastrin levels should be confirmed and evaluated with gastric acid testing. Periodic abdominal imaging should be performed only if the team is prepared to treat abnormal findings.[52,71]

GENE CARRIERS AND THE APPLICATION OF GENETIC TESTING TO DIAGNOSIS

Genetic consultation is important to ensure patient understanding of the inheritance pattern of the disease and discussing the consequences for future generations. Recently, the genetic abnormalities responsible for MEN type I have been elucidated, and testing for families in which the genetic abnormality is known can be done in many centers. Direct testing for families in whom the abnormality is not known can still be labor intensive. The gene is large, and the defects are spread throughout the gene, making screening difficult.[2,3]

REFERENCES

1. Larsson C, Skogseid B, Oberg K, et al. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature 1988;332:85–7.
2. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 1997;276:404–7.
3. Mutch MG, Dilley WG, Sanjurjo F, et al. Germline mutations in the multiple endocrine neoplasia type 1 gene: evidence for frequent splicing defects. Hum Mutat 1999;13:175–85.
4. Majewski JT, Wilson SD. The MEA-I syndrome: an all or none phenomenon? Surgery 1979;86:475–84.
5. Ballard HS, Frame B, Hartsock RT. Familial multiple endocrine adenoma-peptic ulcer complex. Medicine 1964;43:481.
6. Marx SJ, Vinik AI, Santen RJ, et al. Multiple endocrine neoplasia type 1: assessment of laboratory tests to screen for the gene in a large kindred. Medicine 1986;65:226–41.
7. Vasen HFA, Lamers CBW, Lips CJM. Screening for the multiple endocrine neoplasia syndrome type 1. Arch Intern Med 1989;149:2717–22.
8. Skogseid B, Eriksson B, Lindqvist G, et al. Multiple endocrine neoplasia type 1: a 10-year prospective screening study in four kindreds. J Clin Endocrinol Metab 1991;73:281–7.
9. Heath H, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity and potential economic impact in a community. N Engl J Med 1980;302:189–93.
10. Norton JA, Cornelius MJ, Doppman JL, et al. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome, and multiple endocrine neoplasia type 1: a prospective study. Surgery 1987;102:958–66.
11. Veldhuis JD, Norton JA, Wells J, et al. Surgical versus medical management of multiple endocrine neoplasia (MEN) type 1. J Clin Endocrinol Metab 1997;82:357–64.
12. Marx SJ, Menczel J, Campbell G, et al. Heterogeneous size of the parathyroid glands in familial multiple endocrine neoplasia type 1. Clin Endocrinol 1991;35:521–6.
13. Norton JA, Levin B, Jensen RT. Cancer of the endocrine system. In: De Vita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 4th ed. Philadelphia: JB Lippincott; 1993. p. 1333–435.
14. Benya RV, Metz DC, Venzon DJ, et al. Zollinger-Ellison syndrome can be initial endocrine manifestation in patients with multiple endocrine neoplasia type 1. Am J Med 1994;97:436–44.
15. Eberl F, Grun R. Multiple endocrine neoplasia type I. Adv Intern Med Pediatr 1981;5:76.

16. Metz DC, Jensen RT, Bale AE, et al. Multiple endocrine neoplasia type 1: clinical features and management. In: Bilezekian JP, Levine MA, Marcus R, editors. Parathyroids: basic and clinical concepts. 1st ed. New York: Raven Press; 1994. p. 591–646.
17. Jensen RT, Gardner JD. Gastrinoma. In: Go VLW, Reber HA, DiMagno EP, et al, editors. The pancreas: biology, pathobiology, and disease. 2nd ed. New York: Raven Press; 1993. p. 931–78.
18. Stabile BE, Morrow DJ, Passaro E. The gastrinoma triangle: operative implications. Am J Surg 1984;147:25–31.
19. Pipeleers-Marichal M, Somers G, Willems G, et al. Gastrinomas in the duodenums of patients with multiple endocrine neoplasic type 1 and the Zollinger-Ellison syndrome. N Engl J Med 1990;322:723–7.
20. Galbut DL, Markowitz AM. Insulinoma: diagnosis, surgical management and long-term followup. Am J Surg 1980; 139:682.
21. Service FJ, Dale AJ, Elveback LR, Jiang N. Insulinoma: clinical and diagnostic features of 60 consecutive cases. Mayo Clin Proc 1976;51:417–29.
22. Lips CJM, Koppeschaar HPF, Berends MJH, et al. The importance of screening for the MEN 1 syndrome: diagnostic results and clinical management. Henry Ford Hosp Med 1992;40:171–2.
23. Leichter SB. Clinical and metabolic aspects of glucagonoma. Medicine 1980;59:100.
24. Boden G. Glucagonomas and insulinomas. Gastroenterol Clin North Am 1989;18:831.
25. Long RG, Bryant MG, Mitchell SJ, et al. Clinicopathological study of pancreatic and ganglioneuroblastoma tumors secreting vasoactive intestinal polypeptide (VIPomas). BMJ 1981;282:1767.
26. Rivier J, Spress J, Thorner M, Vale W. Characterization of a growth-hormone releasing factor from a human pancreatic islet cell tumor. Nature 1982;300:276.
27. Sano T, Sasa SL, Kovacs K. Growth hormone releasing-producing tumors: clinical, biochemical and morphological manifestations. Endocr Rev 1988;9:357–73.
28. Vinik AI, Strodel WE, Eckhauser FE, et al. Somatostatinomas, PPomas, neurotensinomas. Semin Oncol 1987;14:263.
29. Larsson LI, Hirsch MA, Holst J, et al. Pancreatic somatostatinoma clinical features and physiologic implications. Lancet 1977;1:666.
30. Eckhauser FE, Cheung PS, Vinik AI, et al. Nonfunctioning malignant neuroendocrine tumors of the pancreas. Surgery 1986;100:978.
31. Friesen SR, Tomita T, Kimmel JR. Pancreatic polypeptide update: its role in detection of the trait for multiple endocrine adenopathy syndrome, type I and pancreatic polypeptide-secreting tumors. Surgery 1983;94:1028–37.
32. Langstein HN, Norton JA, Chiang HCV, et al. The utility of circulating levels of human pancreatic polypeptide as a marker of islet cell tumors. Surgery 1990;108:1109–16.
33. Mutch MG, Frisella MM, DeBenedetti MK, et al. Pancreatic polypeptide is a useful plasma marker for radiographically evident pancreatic islet cell tumors in patients with multiple endocrine neoplasia type 1. Surgery 1997;112:1012–20.
34. Williams ED, Sanders M. The classification of carcinoid tumors. Lancet 1963;1:238–40.
35. Duh Q-Y, Hybarger CP, Geist R, et al. Carcinoid associated with multiple endocrine neoplasia syndromes. Am J Surg 1987;154:142–8.
36. Thompson GB, van Heerden JA, Martin JK, et al. Carcinoid tumors of the gastrointestinal tract: presentation, management and prognosis. Surgery 1985;98:1054–63.
37. Bilchik HJ, Nilsson V, Modlin IM, et al. H2-receptor blockade induces peptide YY and enteroglucagon gastric carcinoids in mastomys. Surgery 1989;106:1119–27.
38. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome: results of a 10 year prospective study. Ann Surg 1992;215:8–18.
39. Solcia E, Capella C, Fiocca R, et al. Gastric argyrophil carcinoidosis in patients with Zollinger-Ellison syndrome due to type 1 multiple endocrine neoplasia: a newly recognized association. Am J Surg Pathol 1990;16:503–13.
40. Hershon KS, Kelly WA, Shaw CM, et al. Prolactinomas as part of the multiple endocrine neoplasia syndrome. Am J Med 1983;74:713–20.
41. Scheithauer BW, Laws J, Kovacs K, et al. Pituitary adenomas of the multiple endocrine neoplasia type I syndrome. Semin Diagn Pathol 1987;4:205–11.
42. Fig LM, Gross D, Shapiro B, et al. Adrenal localization in the adrenocorticotropic hormone-independent Cushing syndrome. Ann Intern Med 1988;109:547–53.
43. Perry RR, Nieman LK, Cutler GB, et al. Primary adrenal causes of Cushing's syndrome: diagnosis and surgical management. Ann Surg 1989;210:59–68.
44. Flack MR, Oldfield EH, Cutler GB Jr, et al. Urine free cortisol in the high-dose dexamethasone suppression test for the differential diagnosis of the Cushing syndrome. Ann Intern Med 1992;116:211–7.
45. Oberg K, Skogseid B, Ericksson N. Multiple endocrine neoplasia type I. Acta Oncol 1989;28:383–7.
46. Doherty GM, Olson JA, Frisella MM, et al. Lethality of multiple endocrine neoplasia type 1. World J Surg 1998;22:581–6.
47. Rizzoli R, Green J III, Marx SJ. Primary hyperparathyroidism in familial multiple endocrine neoplasia type I: long-term follow-up of serum calcium levels after parathyroidectomy. Am J Med 1985;78:467–74.
48. Hellman P, Skogseid B, Oberg K, et al. Primary and reoperative parathyroid operations in hyperparathyroidism of multiple endocrine neoplasia type 1. Surgery 1988;124:993–9.
49. Wells SA Jr, Farndon JR, Dale JK, et al. Long-term evaluation of patients with primary parathyroid hyperplasia managed by total parathyroidectomy and heterotopic autotransplantation. Ann Surg 1980;192:451.
50. Miller DL, Doppman JL, Shawker TH, et al. Localization of parathyroid adenomas in patients who have undergone surgery. Part I. Noninvasive imaging methods. Radiology 1987;162:133–7.
51. Miller DL, Doppman JL, Krudy AG, et al. Localization of parathyroid adenomas in patients who have undergone surgery. Part II. Invasive procedures. Radiology 1987; 162:138–41.
52. Skogseid B, Oberg K, Eriksson B, et al. Surgery for asymptomatic pancreatic lesion in multiple endocrine neoplasia type 1. World J Surg 1996;20:872–7.
53. Weber HC, Venzon DJ, Lin J-T, et al. Determinants of

metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995;108:1637–49.
54. Lowney JK, Frisella MM, Laimore TC, Doherty GM. Islet cell tumor metastasis in multiple endocrine neoplasia type I: correlation with primary tumor size. Surgery 1998; 124:1043–9.
55. Metz DC, Pisegna JR, Fishbeyn VA, et al. Current maintenance doses of omeprazole in Zollinger-Ellison syndrome are too high. Gastroenterology 1992;103:1498–508.
56. Maton PN, Dayal Y. Clinical implications of hypergastrinemia. In: Dannenberg A, Zakim D, editors. Peptic ulcer and other acid-related diseases. New York: New York Academic Research Association; 1991. p. 213–46.
57. Mignon M, Ruszniewski P, Podevin P, et al. Current approach to the management of gastrinoma and insulinoma in adults with multiple endocrine neoplasia type I. World J Surg 1993;17:489–97.
58. O'Riordain DS, O'Brien T, VanHerrden JA, et al. Surgical management of insulinoma associated with multiple endocrine neoplasia type 1. World J Surg 1994;18:488–94.
59. Maton PN. The use of the long-acting somatostatin analogue octreotide in patients with islet cell tumors. Gastroenterol Clin North Am 1989;18:897–922.
60. Holst JJ. Glucagon-producing tumors. In: Cohen S, Soloway RD, editors. Hormone-producing tumors of the gastrointestinal tract. New York: Churchill Livingston; 1985. p. 57.
61. Norton JA, Kahn CR, Schieberger R, et al. Amino acid deficiency and skin rash associated with glucagonoma. Ann Intern Med 1979;91:213–5.
62. Boden G, Shimoyama R. Somatostatinoma. In: Cohen S, Soloway RD, editors. Hormone-producing tumors of the gastrointestinal tract. New York: Churchill Livingstone; 1985. p. 85.
63. Yim JH, Siegel BA, DeBenedetti MK, et al. Prospective study of the utility of somatostatin receptor scintigraphy in the evaluation of patients with multiple endocrine neoplasia type I. Surgery 1998;124:1037–42.
64. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 1980;303:1189.
65. Doherty GM, VIPoma, glucaginoma and other rare islet cell tumors. In: Doherty GM, Skogseid BM, editors. Surgical endocrinology. Philadelphia: Lippincott, Williams and Wilkins; 2001. p. 375–80.
66. Eriksson B, Oberg K, Alm G, et al. Treatment of malignant endocrine pancreatic tumors with human leukocyte interferon. Lancet 1986;2:1307–9.
67. Moertel CG. An odyssey in the land of small tumors. J Clin Oncol 1987;5:1502–22.
68. Moertel CG, May GR, Martin JK, et al. Sequential hepatic artery occlusion and chemotherapy for metastatic carcinoid tumor and islet cell carcinoma. Proc Am Soc Clin Oncol 1985;4:80.
69. The BT, Zedenius J, Kytola S, et al. Thymic carcinoids in multiple endocrine neoplasia type 1. Ann Surg 1998;228: 99–105.
70. Skogseid B, Grama D, Rastad J, et al. Operative tumour yields obviates preoperative pancreatic tumor localization in multiple endocrine neoplasia type 1. J Intern Med 1995;238:281–8.
71. Wiedenmann B, Jensen RT, Mignon M, et al. General recommendations for the preoperative diagnosis and surgical management of neuroendocrine gastroenteropancreatic tumors. World J Surg 1998;22:309–18.

17

Multiple Endocrine Neoplasia Type II Syndromes

JEFFREY F. MOLEY, MD
STEVEN R. HUNT, MD

EPIDEMIOLOGY AND CLINICAL FEATURES

The multiple endocrine neoplasia (MEN) type II syndromes include types IIA and IIB and familial, non-MEN medullary thyroid carcinoma (FMTC). These are autosomal dominant inherited syndromes that are caused by germline mutations in the *RET* proto-oncogene. The hallmark of these syndromes is the development of medullary thyroid carcinoma (MTC), which is multifocal and bilateral and occurs at a young age. In patients affected by MEN types IIA and IIB or FMTC, there is complete penetrance of MTC; all persons who inherit the disease allele develop MTC. Other features of the syndromes are variably expressed, with incomplete penetrance. These features are summarized in Table 17–1.

In MEN type IIA, all patients develop multifocal, bilateral MTC (Figure 17–1), against a background of C-cell hyperplasia. Approximately 42% of affected patients develop pheochromocytomas, which may also be multifocal and bilateral and are associated with adrenal medullary hyperplasia. Hyperparathyroidism develops in 25 to 35% of patients and is caused by hyperplasia, which may be asymmetric, with one or more glands becoming enlarged. Cutaneous lichen amyloidosis has been described in some patients with MEN type IIA. In this entity, macular amyloidosis presents as brownish plaques of multiple tiny papules, usually in the interscapular area. Microscopically, these lesions demonstrate a hyperplastic epidermis, acanthosis, lymphocytic infiltrate, and amyloid goblets. Lastly, Hirschsprung's disease is infrequently associated with MEN type IIA. This disease is characterized by absence of autonomic ganglion cells within the distal colonic parasympathetic plexus, resulting in obstruction and megacolon (Figure 17–2).[1]

In MEN type IIB, as in type IIA, all patients who inherit the disease develop MTC. All MEN type IIB individuals develop mucosal neuromas, whereas 40 to 50% of patients develop pheochromocytomas. These patients often have a distinct physical appearance with a prominent mid-upper lip, prominent eyelids, and multiple tongue nodules. A marfanoid body habitus, with a relatively small torso and long limbs, is also associated with MEN. MEN type IIB patients do not develop hyperparathyroidism. MTC in MEN type IIB patients develops at a very young age, in infancy, and appears to be the most aggressive form of hereditary MTC, although its aggressiveness may be more related to the extremely early age of onset rather than to the biologic virulence of the tumor. Once it presents clinically, MTC in patients with MEN type IIB is rarely curable.

FMTC is characterized by the development of MTC without any other endocrinopathies. MTC in these patients has a later age of onset and a more indolent clinical course than MTC in patients with MEN types IIA and IIB. Occasional patients with FMTC will never manifest clinical evidence of MTC (symptoms or a palpable neck mass), although biochemical testing and histologic evaluation of the thyroid always demonstrate MTC.

Table 17–1. CLINICAL FEATURES OF SPORADIC MTC, MEN TYPES IIA AND IIB, AND FMTC

Clinical Setting	Features of MTC	Inheritance Pattern	Associated Abnormalities	Genetic Defect
Sporadic MTC	Unifocal	None	None	Somatic *RET* mutations in > 20% of tumors
MEN type IIA	Multifocal, bilateral	Autosomal dominant	Pheochromocytomas, hyperparathyroidism	Germline missense mutations in extracellular cysteine codons of *RET*
MEN type IIB	Multifocal, bilateral	Autosomal dominant	Pheochromocytomas, mucosal neuromas, megacolon, skeletal abnormalities	Germline missense mutation in tyrosine kinase domain of *RET*
FMTC	Multifocal, bilateral	Autosomal dominant	None	Germline missense mutations in extracellular or intracellular cysteine codons of RET

FMTC = familial, non-MEN medullary thyroid carcinoma; MTC = medullary thyroid carcinoma; MEN = multiple endocrine neoplasia.
Reproduced with permission from Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. Curr Probl Surg 1999;36:653–764.

