Surgical Management of Nonmultiple Endocrine Neoplasia Endocrinopathies: State-of-the-Art Review

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KEYWORDS

- Endocrinopathy
- Familial
- Adrenal
- Pancreas
- Thyroid
- Parathyroid

Endocrinopathy is defined as “a disorder in the function of an endocrine gland and the consequences thereof.”\textsuperscript{1} In many endocrinopathies, surgical intervention is a necessary part of the treatment algorithm to achieve cure. In fact, surgical treatment of endocrine organs is centuries old. Pierre-Joseph Desault of Paris performed the first documented successful thyroidectomy in 1791.\textsuperscript{2} At that time, thyroidectomy had a 40% mortality rate from complications of bleeding and sepsis.\textsuperscript{2}

As the development of general anesthesia, hemostasis, and antisepctic techniques transformed the discipline of surgery, systematic surgical intervention of endocrine glands emerged by the early 1900s as a treatment to control hypersecretion of hormones.\textsuperscript{2} Theodor Kocher was awarded the Nobel Prize in Medicine in 1909 for his work on physiology, pathology, and surgery of the thyroid gland.\textsuperscript{3} Endocrine surgery was further advanced when Charles Huggins discovered that certain malignancies are sensitive to specific hormones, and removal of these hormones can induce tumor regression; this discovery earned him the Nobel Prize in 1966.\textsuperscript{4}
Over the last 50 years, endocrine surgery has evolved even more with the development of genetic testing to help identify patients with familial disorders. The discovery of multiple endocrine neoplasia syndrome (MEN) had a profound impact on endocrine surgery. This article focuses on the identification and surgical management of non-MEN familial endocrinopathies (Table 1).

**THYROID ENDOCRINOPATHIES**

**Hereditary Nonmedullary Carcinoma of the Thyroid**

Hereditary nonmedullary thyroid cancer (HNMTC) accounts for 3% to 6% of all thyroid malignancies, and is transmitted in an autosomal dominant pattern with incomplete penetrance.5,6 More than 90% of patients with HNMTC have papillary thyroid cancer, whereas the remainder have follicular thyroid cancer or Hurthle cell carcinoma.6 No single causative gene has been identified, but linkages to 1q21, 2q21, and 19p13.2 have been reported.5,6 Thyroid malignancies in patients with HNMTC are thought to be more aggressive and to have higher rates of multicentricity, lymph node metastasis, and invasion into adjacent tissues compared with thyroid malignancies in patients with sporadic disease.5–9 HNMTC has also been associated with renal malignancies, benign thyroid tumors, and nonautoimmune hyperthyroidism.6 According to statistical analyses of the incidence of thyroid cancer in the United States, there is a 94% chance of familial predisposition to nonmedullary thyroid cancer when 3 or more family members have the disease.10 However, when only 2 family members are affected, 62% to 69% of nonmedullary thyroid cancer cases are sporadic rather than familial.10 Screening recommendations for HNMTC have not been fully established, but it has been suggested that families with 2 or more affected members should be screened with physical examination, thyroid ultrasound, and serum thyroid-stimulating hormone levels.6,11 Surgical management of patients with HNMTC is similar to patients with sporadic thyroid cancer.

**Cowden Disease**

Cowden disease, named after a patient’s surname in 1962 by Llyod and Dennis, is an autosomal dominant disorder characterized by multiple hamartomas, and breast and thyroid malignancies.12 Other manifestations include uterine leiomyoma, megacephaly, mucocutaneous lesions (eg, facial trichilemmoma, acral keratoses, and oral papillomatous papules), benign tumors of the breast and thyroid gland, Lhermitte-Duclos disease, and endometrial carcinoma (Box 1).13 Eighty percent of patients diagnosed with Cowden disease have germ-line mutations of the PTEN gene, a tumor suppressor gene located on chromosome 10q23.3.14–18 An additional 10% of patients have mutations in the PTEN promoter region, and there are likely other patients with deletions and rearrangements of the PTEN gene.19 By 20 years of age, more than 90% of individuals with Cowden disease present with mucocutaneous lesions.13,20 By age 29, more than 99% of affected patients show signs of the disease.13

Up to 10% of patients with Cowden disease develop follicular carcinoma, and 50% to 75% develop benign lesions of the thyroid gland.20,21 There have been a few reports of papillary thyroid cancer, but the predominant histopathology associated with Cowden disease is follicular thyroid cancer.20 Follicular adenomas, which are often multicentric, may progress to follicular carcinoma.20,22 Patients with Cowden disease should undergo annual physical thyroid examinations beginning at age 18 years or 5 years younger than the age of first diagnosis of thyroid cancer in the family, whichever is earlier.23 Likewise, a baseline thyroid ultrasound with repeat studies annually or biannually may be useful.20
<table>
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The percentage of patients with Cowden disease who develop breast cancer during their lifetime ranges from 25% to 50%, and 75% develop benign breast diseases, such as fibroadenoma or fibrocystic breast disease. Patients with Cowden disease who develop breast cancer are diagnosed approximately 10 years younger than sporadic breast cancer counterparts. Likewise, breast cancer in these patients is more likely to be multifocal and bilateral than in sporadic breast cancer patients. The predominant histopathology for patients who develop breast cancer is ductal adenocarcinoma. Screening of patients with Cowden disease should include monthly breast self-examinations with alternating mammograms and breast MRI every six months starting at age 30 years or 5 years younger than the earliest diagnosis of breast cancer in the family.

### Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant condition associated with multiple polyps in the colon that develop during early adulthood. This disease has been linked to the APC gene on chromosome 5q21-22. Other characteristics of the disease include desmoid tumors, osteomas, epidermal cysts, hepatoblastomas, congenital hypertrophy of retinal pigmented epithelium, nonfunctioning adrenal adenomas, and upper gastrointestinal tract polyps. Approximately 2% of patients with FAP are diagnosed with papillary carcinoma of the thyroid gland. Females with FAP have a 160 times greater risk of developing papillary carcinoma than the general population. The average age at diagnosis is 27 years. Papillary thyroid carcinomas that are associated with FAP are usually multifocal, bilateral, and often have a rare cribriform-morular histologic subtype. Patients who are found to have a cribriform-morular histologic pattern should be screened for FAP, because 90% of patients with FAP and papillary thyroid carcinoma have this histology. Furthermore, this histologic subtype comprises 0.1% to 0.2% of all papillary thyroid carcinoma cases.

Screening recommendations for FAP-associated thyroid disease are not currently established, although many institutions recommend yearly thyroid physical and ultrasonographic examinations. These screening techniques reportedly detected papillary thyroid carcinomas in 7% of patients at one center. The treatment for patients with papillary thyroid carcinoma and FAP is the same as patients with sporadic papillary thyroid cancer.
Carney Complex

First described by Mayo Clinic pathologist J. Aidan Carney, Carney complex is an autosomal dominant disorder associated with spotty skin pigmentation, myxomas, endocrine disorders, and schwannomas (Box 3). Patients with this disease commonly have multinodular thyroid glands and multiple follicular adenomas. Approximately 15% of these patients are diagnosed with papillary or follicular carcinoma of the thyroid gland. Annual cervical ultrasonographic examination is recommended as a primary screening tool. Surgical resection is the appropriate treatment when a malignancy or suspicious lesions are identified. Other endocrine findings associated with Carney complex are discussed later in this article.

Werner Syndrome

Werner syndrome, named after the German physician C.W. Otto Werner, is a rare autosomal recessive disease characterized by premature aging, skin atrophy, and bilateral cataracts (Box 4). This condition has been linked to a gene, referred to as the WS gene, located at chromosome 8p11-21. Patients with this disease have an increased incidence of papillary and follicular thyroid carcinoma, with a mean

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**Box 2**

**Familial adenomatous polyposis**

- Papillary thyroid carcinoma
- Adrenal adenomas
- Colon polyps
- Desmoid tumors
- Osteomas
- Hepatoblastomas
- Retinal pigmented epithelial hypertrophy

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**Fig. 1.** Histopathology of thyroid cancer in FAP. Papillary thyroid carcinomas associated with FAP are usually multifocal and bilateral, and often have a rare cribriform-morular histologic subtype. Ninety percent of patients with FAP and papillary thyroid carcinoma have this histology.
age of 34 years at presentation. Moreover, as many as 2% of patients with Werner syndrome develop anaplastic carcinoma of the thyroid.

**Familial Medullary Thyroid Carcinoma**

Historically, medullary thyroid carcinoma (MTC) is thought to occur in both familial and sporadic forms, or as a part of MEN type 2. In 2009, the American Thyroid Association (ATA) Guidelines Task Force defined familial medullary thyroid carcinoma (FMTC) as “a clinical variant of MEN 2A in which MTC is the only manifestation.” For patients to be diagnosed with FMTC, they must have a RET mutation identified in kindreds with only FMTC, or demonstrate the absence of pheochromocytoma or primary hyperparathyroidism in two or more generations within a family. Because this observation is a new development, and some individuals consider FMTC to be a distinct entity from MEN, we have included FMTC in this chapter. The remainder of this section outlines the guidelines from the most recent ATA Task Force. These guidelines are intended to assist physicians with the management of medullary thyroid cancer, but each patient should be treated on an individual basis.

FMTC is transmitted in an autosomal dominant pattern and typically presents with bilateral and multicentric disease at a later age than patients with MEN. Thyroid glands in these patients are characterized by the presence of C-cell hyperplasia prior to the development of carcinoma. Because 25% of MTCs are hereditary, all patients who are diagnosed with primary C cell hyperplasia, MTC, or MEN 2 should be offered RET (rearranged during transfection) genetic testing. Similarly, because 88% of individuals with FMTC have an identifiable RET mutation, everyone who has a first-degree relative with FMTC or MEN 2A should be offered RET genetic testing during childhood.

The biologic behavior of MTC can be predicted by the specific RET mutation and the patient’s age when MTC becomes clinically apparent. The ATA Task Force...
created a classification system of RET mutations based on the historical aggressiveness of MTC, allowing screening and surgical intervention to be optimized for the best overall outcome. Patients with ATA level A RET mutations (codons 768, 790, 791, 804, 891) or ATA level B RET mutations (codons 609, 611, 618, 620, 630) have the lowest risk of aggressive MTC, and may undergo prophylactic thyroidectomy after 5 years of age if they have a normal annual serum calcitonin level, normal annual neck ultrasound, and a less aggressive family history. However, if the calcitonin level is elevated, the family history is aggressive, or the ultrasound is abnormal, then prophylactic thyroidectomy is warranted. Patients with ATA level C RET mutations (codon 634) have a higher risk of aggressive MTC, and should undergo prophylactic total thyroidectomy before 5 years of age. Individuals with ATA level D (MEN 2B) RET mutations (codons 883, 918) have the youngest age of onset and the highest risk of metastatic disease. These patients should undergo prophylactic total thyroidectomy within the first year of life.

Preoperative calcitonin levels and cervical ultrasound may be considered in children who undergo prophylactic thyroidectomy after 3 years of age to rule out the possibility of metastatic MTC. Caution should be used when interpreting calcitonin values in children less than 3 years old as preoperative testing in this age group has not been established. In addition, patients who undergo prophylactic thyroidectomy