Medullary Thyroid Carcinoma

Twenty-five percent of all MTC cases are familial in origin. MTC originates from the parafollicular cells, or C cells, of the thyroid. These cells comprise 1% of the total thyroid mass and are dispersed throughout the gland, with the highest concentration in the upper poles. The C cells produce, store, and secrete calci-

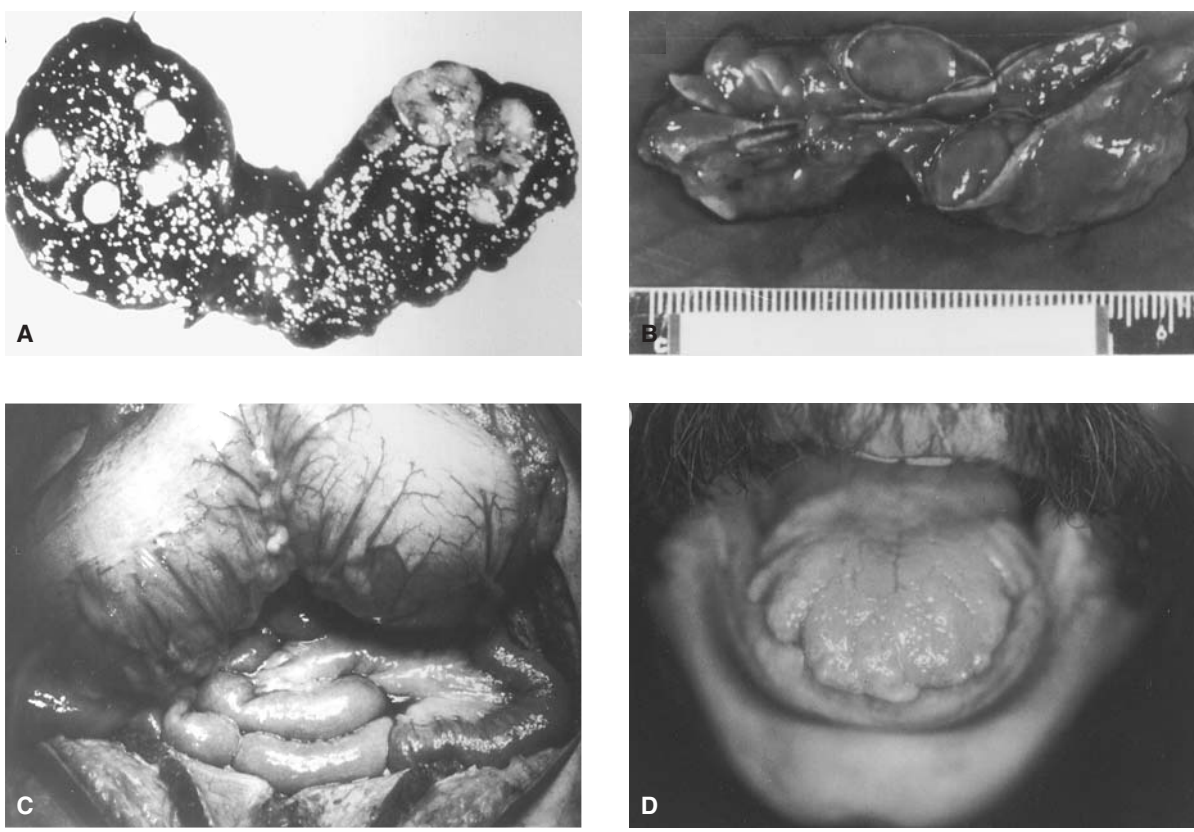


Figure 17–1. Features of patients with hereditary MTC. *A*, Bisected thyroid gland from a patient with multiple endocrine neoplasia (MEN) type IIA showing multicentric, bilateral foci of medullary thyroid carcinoma. *B*, Adrenalectomy specimen from patient with MEN type IIB demonstrating pheochromocytoma. *C*, Megacolon in patient with MEN type IIB. *D*, Midface and tongue of patient with MEN type IIB showing characteristic tongue notching secondary to plexiform neuromas. *A* courtesy of Dr. S. A. Wells. *B*, *C*, and *D* courtesy of Dr. R. Thompson. Reproduced with permission from Moley JF. Medullary thyroid cancer. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997.

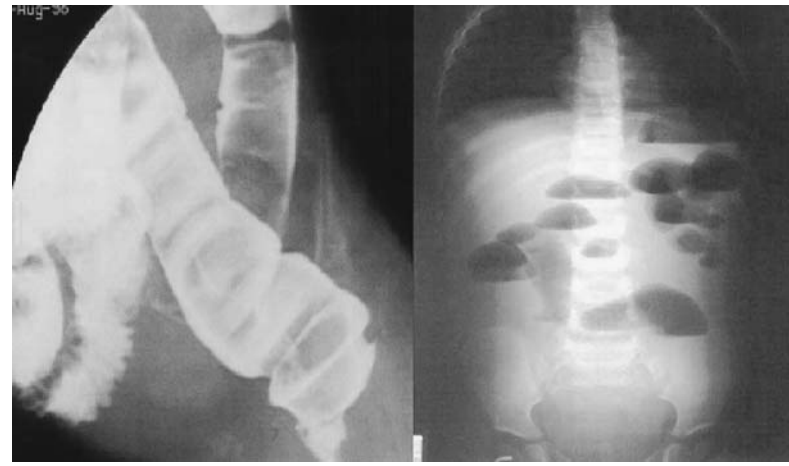


Figure 17–2. Abdominal radiographs from a 1-month-old child with multiple endocrine neoplasia type IIA and Hirschsprung's disease. Note narrowing of rectosigmoid with proximal dilatation (*left*) and multiple dilated loops of small bowel with air-fluid levels (*right*). Reproduced with permission from Cohen MS et al.[1]

tonin. Although calcitonin has been shown to be integral in calcium homeostasis in other vertebrate species, its role in humans is unclear. C-cell hyperplasia is the first histologic abnormality in the progression toward development of MTC. In MEN type II, C-cell hyperplasia progresses from multifocal to diffuse hyperplasia to carcinoma. A lesion can be characterized as MTC by evidence of invasion through the follicular basement membrane. MTCs are well-demarcated, firm, gray-white tumors that may have a gritty consistency owing to calcification. Histologically, MTC can be identified by calcitonin staining and by the presence of amyloid within the tumors (Figure 17–3). Hereditary MTC is often multifocal and develops within areas of C-cell hyperplasia. The hormone calcitonin is a specific tumor marker for MTC. Basal and stimulated serum calcitonin levels correspond to tumor load and are almost always elevated in patients with palpable thyroid tumors. MTCs may also secrete other hormones, including carcinoembryonic antigen. Secretory diarrhea and flushing, most often attributed to elevated calcitonin, are the main paraneoplastic manifestations of advanced MTC. These systemic symptoms have been identified in approximately 30% of patients with MTC and markedly elevated calcitonin levels.

Early diagnosis in MTC is critical as metastases occur in the early stages of disease. Lymph node metastases are rarely present in patients in whom MTC is discovered by genetic screening or by biochemical testing, without a palpable mass in the thyroid. In contrast, most cases of sporadic MTC and cases of hereditary MTC not detected by genetic screening present as a neck mass detected on physical examination. Diagnosis is made by biopsy (fine-needle aspiration cytology) and measurement of calcitonin levels.

MTC spreads within the central compartment to perithyroidal and peritracheal lymph nodes (level VI nodes) (Figure 17–4). The central compartment includes tissue on the trachea, extending laterally to the carotid sheath and from the hyoid bone to the innominate vein. Within this compartment, spread is commonly bilateral. Upper mediastinal nodes (level VII) are also frequently involved. Further lymphatic spread can also occur to the lateral neck compartment, including jugular (levels II, III, and IV), posterior triangle (level V), and supraclavicular nodes (Figure 17–5). Spread to the lower tracheobronchial lymph

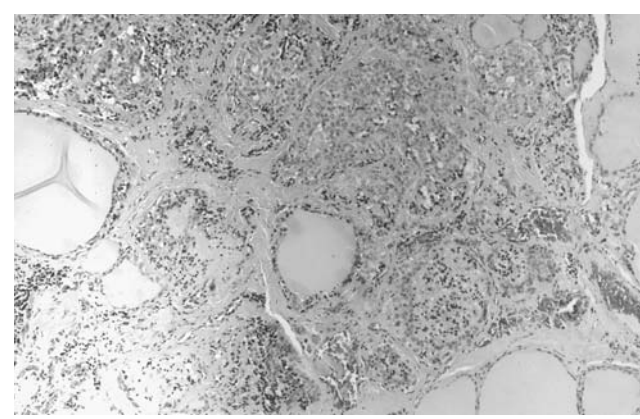


Figure 17–3. Photomicrograph of medullary thyroid carcinoma. The photomicrograph shows nests and sheets of small, uniform cells with scant to moderate amounts of amphophilic cytoplasm infiltrating around normal thyroid follicles. Reproduced with permission from Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. Curr Prob Surg 1999;36:653–764.

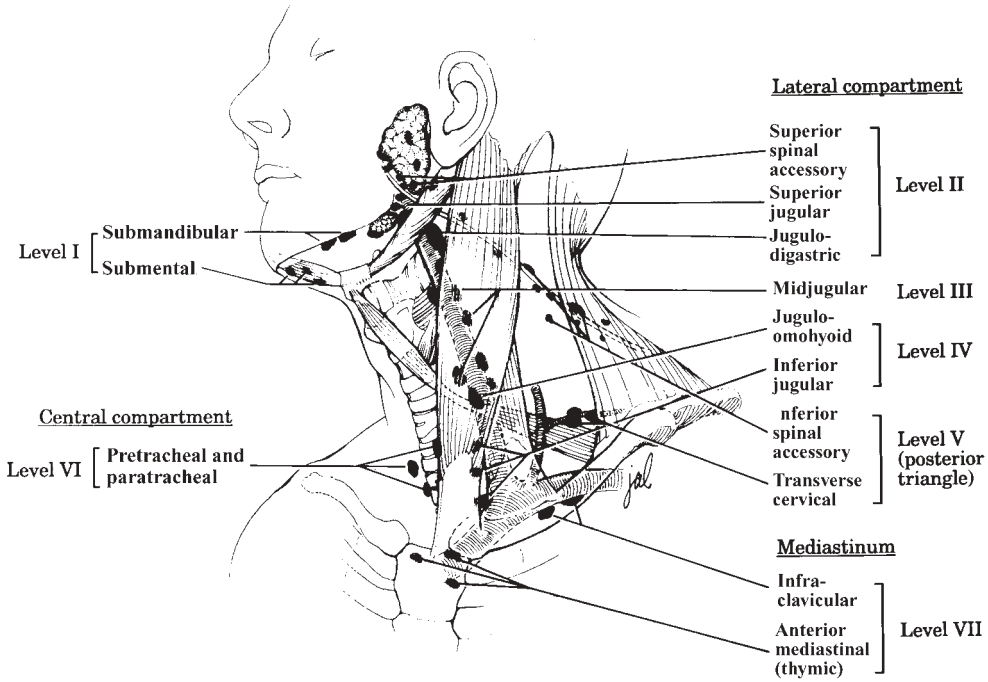


Figure 17–4. Schematic representation of the anatomic landmarks and lymph node compartments in the neck and upper mediastinum encountered in surgical reinterventions in medullary thyroid carcinoma. The central compartment is delimited inferiorly by the innominate vein, superiorly by the hyoid bone, laterally by the carotid sheaths, and dorsally by the prevertebral fascia. It comprises lymphatic and soft tissues around the esophagus as well as pretracheal and paratracheal lymph nodes, which drain the thyroid bed (level VI). The submandibular nodal group (level I) is subsumed in the central compartment by some classifications. The lateral compartments span the area between the carotid sheath, sternocleidomastoid muscle, and trapezius muscle. The inferior border is defined by the subclavian vein, and the hypoglossal nerve determines the superior boundary. The lymph node chain adjacent to the jugular vein is divided cranially to caudally in superior jugular nodes (level II), midjugular nodes (level III), and inferior jugular nodes (level IV). Lymph nodes situated in the posterior triangle between the dorsolateral sternocleidomastoid muscle, trapezius muscle, and subclavian vein are classified as level V nodes. Mediastinal lymphatic tissue is referred to as level VII lymph nodes. Reproduced with permission from Musholt TJ, Moley JF. Management of persistent or recurrent medullary thyroid carcinoma. Probl Gen Surg 1997;14:89–109.

nodes is equivalent to distant metastases. In a recent report, we analyzed the distribution of nodal metastases in a series of MTCs that presented as a palpable neck mass and in which central and bilateral cervical nodes were removed and examined histologically. We found that the incidence of central (levels VI and VII) node involvement was extremely high (79%), regardless of the size of the primary tumor. There was also frequent involvement of ipsilateral (75%) and contralateral (47%) level II, III, and IV nodes.[2]

Primary MTC and tumor in lymph node metastases may involve adjacent structures by direct invasion or compression. Structures most commonly affected include the trachea, recurrent laryngeal nerve, jugular veins, and carotid arteries. Invasion of these structures may result in stridor, upper airway obstruction, hoarseness, dysphagia, and bleeding or arterial stenosis or occlusion. MTC in the thyroid or in cervical metastases may cause localized pain.

Distant metastases to the liver, lung, adrenal glands, and bone occur with large primary lesions. In a study from a Swedish registry, it was noted that MTC patients with a palpable mass in the neck had distant metastatic disease in 20% of cases, regardless of heritability.[3] Furthermore, occult remote micrometastases are most likely the cause of most cases of persistent hypercalcitoninemia after extensive lymph node dissection.

Pheochromocytoma

Pheochromocytomas occur in 40 to 50% of patients with MEN types IIA and IIB, with the incidence increasing with age. Pheochromocytomas develop

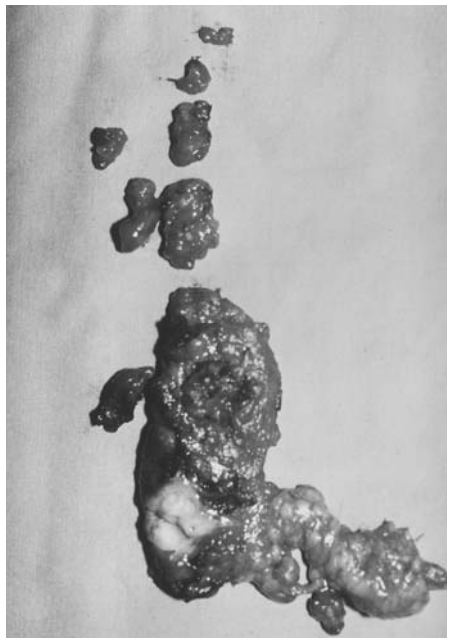


Figure 17–5. Photograph of left level III and IV nodes from a patient with medullary thyroid carcinoma. A large metastatic deposit can be seen in the lower portion of the nodal groups. Reproduced with permission from Moley JF and DeBenedetti MK.[2]

from the catecholamine-secreting adrenal medullary cells. They are hormonally active and can present with classic signs and symptoms of excess catechol secretion: hypertension, headache, heart palpitations, anxiety, and tremulousness. Complications of unrecognized disease include malignant hypertension, stroke, myocardial infarction, and cardiac arrhythmias. There are frequent reports of sudden death in patients with known or unsuspected pheochromocytomas who have undergone unrelated surgical procedures or during childbirth.

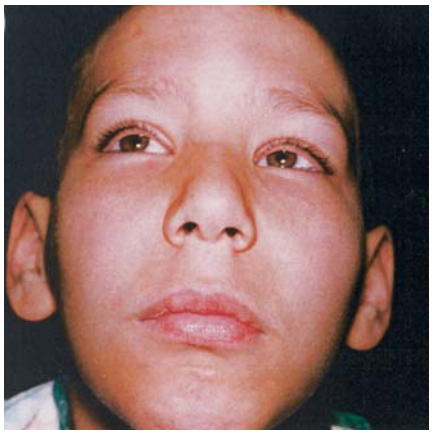
Pheochromocytomas rarely precede the development of C-cell abnormalities in MEN type II syndrome as nearly all patients with pheochromocytomas have at least biochemical evidence of C-cell hyperplasia.[4] Approximately 10% of MEN type II patients present with signs or symptoms of pheochromocytomas that precede those of MTC. As with the thyroid C cells, adrenal medullary cells undergo similar, predictable, morphologic changes in the development of a pheochromocytoma. Histologically, the lesion progresses from diffuse hyperplasia to nodular hyperplasia, with nodules > 1 cm being defined as pheochromocytomas. In MEN type II, pheochromocytomas are often multifocal, with bilateral tumors occurring in more than half of those patients who develop pheochromocytomas. As opposed to the sporadic form of the disease, malignant and extra-adrenal pheochromocytomas are very rare within MEN type II populations. The frequency of development of pheochromocytomas varies among MEN type II kindreds, with some kindreds displaying the tumor as the dominant characteristic. In MEN type II patient populations, pheochromocytomas may be clinically silent in up to 60% of cases.[5] However, multiple biochemical markers for this tumor exist, including epinephrine, norepinephrine, dopamine, vanillylmandelic acid, and metanephrines.

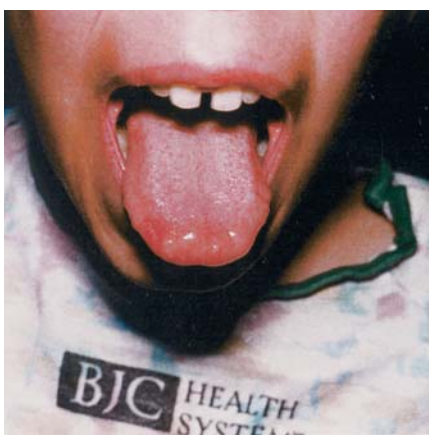
Parathyroid Disease

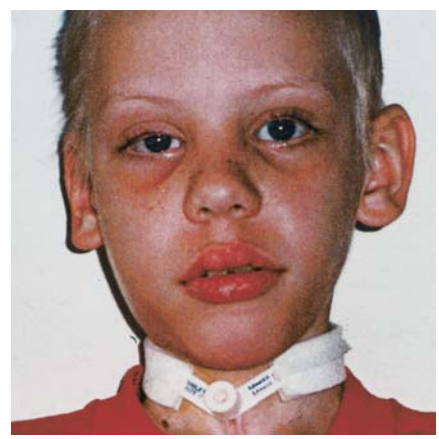
Hyperparathyroidism occurs in 25 to 35% of patients with MEN type IIA. Parathyroid hormone is secreted by the parathyroid glands and is integral in calcium homeostasis. Serum excess of this hormone can lead to hypercalcemia and its associated symptomatology, such as renal stone formation, osteopenia, and mental status changes. Unlike MEN type I, hyperparathyroidism is rarely the initial presenting problem in patients with MEN type IIA. Hyperparathyroidism in MEN type IIA is characterized by multiglandular hyperplasia. Fewer than one in five patients have a single parathyroid adenoma. Parathyroid hyperplasia is not found in patients with sporadic MTC or in patients with MTC in MEN type IIB. Parathyroid hyperplasia, in the absence of hyperparathyroidism, is common in MEN type IIA. Many patients with MEN type IIA are found to have enlarged parathyroid glands at the time of surgery for MTC.

Phenotypic Features of MEN Type IIB

Unlike MEN type IIA and FMTC, in which patients have a normal outward appearance, MEN type IIB is distinguished by characteristic physical features (Figure 17–6). As described earlier, mucosal neuromas and a marfanoid habitus are present. The mucosal neuromas are an unencapsulated, thickened proliferation of nerves that occur principally on the lips and tongue but can also be found on the gingiva, buccal mucosa, nasal mucosa, vocal cords, and con-







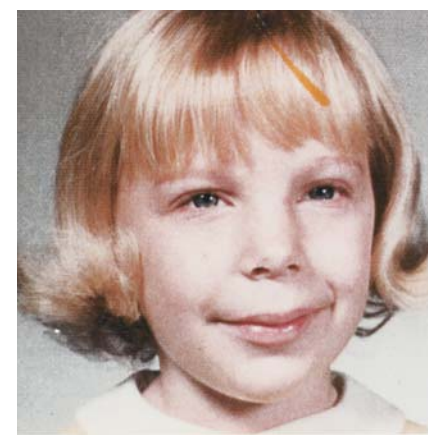


Figure 17–6. Typical facial features of multiple endocrine neoplasia type IIB patients, with a prominent mid-upper lip, everted lower eyelid, and multiple tongue nodules. Reproduced with permission from Moley JF. American Society of Clinical Oncology's Cancer Genetics and Cancer Predisposition Testing curriculum; 1998.

junctiva. MEN type IIB patients can also develop ganglioneuromas of the intestine in the submucosal and myenteric plexus. Intestinal dysfunction from ganglioneuromatosis may manifest early in life with poor feeding, failure to thrive, constipation, or pseudo-obstruction. Adults with this disorder may have dysphagia from esophageal dysmotility. Rarely, a patient can present with toxic megacolon. Neonates and infants with severe intestinal ganglioneuromatosis have a clinical course similar to that of Hirschsprung's disease.

GENETICS

MEN type II is inherited in a classic autosomal dominant mendelian fashion. Initially, using genetic linkage analysis, the genetic defect in FMTC and MEN types IIA and IIB was mapped to the centromeric region of chromosome 10. Subsequent work demonstrated that the *RET* proto-oncogene was mutated in the vast majority of MEN type II kindreds.[6,7] The *RET* gene product is a single transmembrane tyrosine kinase–linked receptor (Figure 17–7). The RET protein is expressed by a variety of cells of neural crest origin, including the thyroid C cells and the adrenal medullary cells. This gene product has a large number of cysteine residues in the extracellular domain of the protein. These residues are encoded by exons 10 and 11 of the *RET* gene. Within this cluster of cysteines, many of the known MEN type IIA and FMTC mutations are found. MEN type IIB is usually caused by a single mutation in the tyrosine kinase domain of the gene, encoded by exon 16 of the *RET* gene. *RET* mutations have been found in 97% of MEN type IIA kindreds, 95% of MEN type IIB kindreds, and 88% of those with FMTC.[8,9] Notably, the exon 16 mutation common in MEN type IIB patients has also been identified in approximately 40% of sporadic MTC tumors, where it is assumed to be a somatic, rather than an inherited, mutation in the tumor cells only.[10] Within an affected kindred, a single *RET* mutation is present, and the specific type of mutation is related to the phenotypic expression of the disease within that kindred. The aggressiveness of MTC and the

probability of developing pheochromocytoma and parathyroid disease are influenced by the specific *RET* mutation in a kindred.

In most other hereditary cancer syndromes, the genetic abnormality is a loss-of-function mutation, deletion, or rearrangement in the predisposing gene (eg, MEN type I, von Hippel-Lindau disease, retinoblastoma, and familial polyposis). In contrast, the *RET* gene is a proto-oncogene rather than a tumor suppressor gene.[11] Loss of function of the normal allele has not been demonstrated. Amplification of the mutant allele has been suggested by several recent studies.[12] *RET* gene mutations in the MEN type II syndromes lead to an alteration of function rather than a loss of function. This alteration of function predisposes cells with mutant *RET* gene-product expression to tumor formation. Given the variable expression of MEN type IIA, it is likely that other genes have an influence on the clinical expression and progression of the disease. Pheochromocytomas from patients with MEN types IIA and IIB have been shown to consistently demonstrate allelic loss of chromosome 1p, but this abnormality is noted infrequently in MTCs.[13]

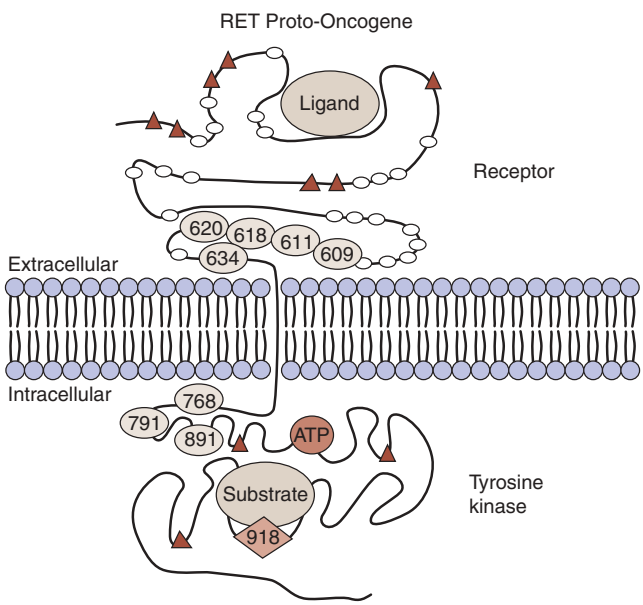


Figure 17–7. Diagram of *RET* gene product and its mutations in multiple endocrine neoplasia (MEN) type II syndrome. Ovals = locations of germline mutations found in MEN type IIA and familial, non-MEN medullary thyroid carcinoma. Diamonds = location of germline mutations in MEN type IIB. The *RET* gene product is divided into the intracellular, transmembrane, and extracellular domains. Adapted from Moley JF. Medullary thyroid cancer. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997.

Prior to the identification of specific *RET* gene mutations, researchers used linkage analysis to determine if a given patient within a MEN type II kindred had inherited the disease. This technique requires that at least four other family members are affected and is time and effort intensive. Because the mutations that cause the MEN type II syndromes occur in a limited region of the gene and are relatively few, it is now possible to define the specific mutation within almost all affected patients and then screen other family members for that same mutation. This is a much simpler approach. There are no reported cases in which a person from a kindred with a known mutation has had a negative genetic analysis and subsequently developed clinical MEN type II syndrome. Sample mix-ups may occur, however, and must be diligently prevented. Repeat, confirmatory genetic testing is often advisable.

In contrast to MEN type IIA and FMTC, 50% of mutations in MEN type IIB patients arise de novo and cannot be found on genetic screens of the patient's parents. In almost all of these cases, the mutation occured in the patient's paternal allele. In offspring of the patients with de novo mutations, the disease is passed down in a normal autosomal dominant fashion. The rate of de novo cases of MEN type IIA and FMTC is extremely low.

DIAGNOSIS

Medullary Thyroid Carcinoma

The age of onset and aggressiveness of MTC may vary considerably, depending on the clinical situation. Sporadic MTC is unilateral and unifocal in the majority of cases, whereas MTC in the MEN type II syndromes is usually bilateral and multifocal. MTC in MEN type IIA usually appears in late childhood or in the teenage years. In FMTC, the tumors are indolent and appear later in life, whereas MTC in MEN type IIB presents in infancy or early childhood, with gross evidence of cancer present in children as young as 6 months of age.

The prognosis of MTC is associated with disease stage at the time of diagnosis. Numerous studies of patients with MEN type IIA who are treated for MTC have demonstrated a direct corre-

lation between early diagnosis and cure of the disease. Patients with MEN type IIA and FMTC have a completely normal outward appearance. In these patients, the diagnosis of MTC has been made through screening efforts (measurement of calcitonin levels or *RET* gene mutation testing), undertaken because of other affected family members, or by detection of a thyroid nodule on physical examination. Over 50% of patients with MEN type IIB have normal parents, and the diagnosis in these de novo cases is not usually made until a mass is discovered in the neck. Very rarely, the diagnosis is made earlier by an astute clinician, who notes the characteristic phenotype. Most index cases of MEN types IIA and IIB and FMTC present with a thyroid mass, which is identified as MTC either on biopsy or at the time of thyroidectomy. Palpable cervical lymphadenopathy is present in over 50% of patients who present with palpable MTC, and microscopic metastases are present in 85%. Respiratory complaints, hoarseness, and dysphagia can be seen in about 13% of patients. Approximately 12 to 20% of patients with palpable MTC present with evidence of distant metastatic disease.[3,14] Relatively few index cases of MEN type II present with clinical pheochromocytoma or hyperparathyroidism.

Twenty-five percent of all patients who present with MTC have MEN type IIA or IIB or FMTC. Because of this, we feel that genetic testing should be considered in all patients with MTC. An in-depth family history with close attention to any relatives with severe hypertension or thyroid and adrenal tumors is essential. A careful review of systems to identify any evidence of symptomatic pheochromocytoma or hyperparathyroidism should be conducted. The caregiver should also note any phenotypic physical characteristics that might suggest MEN type IIB. If a *RET* mutation is found on genetic screening, all family members are tested for the same mutation. Patients found to have a mutation in the *RET* proto-oncogene should undergo biochemical testing for pheochromocytoma prior to operation if possible. Failure to identify a pheochromocytoma in a patient who undergoes thyroid surgery can have disastrous consequences as induction of anesthesia may cause a catechol surge with resultant malignant hypertension and cardiac events.

Thyroid C cells and MTC cells secrete calcitonin, which has been an invaluable marker for the presence of disease in screening and follow-up settings. Peripheral serum levels of this hormone are measured by radioimmunoassay. Over 30% of patients with MTC have normal basal levels of calcitonin. Therefore, provocative calcium-pentagastrin–stimulated calcitonin tests are routinely performed. The gastric hormone pentagastrin stimulates calcitonin secretion and is widely used (with or without additional calcium infusion) as a secretagogue in provocative calcitonin stimulation tests. The development of immunoradiometric assays has greatly improved the sensitivity and specificity of the provocative calcitonin stimulation test.

Routine stimulated calcitonin testing, however, has several disadvantages. First, the test is very uncomfortable; patients often complain of nausea, diaphoresis, agitation, and urinary urgency. Historically, members of MEN type II kindreds at risk of inheriting the diseases were screened at early ages, usually around 5 years of age, and required annual testing until the age of 45. It is understandable, therefore, why compliance was often poor, especially among adolescents and young children. Second, because the disease is inherited in an autosomal dominant fashion, 50% of at-risk patients will never develop disease and would be spared the expense and inconvenience of routine scheduled testing if a definitive genetic test were applied. Third, calcitonin testing only detects the presence of existing disease and requires sufficient tumor mass to produce elevations of plasma calcitonin levels. On the other hand, routine genetic testing identifies *RET* mutation carriers earlier and more reliably than biochemical testing and obviates the need for continued testing in individuals found to be unaffected. Stimulated calcitonin testing remains important, however, in the follow-up of patients treated for MTC.

Genetic screening of all individuals within a known MEN type II kindred is the standard of care. If patients from a kindred with a known mutation are shown not to have inherited the mutation, they need no further follow-up. Controversy exists over the management of patients found to have a *RET* mutation with no clinical or biochemical evidence of dis-

ease. At present, we recommend in-depth genetic counseling and encourage prophylactic thyroidectomy in childhood for carriers of the mutant gene. The near-complete penetrance of MEN type II manifesting as MTC, combined with the morbidity and mortality associated with the tumor, warrants surgery before the tumor can be detected biochemically. In a study by Wells and colleagues, seven MEN type IIA kindreds were evaluated by genetic screening.[15] Twenty-one patients had *RET* mutations and were offered prophylactic thyroidectomy. Thirteen patients opted for surgery and all were found to have either C-cell hyperplasia or foci of MTC on pathologic examination. Of these 13 patients, only 7 had abnormal calcium-pentagastrin–stimulated calcitonin testing preoperatively. Recent studies have shown that 10% of patients diagnosed by abnormal biochemical testing had metastatic MTC despite diligent screening.[16]

Pheochromocytoma

Biochemical screening for pheochromocytoma is best done by measurement of plasma or 24-hour urine catecholamines and metanephrines. This test should be done on an annual basis. If this test is negative, no further workup is necessary until the next year. If the test is positive or borderline, imaging is needed to determine if a pheochromocytoma is present. Almost all patients with MEN types IIA and IIB have some degree of adrenal medullary hyperplasia and may have borderline elevations of urinary catechols without a definite pheochromocytoma.

Adrenal computed tomography (CT) or magnetic resonance imaging (MRI) can detect tumors 1 cm or larger (Figure 17–8). Opposed-phase chemical shift MRI may distinguish a pheochromocytoma from an adrenal adenoma, which occurs in up to 9% of normal patients.[17] Radioactive iodine (^{131}I)-metaiodobenzylguanidine scanning is useful in detecting extra-adrenal pheochromocytomas, although extra-adrenal tumors are extremely rare in patients with MEN types IIA and IIB.

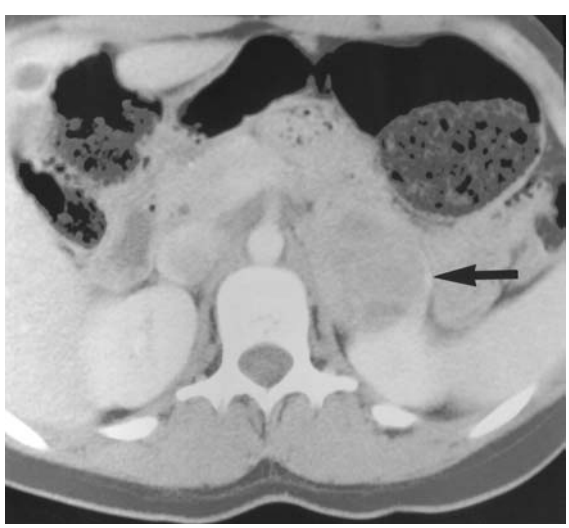


Figure 17–8. Adrenal computed tomographic scan showing a large left adrenal pheochromocytoma in a patient with multiple endocrine neoplasia type IIA.

Parathyroid Disease

All known MEN type IIA carriers should be screened annually for the presence of hyperparathyroidism by serum calcium measurements. Parathyroid hormone levels should be measured if the serum calcium is high or borderline.

MEDICAL AND SURGICAL THERAPY

Medullary Thyroid Carcinoma

Recommended surgical treatment of MTC is influenced by several factors. First, the clinical course of MTC is usually more aggressive than that of differentiated thyroid cancer, with higher recurrence and mortality rates. Second, MTC cells do not take up radioactive iodine, and radiation therapy and chemotherapy are ineffective. Third, MTC is multicentric in 90% of patients with the hereditary forms of the disease. Fourth, in patients with palpable disease, over 70% have nodal metastases. Lastly, the ability to measure postoperative stimulated calcitonin levels has allowed assessment of the adequacy of surgical extirpation. Screening for pheochromocytoma should be done before performing thyroid surgery. If patients are found to have evidence of pheochromocytoma, adrenal surgery with perioperative alpha-blockade should precede other procedures.

Preventive thyroidectomy is recommended before age 6 years in patients with MEN type IIA and FMTC. Patients with MEN type IIB should undergo thyroidectomy during infancy because of

the aggressiveness and earlier age of onset of MTC in these patients. These procedures are best performed by surgeons experienced in thyroid surgery in children as finding the parathyroids can be extremely difficult owing to their small size and translucent appearance.

Thorough surgical extirpation is the only curative treatment for MTC. In patients without a palpable neck mass who are found to be carriers of a *RET* mutation by genetic testing, total thyroidectomy and central node dissection are recommended. At our institution, total parathyroidectomy with autotransplantation is often done at the same time as total thyroidectomy for MTC. This is because the parathyroid glands are closely associated with perithyroidal lymph nodes and preservation of these glands is difficult if the central nodes are removed. The vascular supply to a parathyroid gland may be interrupted by dissection and excision of perithyroidal and central nodes. Parathyroid glands are therefore removed and preserved in cold saline at the time of thyroidectomy for MTC. The glands are sliced into 20 1×3 mm fragments and autotransplanted into the muscle of the nondominant forearm (in patients with MEN type IIA) or sternocleidomastoid muscle (in patients with FMTC or MEN type IIB). Patients are maintained on calcium and vitamin D supplementation for 4 to 8 weeks postoperatively. In a recent series of thyroidectomies performed in 13 patients with hereditary MTC identified by genetic screening, total thyroidectomy and central node dissection with parathyroidectomy and parathyroid autografting were performed in all patients. All patients were normocalcemic after stopping calcium supplementation 8 weeks postoperatively.[12] In other series, the percentage of patients requiring calcium supplementation following parathyroidectomy with parathyroid autografting has ranged from 0 to 18%.[15] Other experts in this field attempt to preserve the glands with vascular supply intact during thyroidectomy for MTC. Parathyroidectomy with autotransplantation should be done in all patients with gross parathyroid enlargement or biochemical evidence of parathyroid disease at the time of operation for MTC.

In patients who present with palpable thyroid masses, the risk of more extensive nodal metastatic disease is increased. In the past, authors have recommended total thyroidectomy with node dissections only if nodes are clinically palpable. This is an effective strategy for differentiated thyroid cancer, for which suppression with thyroxine and radioactive iodine ablation are extremely effective adjuncts to surgery, but MTC cells do not respond to these nonsurgical treatments. Surgery is the only effective therapeutic modality for MTC at the present time. Overall, persistent disease, evidenced by elevation of calcitonin levels, is present in over 50% of patients following surgery for MTC. In the absence of effective adjuvant therapy, there is a need to better define or predict the extent of spread of these tumors at the time of diagnosis so that appropriate operative resection can be performed.

There is a high incidence of metastatic disease in central and bilateral level II to V lymph nodes in patients with palpable tumors. Based on these results, our recommendation for patients who present with palpable MTC is total thyroidectomy, parathyroidectomy with autotransplantation, central neck dissection (right and left levels VI and VII), and ipsilateral or bilateral level II to V node dissections, depending on the extent of nodal involvement apparent at operation. The central node dissection encompasses all tissue from the level of the hyoid bone superiorly to the innominate vessels inferiorly and laterally to the carotid sheaths (Figure 17–9). Nodal tissue on the

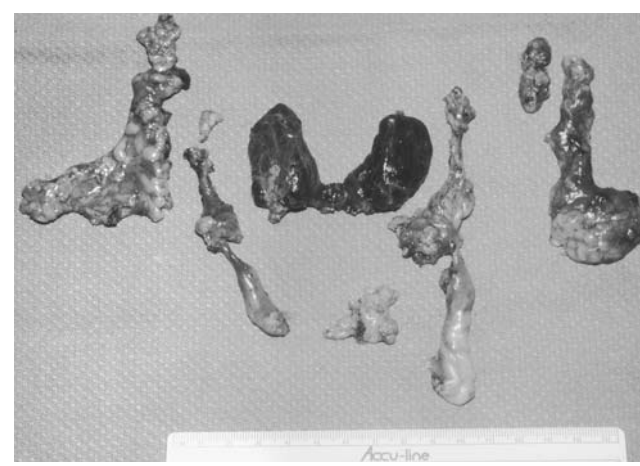


Figure 17–9. Total thyroidectomy and central (levels VI and VII) and bilateral level II to V node dissections from a thin young male with multiple endocrine neoplasia type IIA and bilateral palpable thyroid masses (parathyroids not shown). Microscopic metastases were present in all nodal groups. Reproduced with permission from Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. Curr Probl Surg 1999;36:653–764.

anterior surface of the trachea is removed, exposing the superior surface of the innominate vein behind the sternal notch. Fatty and nodal tissue between the carotid artery and the trachea is removed, including paratracheal nodes along the recurrent nerves. On the right, the junction of the innominate and right carotid arteries is exposed, and on the left, nodal tissue is removed to a comparable level behind the head of the left clavicle. A systematic approach to the removal of all nodal tissue in these patients has been reported to improve recurrence and survival rates when compared retrospectively with procedures in which only grossly involved nodes were removed.[19]

PERSISTENT OR RECURRENT DISEASE

Patients who present with palpable MTC often have elevated calcitonin levels following primary surgery, indicating residual or recurrent MTC. Currently, there is no defined role for chemo- or radiation therapy in these patients. Reoperation for patients with recurrent disease can be done with curative or palliative intent. Evidence of distant metastases is a contraindication to surgery unless some palliative benefit can be identified (Figure 17–10). Two such indications are to prevent compromise of the airway and to debulk large tumors that cause profuse, intolerable diarrhea secondary to hormone secretion. If no evidence of distant metastases is found in a patient who has not had previous cervical node dissections, re-exploration of the neck with completion of node dissection is an option for patients with persistent or recurrent elevations of calcitonin. At our institution, metastatic workup consists of neck, chest, and abdominal CT or MRI. We have not found octreotide, technecium/thallium, or [^{18}F]fluorodeoxyglucose positron emis-

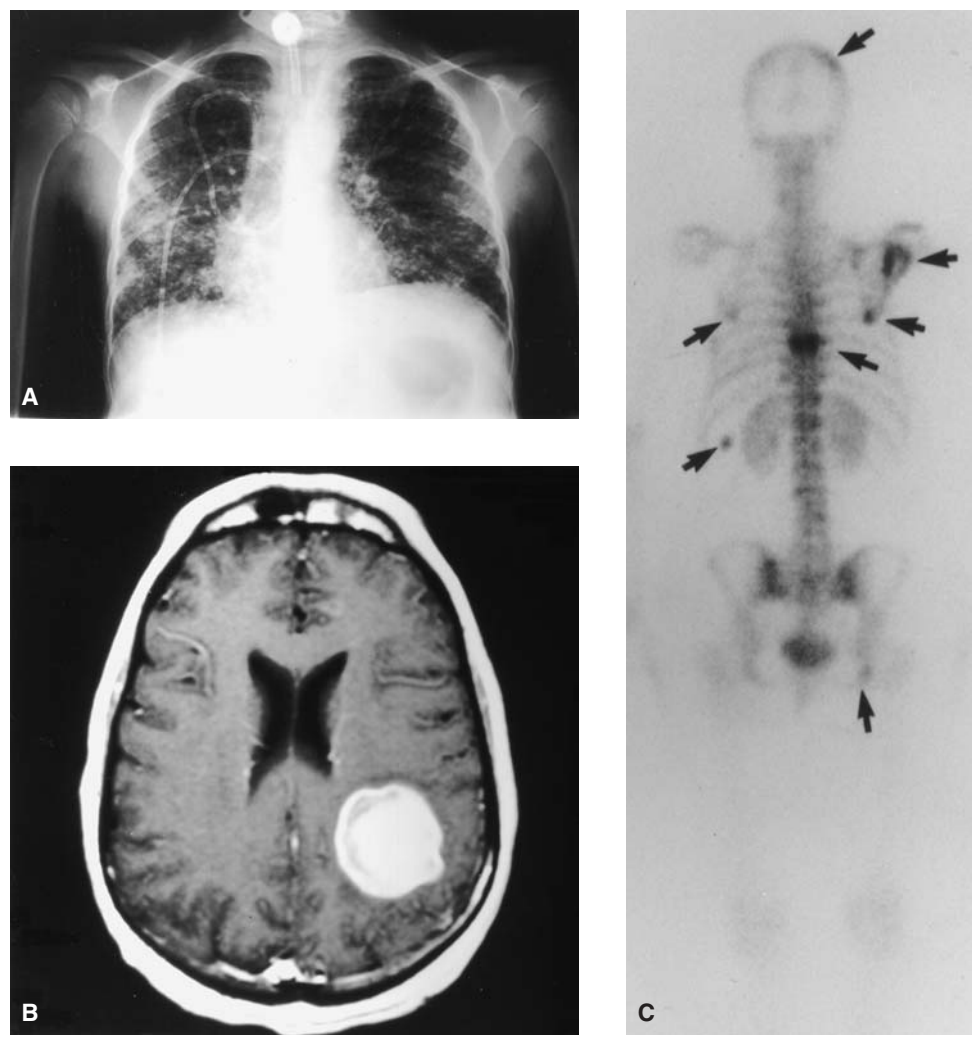


Figure 17–10. Distant metastatic disease in patients with medullary thyroid carcinoma (MTC). *A*, Radiograph of lymphangitic pulmonary spread in a child with multiple endocrine neoplasia (MEN) type IIB and MTC. *B*, Sonogram of solitary brain metastasis in a patient with MEN type IIA and MTC. *C,* Multiple skeletal metastases in a patient with sporadic MTC. Reproduced with permission from Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. Curr Probl Surg 1999;36:653–764.

sion tomography to be more sensitive than CT or MRI. If no evidence of metastatic disease is found, surgery with completion node dissections is discussed with the patient as an option. In patients with elevated calcitonin levels only and no palpable or imageable disease, observation is another option.

Diagnostic laparoscopy with direct examination of the liver is extremely useful in detecting distant metastases in these patients prior to reoperation on the neck (Figure 17–11). We have found liver metastases at laparoscopy in 25% of patients with persistent elevation of calcitonin levels despite negative CT or MRI of the liver.[20] If the laparoscopy shows no evidence of metastatic disease, re-exploration of the neck may be performed with removal of any residual nodal tissue. Our approach to the nodal dissection is governed by the previous operation performed and by imaging studies, which can often localize recurrent disease in the neck (Figure 17–12). Our first priority in reoperations is to identify and remove any thyroid or nodal tissue in the central and lateral compartments that was not resected at the first operation (Figure 17–13).

Pheochromocytoma

Partial or complete adrenalectomy is recommended in patients with MEN types IIA and IIB who are found to have a pheochromocytoma. It is important to medically stabilize the patient prior to surgery to avoid any perioperative events owing to excessive catechol secretion. Preoperative alpha-blockade is achieved by administration of phenoxybenzamine (40 to 200 mg/day) for 5 days to 2 weeks prior to surgery. The dose is titrated to the lowest blood pressure tolerated by these patients without symptomatic relative hypotension. Should tachycardia or cardiac arrhythmia result from treatment with phenoxybenzamine, a β-blocker is added to the treatment regimen. After medical stabilization, the patient is taken for operation. During the procedure, it may be necessary to control intraoperative paroxysmal hypertension with short-acting antihypertensives such as sodium nitroprusside or phentolamine.

Traditionally, controversy has existed as to whether unilateral or bilateral adrenalectomy should be performed for unilateral tumors. In a series at our institution, the results of unilateral and bilateral adrenalectomies were compared.[21] Nearly one-quarter of patients undergoing bilateral adrenalectomy experienced at least one episode of acute adrenal insufficiency requiring hospitalization. Two of these patients died from episodes of adrenal insufficiency. Of the patients who had unilateral adrenalectomies, 52% developed contralateral pheochromocytomas after a mean interval of 12 years. Conversely, 48% of patients remained disease free by biochemical and symptomatic standards during a mean interval of 5 years. Based on these results, it is our practice to perform resection

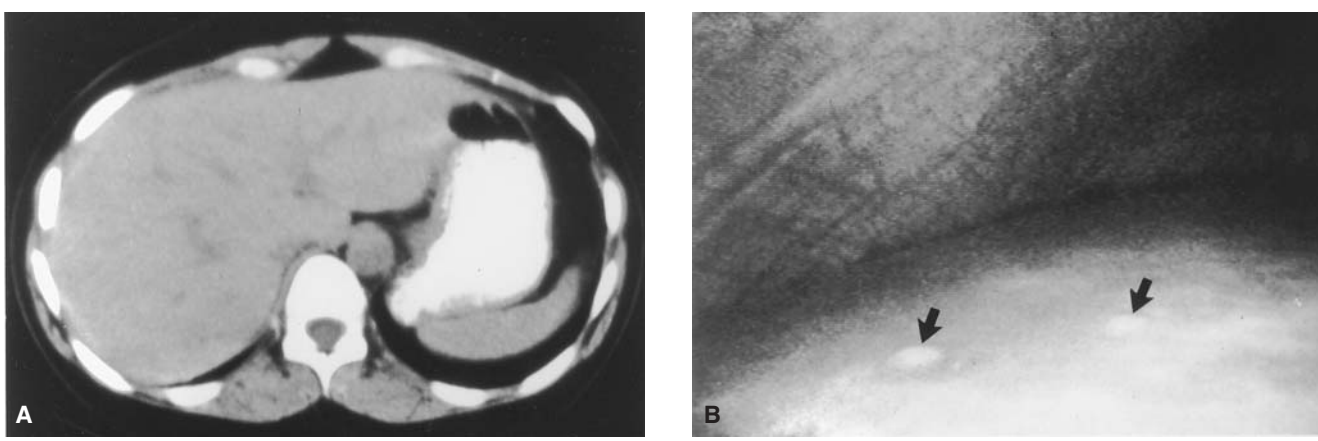


Figure 17–11. *A*, Computed tomographic (CT) scan of the liver of a patient with multiple endocrine neoplasia type IIA, recurrent medullary thyroid carcinoma (MTC), and elevated calcitonin levels. There is no evidence of liver metastases on the scan. *B*, Laparoscopic view of the liver of the same patient showing multiple small raised whitish lesions on and just beneath the surface of the liver, confirmed to be metastatic MTC by biopsy. These small multiple metastases (*arrows*) are often not seen on routine CT scanning or other imaging modalities, including nuclear scanning. Reproduced with permission from Tung WS et al.[19]

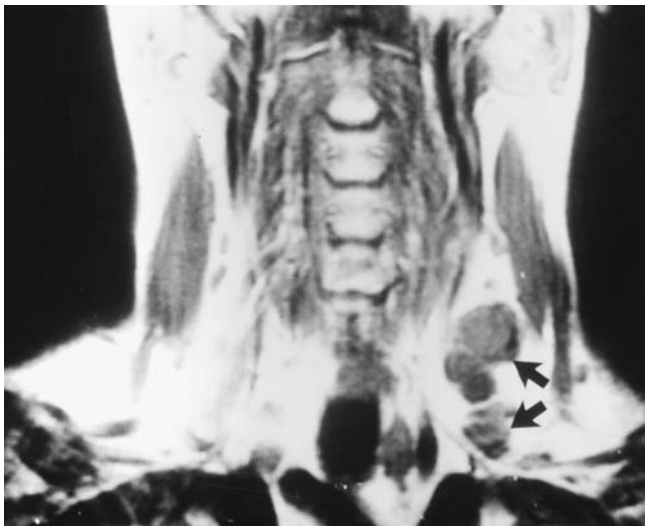


Figure 17–12. Coronal magnetic resonance image showing left-sided jugular nodal metastases (*arrows*) (levels III and IV) from medullary thyroid carcinoma (MTC) in a patient with multiple endocrine neoplasia type IIA many years after total thyroidectomy for MTC. Calcitonin levels are now elevated. Reproduced with permission from Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. Curr Probl Surg 1999;36:653–764.

of the involved adrenal only and maintain yearly biochemical screening thereafter.

The classic surgical approach for adrenalectomy in MEN type II patients is through an anterior abdominal midline incision. The first report of successful laparoscopic removal of adrenal tumors was by Gagner and colleagues in 1992.[22] Since then, several studies have demonstrated the safety and efficacy of laparoscopic adrenalectomy for benign adrenal neoplasms. Patients with MEN types IIA and IIB may be ideally suited to the laparoscopic approach because the pheochromocytomas arising in these syndromes are rarely malignant and almost never extra-adrenal. Pheochromocytomas may be successfully removed by unilateral or bilateral laparoscopic adrenalectomy provided that the adrenal tumors are small, confined to the adrenal gland(s), and accurately localized preoperatively by high-resolution CT or MRI and the patient is adequately prepared pharmacologically. Laparoscopic adrenalectomy is associated with shorter hospital stay, decreased postoperative pain, and more rapid recovery when compared with open adrenalectomy.[23,24] Contraindications to the laparoscopic approach include large tumors (> 8 to 10 cm), malignant pheochromocytomas, and existing contraindications to laparoscopy.

Parathyroid Disease

The need for isolated parathyroidectomy in MEN type II patients is rare. As discussed above, we usually perform routine total parathyroidectomy with

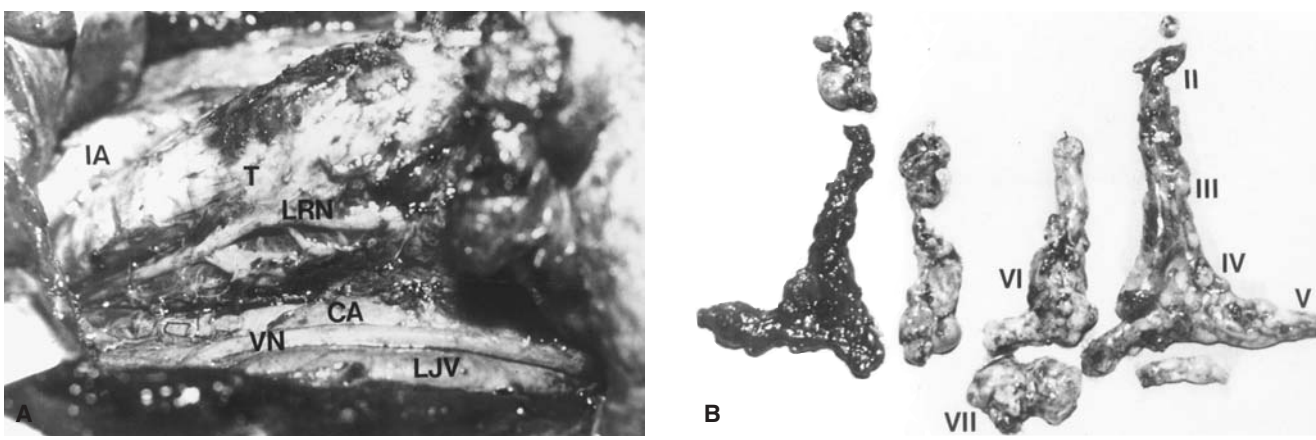


Figure 17–13. This patient with multiple endocrine neoplasia (MEN) type IIB had recurrent elevation of calcitonin levels 20 years after total thyroidectomy for medullary thyroid cancer (MTC). Redo central neck dissection and bilateral functional neck dissections (microdissection) were performed. *A*, View of the trachea and dissected central and left paratracheal compartment. The photograph was taken from the patient's left side. The patient's head is to the right and the chest is to the left. CA = left carotid artery; IA = innominate vein; LJV = left jugular vein; LRN = left recurrent laryngeal nerve; T = trachea; VN = left vagus nerve. Note markedly enlarged nerves characteristic of MEN type IIB. *B*, Surgical specimen from the same patient. The photograph shows central and upper mediastinal nodes (level VII), bilateral paratracheal nodes (level VI), and bilateral jugular chain and posterior triangle nodes (levels II, III, IV, and V). Microscopic foci of MTC were found in paratrachal dissection specimens. Reproduced with permission from Moley JF. Medullary thyroid cancer. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 108–18.

autotransplantation at the time of thyroidectomy, regardless of gross appearance of the parathyroid glands. Should hyperparathyroidism occur at a later time in these patients with forearm grafts, surgical removal of a portion of the graft can be done under local anesthetic in an outpatient setting. If, at the time of the initial neck exploration, the parathyroids are left in situ, subsequent development of hyperparathyroidism requires re-exploration of the neck with identification and removal of all four glands followed by autotransplantation.

COMPLICATIONS AND POSTOPERATIVE CARE

The complications and immediate postoperative care in surgery for the various endocrinopathies in MEN type II are similar to those described in more detail in the previous chapters dealing with each specific disease. In thyroidectomy for MEN type II–related MTC, the complications include injury to the recurrent laryngeal nerve, hypocalcemia secondary to parathyroid damage, and compromise of the airway secondary to hematoma formation. These complications are very unusual in the hands of an experienced thyroid surgeon. If both recurrent nerves have been injured (which may occur in a patient after multiple operations or extensive tumor involvement), a tracheostomy may be necessary. Fiberoptic laryngoscopy is done to monitor vocal cord function.

After total thyroidectomy with parathyroid autotransplantation, it is necessary to supplement calcium, vitamin D, and thyroid hormone. Calcium and vitamin D supplementation is withdrawn 4 to 8 weeks postoperatively as the parathyroid grafts begin to function. Lifelong thyroid replacement is required.

The long-term postoperative care for MEN type II patients demands a close and lifelong relationship between the care provider and the patient. Yearly screenings for MTC recurrences and other manifestations of the syndrome must still be conducted. After thyroidectomy for MTC, calcitonin levels should be documented in the immediate postoperative period and should be followed closely. If a patient is found to have persistent or elevated calcitonin levels postoperatively, an extensive physical examination and imaging workup for focal and metastatic disease must be conducted, as outlined in the previous section.

In patients who have undergone adrenalectomy for pheochromocytoma, routine yearly plasma or 24-hour urine screens must be performed to rule out a contralateral tumor. If catecholamines or metanephrines become elevated, MRI or CT should be repeated to localize the tumor.

MEN type IIA patients must have lifelong screening for evidence of hyperparathyroidism. In patients with MEN type IIB or FMTC who have had a thyroidectomy, they need not undergo further testing once normal postoperative parathyroid function can be established.

PROGNOSIS

Patients with MEN type IIA and FMTC have a better long-term outcome than patients with MEN type IIB or sporadic tumors. Within these clinical settings, however, there is variation. Particularly in the sporadic cases, the disease is unpredictable, and patients may survive many decades or die within several years after presentation. In the MEN type II population, with the relatively recent widespread use of biochemical and genetic screening modalities and related changes in treatment for patients identified by these methods, long-term prognosis in these patients has yet to be established. Prior to the use of these screening techniques, average life expectancy was 50 years for patients with MEN type IIA and 30 years for patients with MEN type IIB. As more kindreds are followed by genetic and biochemical screening, the long-term prognosis for MEN type II patients in the modern era of treatment should become more clear.

CONCLUSIONS

The identification of mutations in the *RET* proto-oncogene associated with MEN types IIA and IIB and FMTC has led to a new paradigm in surgery: the performance of an operation based on the result of a genetic test. Prophylactic thyroidectomy based on direct mutation analysis appears to be curative in MEN type IIA and FMTC patients when they are

screened at a young age. The application of meticulous reoperative strategies for persistent hypercalcitoninemia, combined with more accurate staging studies, has led to better patient selection for surgery and improved outcome.

REFERENCES

1. Cohen MS, Phay JE, Albinson C, et al. Gastrointestinal manifestations of multiple endocrine neoplasia type 2. Ann Surg 2002;235:648–54; discussion 654–5.
2. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg 1999;229:880–8.
3. Bergholm U, Adami HO, Bergstrom R, et al. Clinical characteristics in sporadic and familial medullary thyroid carcinoma. A nationwide study of 249 patients in Sweden from 1959 through 1981. Cancer 1989;63:1196–204.
4. Gagel RF, Tashjian AH Jr, Cummings T, et al. The clinical outcome of prospective screening for multiple endocrine neoplasia type 2a. An 18-year experience. N Engl J Med 1988;318:478–84.
5. Hill CS Jr, Ibanez ML, Samaan NA, et al. Medullary (solid) carcinoma of the thyroid gland: an analysis of the M. D. Anderson Hospital experience with patients with the tumor, its special features, and its histogenesis. Medicine 1973;52:141–71.
6. Mulligan LM, Kwok JB, Healey CS, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature 1993;363:458–60.
7. Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum Mol Genet 1993;2:851–6.
8. Mulligan LM, Eng C, Healey CS, et al. Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat Genet 1994;6:70–4.
9. Eng C, Smith DP, Mulligan LM, cheumann et al. Point mutation within the tyrosine kinase domain of the RET proto-oncogene in multiple endocrine neoplasia type 2B and related sporadic tumours [published erratum appears in Hum Mol Genet 1994;3:686]. Hum Mol Genet 1994; 3:237–41.
10. Hofstra RM, Landsvater RM, Ceccherini I, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature 1994;367:375–6.
11. Santoro M, Carlomagno F, Romano A, et al. Activation of RET as a dominant transforming gene by germline mutations of MEN2A and MEN2B. Science 1995;267: 381–3.
12. Koch CA, Huang SC, Moley JF, et al. Allelic imbalance of the mutant and wild-type RET allele in MEN 2A-associated medullary thyroid carcinoma. Oncogene 2001; 20:7809–11.
13. Moley JF, Brother MB, Fong CT, et al. Consistent association of 1p LOH with pheochromocytomas from patients with MEN-2 syndromes. Cancer Res 1992;52:770–4.
14. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. Medicine 1984;63: 319–42.
15. Wells SA Jr, Chi DD, Toshima K, et al. Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. Ann Surg 1994; 220:237–50.
16. Ledger GA, Khosla S, Lindor NM, et al. Genetic testing in the diagnosis and management of multiple endocrine neoplasia type II. Ann Intern Med 1995;122:118–24.
17. Staren ED, Prinz RA. Selection of patients with adrenal incidentalomas for operation. Surg Clin North Am 1995;75: 499–509.
18. Wells SA, Ross AJ, Dale JK, Gray RS. Transplantation of the parathyroid glands: current status. Surg Clin North Am 1979;59:167–77.
19. Dralle H, Damm I, Scheumann GF, et al. Compartment-oriented microdissection of regional lymph nodes in medullary thyroid carcinoma. Surg Today 1994;24:112–21.
20. Tung WS, Vesely TM, Moley JF. Laparoscopic detection of hepatic metastases in patients with residual or recurrent medullary thyroid cancer. Surgery 1995;118:1024–9; discussion 1029–30.
21. Lairmore TC, Ball DW, Baylin SB, Wells SA Jr. Management of pheochromocytomas in patients with multiple endocrine neoplasia type 2 syndromes. Ann Surg 1993; 217:595–603.
22. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma [letter]. N Engl J Med 1992;327:1033.
23. Guazzoni G, Montorsi F, Bocciardi A, et al. Transperitoneal laparoscopic versus open adrenalectomy for benign hyperfunctioning adrenal tumors: a comparative study. J Urol 1995;153:1597–600.
24. Prinz RA. A comparison of laparoscopic and open adrenalectomies. Arch Surg 1995;130:489–94.

18

Neuroendocrine Tumors of the Gastrointestinal System (Carcinoid Tumors)

LAURENT BRUNAUD, MD
ORLO H. CLARK, MD

Gastroenteropancreatic neuroendocrine tumors (NETs) are malignant tumors derived from neoplastic proliferation of cells of the diffuse neuroendocrine system. These cells have been called enterochromaffin or Kulchitsky's cells. They are ubiquitous throughout the gastrointestinal tract, urogenital tract, and bronchial epithelium and are considered to be the largest endocrine organ of the human body (Figure 18–1).[1–3] The neuroendocrine system has been described as a diffuse network of nerve and endocrine cells with a common phenotype characterized by the simultaneous expression of general protein markers and hormonal products specific to each neuroendocrine cell.[4] NETs have subsequently been reported in a wide range of organs. However, this chapter focuses on NETs of the gastrointestinal tract (gut). We use the traditional classification of gut-related NETs because the biologic behavior of these tumors is related to their site of origin.[5,6] We excluded pheochromocytomas, small cell tumors of the lung, and pancreatic endocrine tumors (or islet cell tumors, including gastrinomas).

Lubarsh was the first to describe a clinical case of carcinoid disease, but it was in 1907 that Oberndorfer used for the first time the word "karzinoid," or cancer-like, to describe a set of ileal tumors that behaved in a more benign manner than carcinomas.[7] These tumors are relatively slow growing, have specific vascular features, and have a high density of somatostatin receptors. About 80% of gut-derived NETs originate in one of four different locations: bronchus/lung, jejunoileum, appendix, or rectum. A marked increase in the percentage of lung/bronchial tumors (11 to 32%) and a decrease in the percentage of appendiceal NETs (38 to 8%) have been lately observed, the latter because prophylactic appendectomy is no longer routinely done during gynecologic procedures (Figure 18–2).[8]

CLASSIFICATION

In 1963, Williams and Sandler classified carcinoids according to their embryologic site of origin.[9] They proposed that tumors be classified into foregut

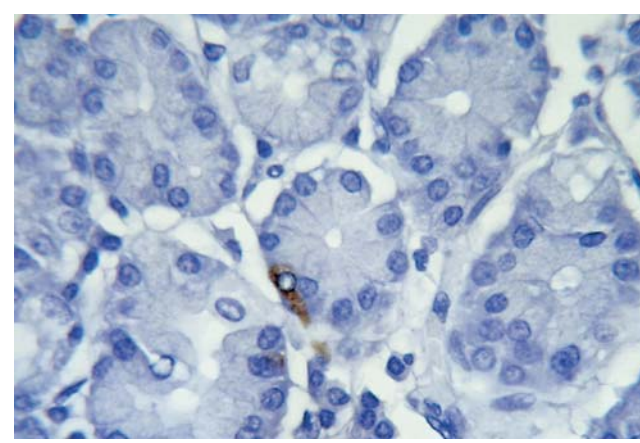


Figure 18–1. Enterochromaffin cell (*brown signal*) from normal antral mucosa (*blue color*) with staining for chromogranin A (chromogranin immunoperoxidase; ×400 original magnification). Courtesy of L. Antunes, MD, PhD, Department of Pathology, Nancy, France.

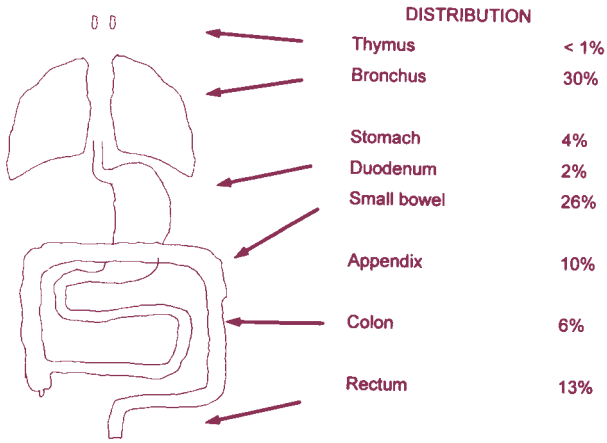


Figure 18–2. The distribution of gastrointestinal neuroendocrine tumor (NET) (percentage of NET of all locations).

(including the respiratory tract, thymus, stomach, and pancreas), midgut (including the small intestine, appendix, and right colon), and hindgut (including the transverse and descending colon, sigmoid, and rectum). It has become apparent, however, that the general term carcinoid fails to describe the diverse spectrum of neoplasms with regard to functional state, localization, derivation from various segments of the primitive embryonal gut, growth pattern, degree of differentiation, expression of different neuroendocrine marker molecules, and prognosis.[10] A new classification therefore emerged in 1995, which includes not only the site of origin but also variations in the histologic characteristics of carcinoid tumors.[4,11] Using this system, carcinoid tumors are classified as well-differentiated NETs and well-differentiated (low grade) and poorly differentiated (high grade) neuroendocrine carcinomas (Table 18–1). Today, the term carcinoid tumor is used for many different kinds of NETs, which is confusing. The term carcinoid tumor should preferably be used for classic midgut carcinoids, whereas other types of carcinoids should be termed NETs followed by their primary location, for example, neuroendocrine thymic, gastric, small bowel, or rectal tumor.[5] Atypical or anaplastic NETs with nuclear atypia, necrosis, and increased mitotic activity are classified as well- or poorly differentiated neuroendocrine carcinomas.[8,12]

PATHOGENESIS AND PATHOLOGY

The genetic mechanisms involved in tumorigenesis of carcinoid tumors remain to be elucidated.[7] The vast majority of cases are sporadic, although familial cancer syndromes associated with an increased risk of carcinoid tumors occur in multiple endocrine neoplasia (MEN) types I and II and in von Recklingausen's disease (duodenum).[13–15] Interestingly, most of the carcinoids associated with MEN type I have been reported to be of foregut origin (thymus, bronchus, and stomach).[15] MEN type I syndrome is attributable to mutations in a 10-exon gene located on chromosome 11q13 that encodes a nuclear protein (Menin) that represses Jun D transcriptional activity.[16] Tumor development in MEN type I is thought to follow Knudson's two-hit hypothesis, that is, individuals affected by familial MEN type I inherit one inactive MEN type I allele; tumorigenesis in specific tissues then occurs after inactivation of the remaining wild-type allele, which can begin in just one cell.[16] MEN type I gene involvement was confirmed in MEN type I pancreatic tumors but has not been confirmed for thymic carcinoid tumors.[17,18] Moreover, recent studies in sporadic carcinoid tumors showed a loss of heterozygosity at the *MEN1* locus in 26 to 78% of these tumors. Mutations were identified at this locus using other techniques in 18% of cases.[19,20] These alterations of the *MEN1* gene have been found in only a subset of foregut sporadic tumors.[21] This shows that *MEN1* gene alterations are also an event in sporadic carcinoid tumor carcinogenesis.[19] Links

Table 18–1. CLASSIFICATION OF NEUROENDOCRINE TUMORS OF THE JEJUNUM AND ILEUM

Benign: Nonfunctioning, well-differentiated small tumor (≤ 1 cm) within the mucosa-submucosa but without angioinvasion. Usually serotonin-producing tumors in the terminal ileum.

Benign or low grade malignant: Nonfunctioning, well-differentiated tumor of intermediate size (> 1 up to 2 cm) but without angioinvasion or extension beyond the submucosa. Usually serotonin-producing tumors of the terminal ileum.

Low grade malignant: (1) Nonfunctioning, well-differentiated large tumor (> 2 cm) or extending beyond the submucosa or angioinvasive (or both). Usually serotonin-producing tumors of the terminal ileum. (2) Functioning, well-differentiated tumor of any size and extension.

High grade malignant: Functioning or nonfunctioning poorly differentiated intermediate or small cell carcinoma.

between carcinogenesis (familial or sporadic tumors) and the *MEN1* gene could be explained by growth factor–related angiogenesis (vascular endothelial growth factor, fibroblastic growth factor, and transforming growth factor), but this relation is difficult to confirm experimentally.[22]

Gains of chromosomes 4, 5, and 19 and losses of chromosome 18 by comparative genomic hybridization have recently been associated with sporadic NETs.[14,23,24] Some of these genetic alterations were shared by foregut and midgut tumors, whereas others discriminated between the two groups.[23] Nuclear oncogenes *NMYC*, *BCL2*, and *CJUN*, as well as *HER2/neu*, have been reported to be overexpressed in cell lines derived from carcinoid tumors.[3] However, in contrast to a number of nonendocrine tumors, neither common oncogenes (*RAS, SRC*) nor common tumor suppressor genes (*P53*) are generally important in the molecular pathogenesis of carcinoid tumors except for the more atypical forms.[19]

Although the histogenesis of NETs is incomplete and varies from organ to organ, it appears that carcinoid tumors and naive endocrine cells arise from the same progenitor cell.[3,10] Although controversial, it appears that NETs and low-grade neuroendocrine carcinomas arise from orthotopic neuroendocrine cells of the epithelium of the respective organs, whereas high-grade neuroendocrine carcinomas derive from a putative stem cell rather than from a neuroendocrine cell.[25] Carcinoid tumor cells have been termed enterochromaffin cells because they stain with potassium chromate. They also take up and reduce silver and are thus termed argentaffin cells. Some tumor cells take up silver but are unable to reduce it and are termed argyrophilic (Figure 18–3).[1]

Because all neuroendocrine cells possess small synaptic vesicles regardless of their state of differentiation, it is essential to use both conventional histologic diagnosis and immunohistochemistry for cytosolic markers such as neuron-specific enolase (NSE) and for granular markers such as chromogranin or synaptophysin.[26] The immunohistologic detection of at least two or three markers is required for an accurate final diagnosis.[27] The exact function of enterochromaffin cells is unknown, but carcinoid tumor cells are able to produce amines and peptides by amine precursor uptake and decarboxylation.[28] Furthermore, carcinoid tumor cells are typically found to contain numerous membrane-bound neurosecretory granules containing hormones and biogenic amines including serotonin, corticotropin, histamine, dopamine, substance P, neurotensin, prostaglandin, kallikrein, and ghrelin.[12,29] Foregut NETs generally have a low serotonin content and occasionally secrete 5-hydroxytryptophan or adrenocorticotrophic hormone (ACTH). Midgut NETs have a high serotonin content and infrequently secrete hydroxytryptophan or ACTH. Hindgut NETs usually contain somatostatin or peptide YY but rarely contain serotonin, hydroxytryptophan, or ACTH.[26] Tumor cells not only make various peptides but also express many cell-surface peptide

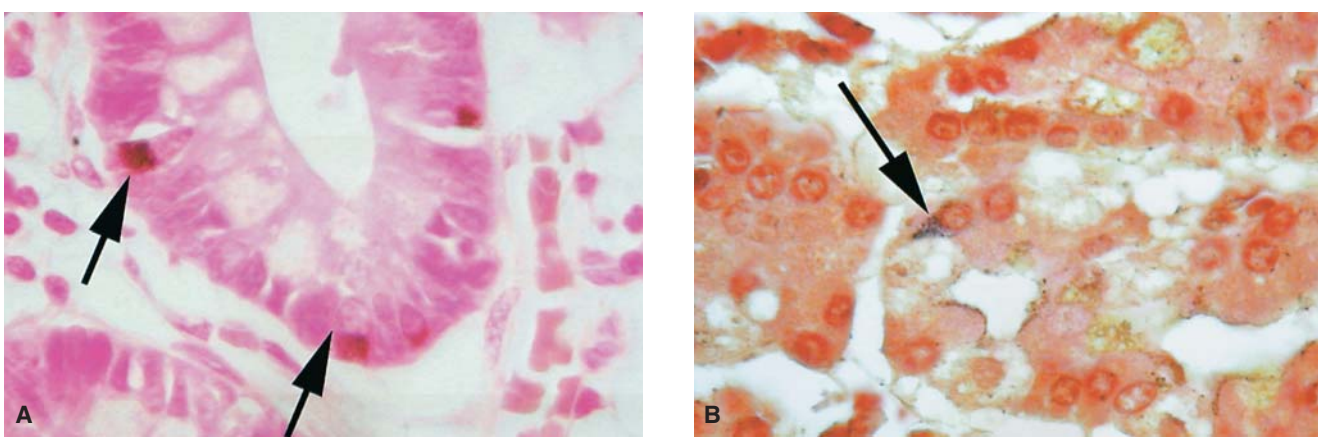


Figure 18–3. Argentaffin and argyrophil enterochromaffin cells. *A*, Enterochromaffin cells (*arrows*), termed argentaffin cells because they take up and reduce silver (Fontana-Masson stain; ×400 original magnification). *B*, Enterochromaffin cells (*arrow*), termed argyrophilic because they take up silver but are unable to reduce the silver (Grimelius' stain; ×400 original magnification). Courtesy of L. Antunes, MD, PhD, Department of Pathology, Nancy, France.

receptors. These membrane receptors enable the tumor cells to respond to several growth factors.[1] The release of serotonin and other vasoactive substances into the systemic circulation results in the carcinoid syndrome, with manifestations of episodic flushing, wheezing, diarrhea, and eventual valvular heart disease (primarily mitral).[12]

PROGNOSIS

Virtually all NETs are malignant, although most are low grade and associated with a good prognosis.[19,30] Malignancy is clearly determined when there is invasion, lymph node involvement, or liver metastases. Generally, routine histopathology is unreliable in predicting tumor aggressiveness. Malignancy is suggested by a size > 2 cm in most locations except the ileum, where nearly all tumors can metastasize.[3] There is a clear correlation between carcinoid tumor mass and urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, which is one of the breakdown products of serotonin excreted in the urine.[26] The presence of the carcinoid syndrome adversely influences survival.

Identifying molecular alterations or other factors that categorize patients with aggressive tumors could be of great clinical value, allowing more aggressive treatment.[19] In general, all cytosolic and granular markers are found in well-differentiated endocrine tumors. In poorly differentiated neuroendocrine carcinomas, however, only cytosolic markers and synaptophysin are generally widely expressed. These markers are useful tools for the assessment of the neuroendocrine nature of such tumor cells almost void of granule markers or specific hormone.[26] The presence or type of a somatic *MEN1* mutation has not been correlated with disease phenotype and, to date, has no role for carcinoid tumors in clinical prognosis.[16] Recently, loss of neuropilin 2 expression in neuroendocrine cells has been shown to accompany tumor progression in NET.[31] Moreover, MIB-1 antibody reacts with the Ki-67 nuclear protein associated with cell proliferation and has been used to profile tumor aggressiveness. The combination of histologic grade, size, number of mitoses, and number of Ki-67–positive cells predicted tumor behavior in 80 of 102 (79%) gastric carcinoid tumors.[32] Although studies of Ki-67 have been helpful in assessing the malignant behavior of neuroendocrine tumors, multiparametric approaches examining the full range of cyclins, cyclin inhibitors, factors controlling apoptosis, oncogenes, and tumor suppressor genes will be essential to resolve this issue (Table 18–2).[33]

FOREGUT TUMORS

Thymic Neuroendocrine Tumors

Rosai and Higa were the first to acknowledge the existence of NET in the thymus and to separate them from more common tumors arising in this location.[34] Thymic NETs account for 2 to 4% of all anterior mediastinal neoplasms.[35] The male-to-female predilection is 3:1, and in MEN type I–associated tumors, the ratio is 7:1.[15,36] The disease occurs mainly in adults, with an average mean age at diagnosis of 45 years.[35,37]

Pathology

The tumors are generally described as large (2 to 20 cm), soft, and tan-brown infiltrative masses. They can display a broad range of cytologic features of atypia that are generally more pronounced than

Table 18–2. PROGNOSIS FACTORS IN NEUROENDOCRINE TUMORS OF THE GASTROINTESTINAL SYSTEM

Criteria	Survival Rate
Clinical	
Gender	Female 66% > male 47%*
Primary tumor site	Appendix > small bowel > colorectal > pancreas
Mode of discovery	Incidentally > symptomatic
Operative intent	Cure 91% > palliative 25%*
Second malignancy	No > yes
Carcinoid syndrome	No > yes
Histologic	
Depth of invasion	Minimal > extensive
Tumor size 2 cm	Less 82% > more 39%*
Histologic features	Well differentiated > poorly differentiated
Flow cytometry features	Ploidy > aneuploidy
Immunohistochemistry: Ki-67 index	Less 5% > more 5%
Lymph node metastases	No 94% > yes 43%*
Liver metastases	No 88% > yes 25%*

*5-year survival rate.

those observed in other foregut NETs. About 80% are malignant.[15] They are classified into well-, moderately, or poorly differentiated types.[35] Staining is commonly positive for chromogranin A, NSE, synaptophysin, Leu-7, and protein gene product. Other hormones that may be produced include ACTH, calcitonin, serotonin, and somatostatin.[18]

Genetic

Between 5 and 25% of all thymic NETs are associated with MEN type I, but an association with MEN type IIA has also been described.[15,36] Only about 50 cases of MEN type I–related thymic carcinoids have been described in the English literature.[38] Conclusive data on genetic alterations in thymic NETs are essentially lacking, and MEN type I–associated tumors do not appear to have somatic deletions of the wild-type allele, as would be expected.[18] Its male predominance associated with the absence of loss of heterozygosity in the MEN type I region, the clustering in some MEN type I families, and the findings of different *MEN1* mutations in these clustered families suggest the involvement of additional etiologic factors.[37]

Clinical Presentation

Most patients with thymic NETs are asymptomatic (25 to 50%) until the late stage of the disease. About 30% of them have endocrine manifestations (ectopic ACTH production, acromegaly). In contrast to sporadic cases, the MEN type I–related cases do not produce ACTH. This contributes to the late detection of these tumors.[36] Local symptoms of compression occur in only about 10% of patients.[35] The carcinoid syndrome has not been described with thymic NETs.[39]

Diagnosis

Hormone analyses should be obtained, including ACTH, urinary cortisol, and plasma chromogranins A and B. Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest is used to evaluate extension of the disease and to plan surgery. Scintigraphy with indium 111 (^{111}In)-octreotide is valuable for tumor localization but is not helpful for the differential diagnosis of thymic NET and thymoma.[18,36] Immunohistochemical studies show positive staining with neuroendocrine tumor markers such as chromogranin, pancytokeratin, and NSE.[36] The high percentage of MEN type I–associated tumors indicates the necessity of genetic testing of all patients with NETs of the thymus. To prevent the late detection of thymic NET, MRI or CT scanning of the superior mediastinum and chest should be performed in asymptomatic *MEN1* gene carriers.[39]

Treatment

Surgical removal of the primary tumor and intrathoracic lymph node metastases is the treatment of choice for patients with localized or locoregional disease. Postoperative radiotherapy may be considered for patients with incompletely resected tumors or symptoms.[40] For patients with MEN type I and primary hyperparathyroidism, prophylactic upper thymectomy should be done during neck exploration because supernumerary parathyroid glands are found in 15 to 20% of these patients and because it also removes the site where thymus tumors may develop (especially in men). Thymectomy in these patients is associated with minimal morbidity, and these thymic tumors are usually aggressive.[15,39,41]

Prognosis

The prognosis is poor, with a median survival of 28 months and an overall 5-year survival of about 30%.[35,42] Patients with Cushing's syndrome or MEN syndrome have a worse prognosis. Tumor behavior correlates closely with the histologic degree of differentiation: disease-free survival at 5 years is 50%, 20%, and 0% for well-, moderately, and poorly differentiated tumors, respectively.[35] Unresectability and advanced clinical stage are associated with decreased survival.[43]

Gastric Neuroendocrine Tumors

The gastric mucosa contains at least seven distinct types of endocrine cells (D [somastostatin] and D1 [unknown secretion] cells, G [gastrin] cells, P and X

[unknown secretion] cells, enterochromaffin [serotonin] cells, and enterochromaffin-like [ECL] [histamine] cells), which constitute about 2% of all of the mucosal cells. ECL cells represent a group of histamine-storing argyrophil cells that are present in the gastric corpus and fundus (oxyntic mucosa) and rarely in the antral mucosa.[44] ECL cells differ from gastric enterochromaffin cells.[45] Relatively little is known about ECL cell function beyond its modulation of acid secretion via histamine secretion: gastrin drives the ECL cell to secrete histamine, which then activates the histamine receptor of the adjacent parietal cells, leading to acid secretion.[46] Gastric NETs are separated into three distinct groups on the basis of both clinical and histologic characteristics. Type I is associated with chronic atrophic gastritis with or without pernicious anemia (Figure 18–4). Gastric atrophy results in hypergastrinemia because the neutral gastric pH leads to stimulation of the antral G cells to produce gastrin.[1,12] ECL cells are exquisitely sensitive to the trophic action of gastrin and thus undergo hyperplastic growth, eventually leading to dysplastic and neoplastic proliferation (ECLomas) over an average 15-year period. In patients with extensive chronic atrophic gastritis type A, fundic ECL hyperproliferation has been noted in up to half of all cases and development of ECLomas in about 10 to 30% of these patients. The most important predisposing factors appear to be the serum gastrin level and the duration of gastric atrophy.[47] However, what constitutes a dangerous degree of gastrin exposure (duration and plasma gastrin level) appears to be variable and has not yet been determined.[46] Type II tumors develop in patients with MEN type I and Zollinger-Ellison syndrome. Like type I tumors, these gastric NETs are thought to arise from ECL cells in patients with hypergastrinemia owing to the gastrinoma (instead of chronic gastric atrophy in type I). Recent reports, however, suggest that such gastric carcinoids can occur in MEN type I patients without hypergastrinemia.[44] Type III tumors are sporadic, arising in normal-appearing mucosa, and thus are independent of the trophic stimulus of gastrin.[1] The latter are more aggressive.

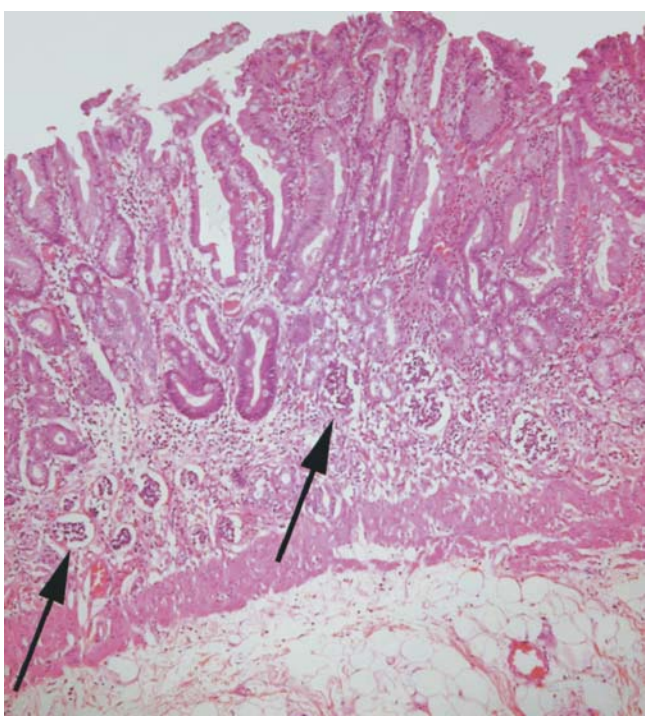


Figure 18–4. Islands of neuroendocrine cells (*arrows*) in chronic atrophic gastritis in a patient with pernicious anemia (hematoxylin and eosin; ×100 original magnification). Courtesy of L. Antunes, MD, PhD, Department of Pathology, Nancy, France.

Pathology

ECL cells are identified by silver staining techniques and more specifically by immunocytochemistry using antibodies against histamine or histidine decarboxylase. The isoform 2 of the human vesicular monoamine transporter (VMAT-2) regulates the intravesicular accumulation of histamine. Thus, VMAT-2 is considered to be the first specific immunohistochemical marker for ECL cells.[44] ECLomas occurring in type I are small, multiple polyps, often submucosal, and are usually confined to the fundus of the stomach.[48] Small (< 1 cm) tumors are considered well differentiated, limited to the mucosa/submucosa, and benign. Larger (1 to 2 cm) tumors may exhibit low-grade malignant behavior with or without vascular invasion.[46] They have a rate of lymph node invasion of 9 to 18% of the cases and are rarely (2%) associated with hepatic metastases.[47] This type constitutes the most common type of gastric NET (68 to 83%).[46] Type II and III tumors are considered to occur in 8 to 10% and 15 to 25%, respectively, of all gastric NETs.[12] In type II lesions, hyperplasia of surrounding ECL cells is specific (Figure 18–5). Invasion of the gastric wall is

limited to the mucosa in 90%, but metastases to lymph nodes are present in 30% and distant metastases occur in about 10% of cases.[49] Sporadic carcinoids (type III) are usually single, isolated tumors arising in normal gastric mucosa.[46] They are usually larger than tumors in the two other types, with a median diameter of 2 to 4 cm. These tumors behave more aggressively, are locally invasive in 15 to 64% of patients, and have distant metastases in 50 to 82% of patients.[46,48,50]

Genetic

Gastric NETs associated with Zollinger-Ellison syndrome (type II) occur almost exclusively in patients with MEN type I. This notion suggests that loss of function of one allele of the *MEN1* gene is probably required for progression to true neoplasia and that this gene may function as a tumor suppressor gene for fundic tumors in Zollinger-Ellison syndrome.[12] However, the problem may be more complex than was initially appreciated because the *MEN1* gene is not lost in some patients with type II lesions.[46] Furthermore, loss of heterozygosity analysis of the *MEN1* gene locus in MEN type I endocrine tumors of the pancreas and stomach showed different genetic alterations in the individual tumors from the same patient, indicating that each results from an independent somatic genetic event.[44]

Clinical Presentation and Diagnosis

Most gastric NETs are asymptomatic. The clinical presentation of type I or II gastric carcinoids varies widely. Symptoms include vomiting, diarrhea, gastrointestinal bleeding, or intermittent gastric outlet obstruction. Carcinoid syndrome resulting from the release of histamine or bradykinin-related peptides is rare with these tumors.[50] Some patients with this foregut-type carcinoid syndrome have an atypical erythematous geographic rash with minimal diarrhea. As previously mentioned, serum gastrin levels are elevated in both type I and II tumors. The gastric mucosa is atrophic in type I tumors and hyperplastic in type II tumors.[46] The secretin test is negative (no increase of gastrin) in patients with type I tumors and positive in patients with type II tumors. Upper gastrointestinal endoscopy determines extent of disease with biopsy of tumor(s) and also of adjacent and distant gastric mucosa and assesses tumor size, number, and histology. Endoscopic ultrasonography provides information about the location and extent of submucosal lesions and, in type II tumors, the position of coexisting pancreatic tumors. Somatostatin scintigraphy with ^{111}In-octreotide has a sensitivity of 75% and a specificity of 95% in localizing gastric NETs.[51] This localizing study also helps determine the extent of local and rarely metastatic tumors and as a baseline study for follow-up study. Patients with type III tumors usually present like patients with gastric adenocarcinomas. However, 30 to 50% of these patients may present variations of the carcinoid syndrome including food- or alcohol-induced flushing, sweating, itching, and lacrimation.[46,50]

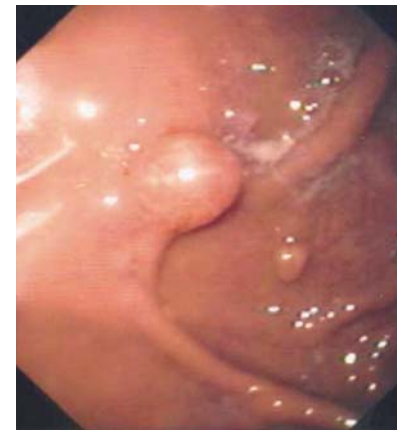


Figure 18–5. Endoscopic appearance of a gastric type II neuroendocrine tumor.

Treatment

Endoscopic polypectomy is appropriate for the management of type I and II tumors, provided that fewer than three to five noninvasive lesions are present and they are smaller than 1 cm.[46] However, some type II gastric NETs appear to regress spontaneously or after long-term treatment with somatostatin analogues.[50,52] When these tumors recur (in about 12% of cases) or when there is diffuse tumor involvement of the stomach and when there are large tumors, definitive treatment is achieved by local tumor excision and antrectomy.[48] This procedure has the dual advantage of removing the NET in addition to the

source of gastrin that stimulates its growth. Although regression of neoplastic and hyperplastic ECL cell foci in the stomach mucosa has occurred after antrectomy, this procedure is not always successful.[48] The latter probably occurs because the sustained hypergastrinemia initiates the development of intrinsic regulatory mechanisms (gastrin autocrine pathway). Consequently, residual clones of ECL cells may continue to proliferate without associated hypergastrinemia. Unfortunately, to date, there are no methods to accurately predict the behavior of ECL cell tumors, that is, whether or not they have developed gastrin independence.[46,48] For patients with advanced proliferative activity or with multiple, diffuse, or recurrent tumors, a more extensive fundic resection or even a total gastrectomy should be considered. For patients with large, invasive, and locally metastatic tumor, gastric resection and regional lymphadenectomy are indicated. This includes virtually all patients with malignant type III tumors.[48]

Prognosis

The 5-year survival rate for all types of gastric carcinoids is about 49 to 64%.[10,53] Type I tumors are usually benign, with a 5-year survival rate of 78% and an age-corrected 100% survival rate.[1,54] The metastatic rate of carcinoids associated with Zollinger-Ellison syndrome is higher than in type I lesions, but the long-term prognosis of these patients appears to be similar.[12,46] The long-term prognosis of type II disease ultimately reflects the course of MEN type I gastrinomas and thymic NETs. Patients with sporadic type III tumors have a poor prognosis, with an overall 5-year survival rate usually below 50%.[46]

Duodenal Neuroendocrine Tumors

Duodenal NETs are rare and represent < 2% of all gastrointestinal NETs. Five major types of NETs are identifiable in the duodenum.[10] Gastrin-producing tumors are most frequent (Figure 18–6). Most of the remaining tumors are rich in somatostatin, but tumors with increased serotonin production or other peptides also exist.[50] Only 92 cases of duodenal somatostatinomas have been reported in the English literature. Their designation as somatostatinomas is made on the basis of immunohistochemical staining. An important association exists between duodenal NETs and von Recklinghausen's disease. Almost 90% of duodenal NETs in patients with von Recklinghausen's disease are pure yet nonfunctioning somatostatinomas. They seem to have a predilection for the ampulla of Vater. By contrast, duodenal NETs not associated with von Recklinghausen's disease are frequently multihormonal.[55] Gangliocytic paragangliomas are predominantly immunohistochemically somatostatin and pancreatic polypeptide positive and usually behave in a benign fashion. Tumors secreting serotonin, calcitonin, or pancreatic

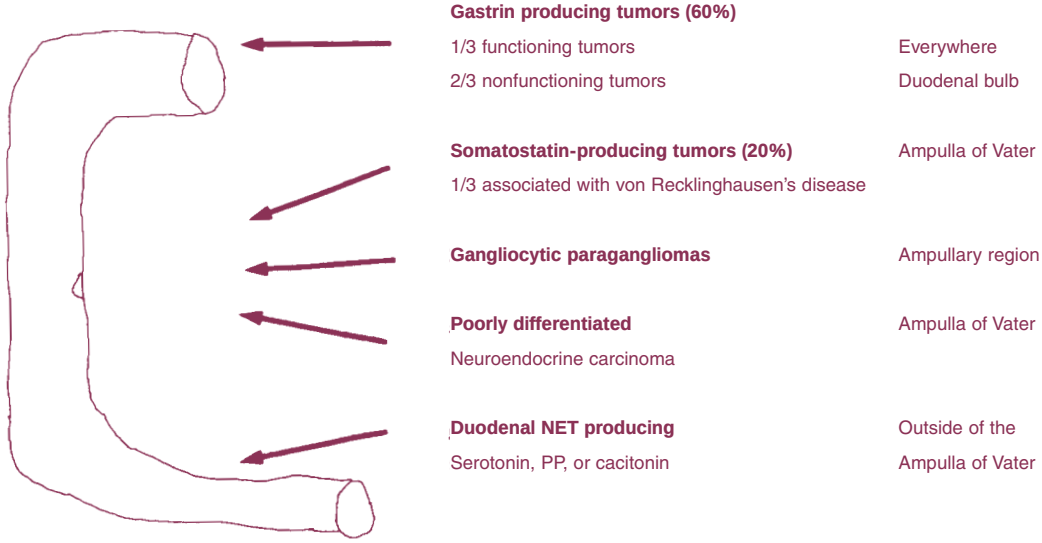


Figure 18–6. Distribution and location of duodenal neuroendocrine tumors (NETs). PP = pancreatic polypeptide.

polypeptide are very rare. Lastly, poorly differentiated neuroendocrine carcinomas are extremely rare and highly aggressive tumors.[10] Duodenal NETs are thought to be composed of cells with endocrine differentiation coming from duodenal mucosa. Carcinoid syndrome is rare with duodenal NETs.[10] The management of these lesions is determined on a case-by-case basis and is dictated by the presence of symptoms.[55,56] Negative prognosis features include tumor size > 2 cm, involvement of the muscularis propria, the presence of mitotic figures, and local or distant metastases.[10]

Pancreatic Neuroendocrine Tumors

Pancreatic NETs are rare.[10] Pancreatic NETs (carcinoid) and pancreatic endocrine tumors (islet cell tumors) are two separate entities; both, however, are NETs that share many similar biologic features, including growth patterns, ability to cause clinical syndromes, pathology, and management.[19] The distinction between these two types of tumors can be difficult or impossible based on routine histology. Although pancreatic NETs are tumors for which the specific peptide secretory product has not yet been defined, they can be defined as tumors with documented excess production of serotonin.[10,50]

Clinically, patients with pancreatic NETs typically present with pain and diarrhea. Carcinoid syndrome is uncommon (6%). These patients have more frequent distant metastases than other foregut tumors (87% versus 42% for gastric tumors) at presentation and have larger tumors (average size is 5.3 cm). Pancreatic NETs have a worse outcome than other foregut tumors, with a 10-year survival of 0 to 15%. The poor prognosis is primarily attributable to the existence of metastatic disease at diagnosis.[50,57,58]

Pulmonary Neuroendocrine Tumors

Pulmonary NETs are similar to intestinal NETs and are unrelated to smoking.[1] Pulmonary NETs account for 1 to 2% of all lung tumors. These tumors are thought to arise from neuroendocrine enterochromaffin cells located in the bronchial mucosa. Pulmonary NETs vary from well-differentiated bronchial tumors to the most malignant small cell lung cancer.[12] Pulmonary NETs are classified as typical and atypical carcinoid tumors, large cell neuroendocrine carcinomas, and small cell lung carcinomas.[18] The majority of the tumors are perihilar in location (about 70%) and appear as red vascular endobronchial polypoid tumors. Peripheal tumors often lack an identifiable connection to a bronchus.[18] Metastases (mediastinal lymph nodes, liver, bone, or skin) occur in < 15% of patients with well-differentiated pulmonary NETs. Deletions in chromosome 11q, including the *MEN1* locus, are common (36%) in both typical and atypical sporadic pulmonary NETs. Atypical carcinoid tumors also frequently have deletions in chromosomes 10q and 13q.[18]

Patients often present with recurrent pneumonia, cough, hemoptysis, wheezing, dyspnea, or chest pain, although 13 to 51% of patients are asymptomatic. Ectopic secretion of corticotropin from pulmonary NET accounts for 1% of all cases of Cushing's syndrome, and ectopic secretion of growth hormone–releasing factor has been reported.[12] The carcinoid syndrome occurs in about 3% of patients. This low frequency may be a consequence of the high pulmonary content of monoamine oxidase, which metabolizes serotonin.[18] MRI and CT are used to identify these tumors as well as delineate tumor growth and identify lymph node metastases. Scintigraphy with ^{111}In-octreotide helps in tumor staging. About 30% of pulmonary NETs fail to take up ^{111}In-octreotide and lack somatostatin receptors.[18]

Surgical resection (from wedge resection to pneumonectomy) is the treatment of choice for resectable bronchopulmonary NETs.[1] Conservative procedures (wedge resection) are preferred for the removal of localized tumors. The adequacy of conservative resection in patients with poorly differentiated carcinomas has, however, been questioned.[12] Resection via bronchoscopy should not be done because these tumors have an extensive extrabronchial component, and the risk for recurrence is high.[18] The overall 5-year survival rate after surgery is 87 to 92%. Approximately one-third of pulmonary NETs are classified as atypical tumors. They tend to be larger tumors and occur commonly in the peripheral lung fields. The 5-year survival rate in these patients is between 40 and 60% versus 90 to 100% in patients with typical tumors.[12]

MIDGUT NEUROENDOCRINE TUMORS

Small Bowel Neuroendocrine Tumors

Midgut NETs originate from the small intestine enterochromaffin cells that are serotonin-producing intraepithelial endocrine cells. The small intestine is the most frequent location for NETs, and lesions at this site comprise about 28% of all NETs.[10] In addition, small bowel NETs make up approximately one-third to half of all small bowel tumors. These tumors are often multicentric (about 28%) and occur primarily in the distal ileum. Because small bowel NETs are commonly associated with the carcinoid syndrome, they are more frequently reported clinically, whereas many midgut NETs never cause clinical symptoms but are found more frequently in autopsy studies.[12,59]

Pathology

The primary midgut NET is typically located in the ileum as a tiny, flat, fibrotic, submucosal tumor with a median size of 1 cm.[59] Foci of hyperplastic intraepithelial endocrine cells have been reported in association with ileal NET, but the cause of this hyperplasia remains unknown.[12] The vast majority of small bowel NETs are classic ileal tumors with production of serotonin and substance P, and 85% exhibit positive reactions for chromogranin, Leu-7, NSE, and serotonin (Figure 18–7). Multiple smaller carcinoid polyps may be detected in neighboring areas of the intestine in about 30% of patients and may represent additional primaries or lymphatic dissemination. Mesenteric metastases are frequent and occur irrespective of the size of the original lesion. These metastases grow conspicuously larger than the primary tumor and are characteristically associated with marked mesenteric fibrosis.[59] Interestingly, fibrosis in the mesentery and in heart chambers are both specific characteristics of small bowel NET, suggesting that desmoplastic reaction in these two locations are likely owing to various substances released by NET cells (serotonin, tachykinins, growth factors).[60] An association with other noncarcinoid cancers is present in 17% and constitutes the largest percentage among all gastrointestinal NETs. This observation supports the hypothesis that the NET cells have a high propensity for the concomitant production of growth factors.[10] Approximately 50% of patients with midgut NET have metastases at the time of diagnosis.[59]

Genetic

Although about 1% of midgut NETs are familial, most midgut NETs are sporadic.[7] The small bowel is not considered a target of the oncologic effects of *MEN1* gene inactivation.[44]

Clinical Presentation

The clinical presentation of jejunoileal NETs differs from those occurring in other sites of the gut in that there is often metastatic disease at the time of presentation. These tumors present in four distinct patterns: the first is local effects of tumor mass, the second is the carcinoid syndrome, the third is fibrosis, and the last but quite frequent pattern (about 50%) is a completely unanticipated finding by biopsy or surgery.[30] Patients most commonly present with abdominal pain or obstructive signs.[10,12,59,60] Because these tumor cells secrete serotonin, tachykinins, and other peptides and amines, small bowel NETs are the most common cause of the carcinoid syndrome.[60] Overall, about 20 to 50% of patients with small bowel NETs have the carcinoid syndrome.[10,59] Most patients with carcinoid syndrome have liver metastases that release serotonin-

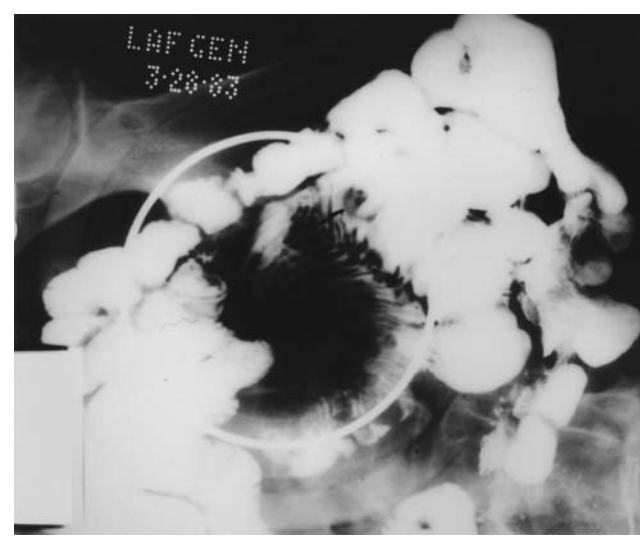


Figure 18–7. Small bowel barium enema showing a small bowel neuroendocrine tumor.

like substances into the systemic circulation, bypassing hepatic deactivation.[30] Intestinal venous ischemia or congestion (occurs in about 30% of advanced midgut NETs) results from both compression of mesenteric vessels by tumor and fibrosis and to a specific angiopathy (elastic vascular sclerosis), consisting of elastic tissue proliferation in the adventitia of mesenteric arteries and veins. Aggravated diarrhea may be a likely result when ischemia affects a limited segment of the small intestine, and severe watery diarrhea can be expected if major mesenteric veins are involved.[60] Because of the moderate size and submucosal location of the primary tumor, intestinal bleeding is uncommon and is generally encountered only with advanced bowel involvement.[59]

Diagnosis

The biochemical diagnosis of midgut carcinoid tumors is often based on the demonstration of elevated 24-hour urinary excretion of 5-HIAA. An elevated platelet serotonin level is also a specific discriminating marker.[61] Elevated plasma chromogranin A levels are another means to diagnose midgut NET, but its sensitivity is relatively low (about 60%). Measuring chromogranin A levels, however, is sometimes helpful for follow-up of patients with advanced disease.[1,59,62]

Primary midgut NETs are initially generally too small to be diagnosed with conventional bowel contrast studies, and localization of these tumors remains a problem. When patients present with symptoms owing to obstruction or the carcinoid syndrome, the tumors are larger and, unfortunately, have usually metastasized to the mesenteric nodes and liver. CT scanning is helpful in localizing the primary tumor in about 55% of cases.[3] The presence of a mesenteric mass with radiating densities is highly suggestive of mesenteric involvement of a midgut carcinoid.[59] CT scanning of a larger tumor often helps determine the size of the mesenteric tumor, its relation to the superior mesenteric artery, and possible extension retroperitoneally or above the pancreas. CT scanning is therefore recommended for appropriate planning prior to surgery. For patients with symptoms of intestinal obstruction, bowel contrast studies are recommended.[60] Selective mesenteric artery angiography is not routinely applied because intestinal impairment of midgut NET usually involves peripheral veins that are often not appropriately revealed by angiography. Somatostatin receptor scintigraphy has an accuracy of 83% and a positive predictive value of 100%. Because of its high sensitivity and ability to detect local and distant metastases, this examination is considered as an essential imaging procedure.[3,63] However, this localization study displays images that are too low in precision for anatomic details to be of help preoperatively.[60] Positron emission tomographic scanning is recommended for patients whose NET fails to be identified with somatostatin scanning. Preliminary studies comparing somatostatin receptor scintigraphy and positron emission tomography seem to show a higher sensitivity for the latter.[3,64]

Treatment

Wide resection of the primary tumor, including radical resection of the mesentery and regional lymph nodes, is the goal of surgery.[10] However, palliative surgery may aim (1) to prevent or treat abdominal complications resulting from growth of the mesentericointestinal lesion and (2) to facilitate treatment of the carcinoid syndrome and the malignant disease by reducing the tumor burden and consequently allowing easier medical treatment. Surgical procedures depend on the level of mesenteric tumor extension along the major mesenteric vessels. Stage I consists of tumors located close to the intestine, stage II of tumors involving arterial branches near their origin in the mesenteric artery, stage III of tumors extending along the superior mesenteric artery trunk, and stage IV of tumors that extend retroperitoneally or involve the origin of proximal jejunal arteries on the left side of the superior mesenteric artery.[60]

Because multicentric lesions, liver metastases, and other noncarcinoid malignancies may occur in these patients, a thorough abdominal exploration should be undertaken at laparotomy.[10] Stage I is removed by conventional mesenteric and small intestinal resection, whereas stage II tumors usually also require a right-sided colectomy. Stage III tumors usually appear impossible to remove without endangering the circulation to the entire small intes-

tine. However, meticulous and time-consuming resection allows these tumors to be dissected from the mesenteric vessels. The majority of these metastases originate from lesions in the most terminal parts of the ileum and therefore tend to be deposited to the right of the mesenteric artery.[59] Stage IV tumors are generally unresectable without leaving macroscopic disease. During all of these operations, great care must be taken to preserve at least 1.5 to 2 m of the small intestine.[60] The risk for short bowel syndrome, which is difficult to manage in combination with the carcinoid syndrome, should always be kept in mind by the surgeon.

Operative removal of the mesentericointestinal lesion may be associated with considerable symptomatic relief in nearly 80% of patients and improved survival with appreciable quality of life, even with patients with more extensive midgut carcinoids.[65] Consequently, even if liver metastases are present at diagnosis or at laparotomy, the primary tumor should be resected to avoid obstruction and other symptoms such as bleeding and perforation.[10]

Unfortunately, about 80% of patients develop tumor recurrence within 20 years. Early diagnosis of recurrence may be better based on determinations of serum chromogranin A than measurements of urinary 5-HIAA.[59] Reoperations are sometimes necessary in patients with advanced tumors, generally because of chronic abdominal pain owing to intestinal obstruction or segmental intestinal ischemia. Reoperations in patients with midgut NET should be undertaken with caution as intestinal fistulation, devascularization, and postoperative short bowel syndrome are known complications.[59,65]

Prognosis

In jejunoileal NET, factors that help predict tumor aggressiveness include distant metastases (liver) at the time of surgery, mitotic rate, multiplicity, female gender, depth of invasion, and the presence of carcinoid syndrome. Tumor size is the most predictive factor correlated with nonlocalized disease. The 5-year survival rate in patients with these NETs is about 55%. The 5-year survival rate of patients with hepatic tumor spread is about 30%.[10,66]

Neuroendocrine Tumors of the Appendix

The precise incidence of appendiceal NETs is unknown but is estimated to be 5 to 6 per 1,000 appendectomies. The relative frequency has appeared to decrease over time.[10] In contrast to carcinoids of the small intestine, these tumors are thought to arise from subepithelial endocrine cells present in the lamina propria and submucosa of the appendix wall.[12] Immunohistochemical staining of appendiceal NETs usually demonstrates enterochromaffin cells that are argentaffin positive and produce serotonin and substance P. However, a much less common nonargentaffin L cell is also encountered that can produce glicentin-related peptides, pancreatic polypeptide, or peptide YY. Subepithelial endocrine cells of the appendix are more numerous toward the tip, which is consistent with the observation that 70 to 80% of appendiceal NETs occur at the tip. An association with noncarcinoid tumors is present in 15% of lesions.[10]

The tumors rarely reach clinical significance (about 10%), and pain and discomfort are then the most frequent clinical signs. These tumors are usually found incidentally at operation for appendicitis or when the appendix is removed prophylactically during gynecologic operations.[10,59] The size of the tumor is the best predictor of prognosis. Approximatively 75 to 90% of appendiceal NETs are smaller than 1 cm in diameter and entail virtually no risk for metastasis (< 3%); these tumors can be treated by simple appendectomy.[12,59] Right hemicolectomy should be considered, however, in patients with tumors < 2 cm or when there is vascular invasion, involvement of the mesoappendix, or nodal spread or when the carcinoid tumor involves the base of the appendix, in close proximity to the cecum.[10] Right colectomy or ileocolectomy and lymph node dissection are recommended for patients with appendiceal carcinoid tumors > 2 cm because local recurrence following simple appendectomy, although uncommon, has been observed. For older patients with other illnesses, simple appendectomy may sometimes be appropriate, even for large tumors.[12] The 5-year survival rates for localized lesions, regional spread, and distant metastases are 94%, 85%, and 34%, respectively.[10]

Neuroendocrine Tumors of the Colon

Carcinoid tumors of the colon are rare and are thought to arise from serotonin-producing epithelial endocrine cells.[12] They comprise about 5% of all carcinoid tumors, and about two-thirds of them are found in the right side of the colon (midgut). These tumors occur most frequently in the cecum (about 45%), and some cecal lesions are probably initially of appendiceal origin.[10] Associated noncarcinoid tumors occur in 13%. Most patients do not become symptomatic until they have advanced disease. When symptomatic, these patients principally present with abdominal pain, weight loss, and weakness. Occasionally, diarrhea or rectal bleeding may occur and suggest a tumor location distal to the hepatic flexure.[10,12] Less than 5% of patients present with the carcinoid syndrome.[12]

Local excision is recommended for patients who present with a tumor size < 2 cm.[10] Unfortunately, the majority of patients present with tumors > 2 cm. Recommended treatment includes radical colectomy with lymph node dissection.[12] Metastases are unfortunately present in two-thirds of patients with tumors > 2 cm in diameter. Patients with colonic carcinoids have one of the worst prognoses among all gastrointestinal NETs (overall 5-year survival of 33 to 42%). The 5-year survival rates are 70% for patients with local disease, 44% for those with regional metastases, and 20% for those with distant metastases.[10,12]

HINDGUT NEUROENDOCRINE TUMORS

Neuroendocrine Tumors of the Rectum

Rectal NETs represent the third largest group of gut NETs, with about 13 to 20% of all carcinoid tumors. They are associated with noncarcinoid tumors in about 20% of cases, so that complete colonic evaluation is essential in all patients with rectal carcinoid tumors.[10,59] Moreover, routine screening examinations with proctosigmoidoscopy in asymptomatic patients have revealed an increased number of previously undetected small (< 1 cm) rectal carcinoid tumors.[59] Rectal tumors are derived from enterochromaffin cells that demonstrate argentaffin silver reaction in only 20% and a positive argyrophil reaction in up to 70% of cases. Rectal NETs generally present as small, mobile, submucosal, polypoid, or sessile nodules or focal areas of submucosal thickening identified after a bleeding episode. They can be separated into two groups: small solitary tumors measuring < 1 cm in about 80% of cases and larger lesions with the possibility of metastases. These tumors have a marked variability in staining with S-100 and Leu-7, in contrast to the positive reaction exhibited by tumors of the foregut and midgut. Immunohistochemical identification of somatostatin, glicentin, pancreatic polypeptide, peptide YY, enkephalin, endorphin, and serotonin has been described. The distribution and presence of immunoreactivity for several different markers are often uneven. This may indicate the development of multiclonal lesions, in which additional genetic derangements are prone to occur, causing more aggressive disease in some tumor cells in individual patients.[10,59] Only rare tumors express somatostatin receptors that yield positive results on scintigraphic scans.

Approximatively 50% of patients with rectal tumors are asymptomatic. Other patients mainly present with rectal bleeding, constipation, rectal syndrome, or rectal pain. Carcinoid syndrome is very rare because it is very unusual for the tumors to release serotonin into the circulation, despite their capacity to synthesize this amine. About 75% of the lesions are within 8 cm of the anal verge and are possible to reach with digital palpation. Luckily, only about 14% of patients with rectal carcinoids present with metastasis. Local excision or transanal resection is recommended for tumors measuring < 1 cm in diameter because these tumors are at low risk for recurrence or metastasis (< 2%). For tumors between 1 and 2 cm in size (10% of cases) without evidence of lymph node metastasis, wide excision with a meticulous evaluation to exclude muscular invasion is usually recommended. Transanal endosonography may be particularly useful in this intermediate group to assess tumor extension. In doubtful cases, these intermediate tumors should be considered as tumors measuring > 2 cm. Patients with tumors ≥ 2 cm (10% of cases) or with muscular invasion or lymph node

Table 18–3. SURVIVAL RATE OF GASTROINTESTINAL NEUROENDOCRINE TUMOR

Location	5-Year Survival (%)
Thymus	30
Bronchus	80
Stomach	55
Type I	80
Type II	80
Type III	40
Duodenum	55
Pancreas	20
Small bowel	55
Appendix	85
Colon	40
Rectum	75

metastases warrant treatment by a low anterior resection with total mesorectal excision or abdominoperineal resection. The overall prognosis of patients with rectal carcinoids is 72% at 5 years.[10,59] As expected, the 5-year survival rate for patients with distant metastases is < 10% (Table 18–3).[59]

METASTATIC DISEASE

Surgical Management of Hepatic Metastases

Hepatic metastases occur in about 85% of patients with small intestine NETs within 10 to 20 years. Primary small bowel NETs are most likely to metastasize to the liver (Figure 18–8), followed by primary tumors usually located in the pancreas, rectum, or lung.[57] Patients with liver metastases are mainly considered for medical therapy because resection of these metastases is possible in only 10% of cases.[59,66] The ideal intervention is a safe procedure (with minimal mortality [< 3%] and low morbidity [< 20%], avoiding specific complications such as hemorrhage, liver failure, or bile leakage) performed for a functional syndrome not amenable by medical treatment.[66] However, the tumor mass must be reduced to 10 to 20% to control the symptoms when cytoreductive hepatic surgery is performed.[57] Asymptomatic patients with resectable primary tumor but with liver masses unresponsive to nonsurgical treatments are also good candidates.[67] Recently, new methods have been recommended to treat hepatic metastases from NETs: (1) hepatic resection in two stages for diffuse metastasis and (2) local tumor destruction (eg, radiofrequency, cryotherapy, or laser ablation).[67] The long-term survival benefit of these interventions is not yet known. The aim of hepatic metastases resection is to increase the overall survival and to provide effective, prompt, and long-term relief of symptoms (in about 90% of cases).[12,67] The overall postoperative survival in patients with resected liver metastases at 5 years is about 47%. In a recent study of 31 patients, this survival rate was 86% in patients with R0 resection (curative surgery) versus 26% in patients with R2 resection (surgery leaving macroscopic remnants).[57] The survival of patients with hepatic metastases is strongly influenced by the degree of differentiation of the primary tumor (5-year survival ranging from 70% for well-differentiated NETs to 17% for poorly differentiated lesions) and by the location of the primary tumor (5-year survival rate of 0% in patients with metastases of pancreatic origin).[6,57,66]

Because the progression of disease in patients with liver metastases from midgut carcinoid tumors is usually slow, some patients may be considered candidates for liver transplantation.[59] The role of liver transplantation in the treatment of metastatic carcinoid tumors is still unclear.[12] The rather unsatisfactory results of liver transplantation in the treatment of unresectable malignant liver tumors, together with a shortage of donor organs, make careful patient selection mandatory.[57] Overall, the 5-year and disease-free survival rates are 47% and 24%,

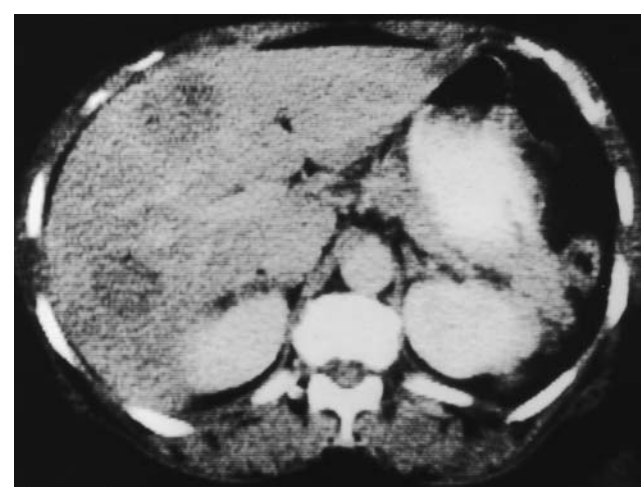


Figure 18–8. Computed tomographic scan showing liver metastases from a primary small bowel neuroendocrine tumor.

respectively. However, patients with NETs and liver metastases have a significantly better prognosis than do patients with other tumors and hepatic metastases (69% versus 36% at 5 years).[68]

Medical Management of Metastatic Disease

In metastatic disease, surgery may be the first option, but a curative intent in such cases is rarely possible (7 to 9%). Systemic therapy is often necessary, either as the only possible approach or after localized treatment has failed. The chances of successful therapy and the severity of side effects must be weighed in each patient against the naturally slow course of the disease.[69] Before systemic treatment, unresectable lesions should be staged by octreotide scintigraphy and CT scanning, as well as plasma chromogranin A and urinary 5-HIAA measurements.[12,70]

There is evidence of only a modest benefit of cytotoxic chemotherapy in the treatment of gut-derived NET. The most frequent combination used is streptozocin and fluorouracil or cyclophosphamide. The role of chemotherapy is confined predominantly to patients with metastatic disease who are symptomatic and unresponsive to other therapies.[1] Overall, response rates of approximately 20% are obtained with both single-agent and combination therapy. Remission times tend to be short, about 3 to 7 months.[69] Interferon-α alone or in combination with somatostatin analogues and interferon in combination with fluorouracil may result in a biochemical response in up to 50% of patients, but evidence of tumor regression is reported in only 10 to 20% of patients.[1] Interferon reacts with specific cell-surface receptors to activate a cytoplasmic signal transduction cascade that ultimately induces the transcription of multiple interferon-inducible genes.[69]

Treatment with somatostatin analogues results in symptomatic improvement in about 80% of patients. The duration of remission, however, is short, with a median of 8 to 12 months. Although the transiency of biochemical markers decreases in about 70% of patients, tumor regression resulting from the antiproliferative effect of somatostatin analogues occurs in fewer than 10% of patients. Stabilization of tumor growth, however, occurs in about 50% of patients, with a duration of response of about 18 months.[69]

Palliative cytoreduction of liver metastases is often performed before the administration of medical treatment, but all patients must be treated with somatostatin analogues to avoid post-treatment complications owing to the release of biologically active agents as tumor necrosis. Surgery alone does not appear to prolong survival in these patients. Alternative approaches have therefore been developed and used either alone or before systemic chemotherapy.[69] Chemoembolization is a combination of hepatic artery embolization with local cytotoxic chemotherapy. This method does not seem to improve survival but may be useful for alleviating symptoms. Eighty-seven percent of patients respond (defined as tumor size reduction or diminution of symptoms) to this therapy for an average duration of 11 months.[66] Cryosurgery has been used. Whether this method of treatment improves long-term survival compared with other methods of cytoreduction is not known. Hepatic radioembolization is an approach combining microspheres labeled with radioactive isotopes but has to be considered an experimental procedure. Lastly, somatostatin receptor–targeted radiotherapy is another, still experimental approach to localized radiotherapy. Prospective clinical trials are necessary to establish the long-term benefits of these therapies.[12,69]

REFERENCES

1. Caplin ME, Buscombe JR, Hilson AJ, et al. Carcinoid tumour. Lancet 1998;352:799–805.
2. Habal N, Sims C, Bilchik AJ. Gastrointestinal carcinoid tumors and second primary malignancies. J Surg Oncol 2000;75:301–6.
3. Ganim RB, Norton JA. Recent advances in carcinoid pathogenesis, diagnosis and management. Surg Oncol 2000;9:173–9.
4. Capella C, Heitz PU, Hofler H, et al. Revised classification of neuroendocrine tumors of the lung, pancreas and gut. Virchows Arch 1995;425:547–60.
5. Oberg K. Carcinoid tumors. Oncologist 1998;3:339–45.
6. Kirshbom PM, Kherani A, Onaitis MW, et al. Carcinoids of unknown origin: comparative analysis with foregut, midgut, and hindgut carcinoids. Surgery 1998;124:1063–70.
7. Oberg KE. Carcinoid and flushing syndromes. In: Doherty G, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 405–12.
8. Jensen RT. Natural history of digestive endocrine tumors. In: Mignon M, Colombel JF, editors. Recent advances in the pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris: John Libbey Eurotext Publishing; 1999. p. 192–219.

9. Williams ED, Sandler M. The classification of carcinoid tumors. Lancet 1963;i:238–9.
10. Lauffer JM, Zhang T, Modlin IM. Review article: current status of gastrointestinal carcinoids. Aliment Pharmacol Ther 1999;13:271–87.
11. Solcia E, Kloppel G, Sobin LH. Histological typing of neuroendocrine tumors. New York: Springer; 2000.
12. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999; 340:858–68.
13. Wheeler MH, Curley IR, Williams ED. The association of neurofibromatosis, pheochromocytoma, and somatostatin-rich duodenal carcinoid tumor. Surgery 1986;100:1163–9.
14. Kytola S, Hoog A, Nord B, et al. Comparative genomic hybridization indentifies loss of 18q22-qter as an early and specific event in tumorigenesis of midgut carcinoids. Am J Pathol 2001;158:1803–8.
15. Duh QY, Hybarger CP, Geist R, et al. Carcinoids associated with multiple endocrine neoplasia syndromes. Am J Surg 1987;154:142–8.
16. Schussheim D, Skarulis M, Agarwal S, et al. Multiple endocrine neoplasia type 1: new clinical and basic findings. Trends Endocrinol Metab 2001;12:173–8.
17. Hessman O, Skogseid B, Westin G, Akerstrom G. Multiple allelic deletions and intratumoral genetic heterogeneity in MEN 1 pancreatic tumors. J Clin Endocrinol Metab 2001; 86:1355–61.
18. Granberg D, Skogseid B. Lung and thymic neuroendocrine tumors. In: Doherty G, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 413–30.
19. Jensen RT. Carcinoid and pancreatic endocrine tumors: recent advances in molecular pathogenesis, localization, and treatment. Curr Opin Oncol 2000;12:368–77.
20. Gortz B, Roth J, Krahenmann AN, et al. Mutations and allelic deletions of the MEN1 gene are associated with a subset of sporadic endocrine pancreatic and neuroendocrine tumors and not restricted to foregut neoplasms. Am J Pathol 1999;154:429–36.
21. Toliat MR, Berger W, Ropers H, et al. Mutations in the MEN 1 gene in sporadic neuroendocrine tumours of gastroenteropancreatic system. Lancet 1997;350:1223.
22. Calender A. New insights in genetics of digestive neuroendocrine tumors. In: Mignon M, Colombel JF, editors. Recent advances in the pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris: John Libbey Eurotext Publishing; 1999. p. 155–76.
23. Tonnies H, Toliat MR, Ramel C, et al. Analysis of sporadic neuroendocrine tumours of the enteropancreatic system by comparative genomic hybridisation. Gut 2001;48:536–41.
24. Lollgen RM, Hessman O, Szabo E, et al. Chromosome 18 deletions are common events in classical midgut carcinoid tumors. Int J Cancer 2001;92:812–5.
25. Helpap B, Kollermann J. Immunohistochemical analysis of the proliferative activity of neuroendocrine tumors from various organs. Virchows Arch 2001;438:86–91.
26. Rindi G, Capella C, Solcia E. Pathobiology and classification of gut endocrine tumors. In: Mignon M, Colombel JF, editors. Recent advances in the pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris: John Libbey Eurotext Publishing; 1999. p. 177–91.
27. Wiedenmann B, John M, Ahnert-Hilger G, Riecken E. Molecular and cell biological aspects of neuroendocrine tumors of the gastroenteropancreatic system. J Mol Med 1998;76:637–47.
28. Roeher HD, Simon D. Carcinoid tumors. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997. p. 643–9.
29. Papotti M, Cassoni P, Volante M, et al. Ghrelin-producing endocrine tumors of the stomach and intestine. J Clin Endocrinol Metab 2001;86:5052–9.
30. Norton JA. Surgical treatment of gastrointestinal endocrine tumors. In: Mignon M, Colombel JF, editors. Recent advances in the pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris: John Libbey Eurotext Publishing; 1999. p. 248–59.
31. Cohen T, Poltarak Z, Brodzky A, et al. Neuroendocrine cells along the digestive tract express neuropilin-2. Biochem Biophys Res 2001;284:395–403.
32. Rindi G, Azzoni C, Larosa S, et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognosis evaluation by pathological analysis. Gastroenterology 1999;116:532–42.
33. Delellis RA. Proliferation markers in neuroendocrine tumors: useful or useless? Verh Dtsch Ges Pathol 1997; 81:53–61.
34. Rosai J, Higa E. Mediastinal endocrine neoplasm of probable thymic origin related to carcinoid tumor. Cancer 1972; 29:1061–74.
35. Moran C, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. Am J Clin Pathol 2000;114:100–10.
36. Teh BT. Thymic carcinoid tumors in multiple endocrine neoplasia type 1. Ann Surg 1998;228:99–105.
37. Teh BT. Thymic carcinoids in multiple endocrine neoplasia type 1. J Intern Med 1998;243:501–4.
38. Sugiura H, Morikawa T, Itoh K, et al. Thymic carcinoid in a patient with multiple endocrine neoplasia type 1: report of a case. Surg Today 2001;31:428–32.
39. Dotzenrath C, Goretzki P, Cupisti K, et al. Malignant endocrine tumors in patients with MEN 1 disease. Surgery 2001;129:91–5.
40. National Cancer Network Comprehensive. Practice guidelines for neuroendocrine tumors. 2001.
41. Mullan M, Gauger P, Thompson N. Endocrine tumors of the pancreas: review and recent advances. Aust N Z J Surg 2001;71:475–82.
42. Montpreville VT, Macchiarini P, Dulmet E. Thymic neuroendocrine carcinoma (carcinoid): a clinicopathologic study of 14 cases. J Thorac Cardiovasc Surg 1996;111:134–41.
43. Gal AA, Kornstein MJ, Cohen C, et al. Neuroendocrine tumors of the thymus: a clinicopathological study. Ann Thorac Surg 2001;72:1179–82.
44. Bordi C, Corleto VD, Azzoni C, et al. The antral mucosa as a new site for endocrine tumors in multiple endocrine neoplasia type I and Zollinger-Ellison syndromes. J Clin Endocrinol Metab 2001;86:2236–42.
45. Capella C, Vassalo G, Solcia E. Light and electron microscopic identification of the histamine-storing argyrophil

(ECL) cell in murine stomach and of its equivalent in other mammals. Z Zellforsch 1971;118:68–70.
46. Modlin IM, Tang LH, Svennevik E. Gastric carcinoid tumors. In: Doherty G, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 431–46.
47. Wiedenmann B, Jensen RT, Mignon M, et al. Preoperative diagnostic and surgical management of neuroendocrine gastroenteropancreatic tumors: general recommendations by a consensus workshop. World J Surg 1998;22:309–18.
48. Schindl M, Kaserer K, Niederle B. Treatment of gastric neuroendocrine tumors. Arch Surg 2001;136:49–54.
49. Rindi G, Bordi C, Rappel S, et al. Gastric carcinoids and neuroendocrine carcinoma: pathogenesis, pathology, and behavior. World J Surg 1996;20:168–72.
50. Kirshbom PM, Kherani A, Onaitis MW, et al. Foregut carcinoids: a clinical and biochemical analysis. Surgery 1999;126:1105–10.
51. Gibril F, Reynolds J, Lubensky I, et al. Ability of somatostatin receptor scintigraphy to identify patients with gastric carcinoids. J Nucl Med 2000;41:1646–56.
52. Tomassetti P, Migliori M, Caletti GC, et al. Treatment of type II gastric carcinoid tumors with somatostatin analogues. N Engl J Med 2000;343:551–4.
53. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. Cancer 1997;15:813–29.
54. Rappel S, Altendorf A, Stolte M. Prognosis of gastric carcinoid. Digestion 1995;56:455–62.
55. Louw VJ, Moosa MR. Carcinoid tumour. Lancet 1998;352: 1554.
56. Walther M, Linehan W, Libutti S. Von Hippel-Lindau disease and Von Recklingausen's disease. In: Doherty G, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 581–91.
57. Nave H, Mossinger E, Feist H, et al. Surgery as primary treatment in patients with liver metastases from carcinoid tumors: a retrospective, unicentric study over 13 years. Surgery 2001;129:170–5.
58. Onaitis MW, Kirshbom PM, Hayward T, et al. Gastrointestinal carcinoids: characteristization by site of origin and hormone production. Ann Surg 2000;232:549–56.
59. Akerstrom G, Hellman P, Ohrvall U. Midgut and hindgut carcinoid tumors. In: Doherty G, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 447–59.
60. Ohrvall U, Eriksson B, Juhlin C, et al. Method for dissection of mesenteric metastases in midgut carcinoid tumors. World J Surg 2000;24:1402–8.
61. Meijer WG, Kema IP, Volmer M, et al. Discriminating capacity of indole markers in the diagnosis of carcinoid tumors. Clin Chem 2000;46:1588–96.
62. Tomassetti P, Migliori M, Simoni P, et al. Diagnostic value of plasma chromogranin A in neuroendocrine tumours. Eur J Gastroenterol Hepatol 2001;13:55–8.
63. Kaltsas G, Korbonits M, Heintz E, et al. Comparison of somatostatin analog and metaiodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. J Clin Endocrinol Metab 2001;86:895–902.
64. Hoegerle S, Altehoefer C, Ghanem N, et al. Whole-body 18F dopa PET for detection of gastrointestinal carcinoid tumors. Radiology 2001;220:373–80.
65. Makridis C, Rastad J, Oberg K, Akerstrom G. Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. World J Surg 1996;20: 900–6.
66. Proye C. Natural history of liver metastasis of gastroenteropancreatic neuroendocrine tumors: place for chemoembolization. World J Surg 2001;25:685–8.
67. Jaeck D, Oussoultzoglou E, Bachelier P, et al. Hepatic metastases of gastroenteropancreatic neuroendocrine tumors: safe hepatic surgery. World J Surg 2001;25: 689–92.
68. Ringe B, Lorf T, Dopkens K, Canelo R. Treatment of hepatic metastases from gastroenteropancreatic neuroendocrine tumors: role of liver transplantation. World J Surg 2001; 25:697–9.
69. Plockinger U, Wiedenmann B. Systemic therapy for metastatic or residual extrapancreatic neuroendocrine tumors. In: Doherty G, Skogseid B, editors. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 461–76.
70. Skogseid B. Nonsurgical treatment of advanced malignant neuroendocrine pancreatic tumors and midgut carcinoids. World J Surg 2001;25:700–3.

Index

Page numbers followed by f indicate figure. Pages numbers followed by t indicate table.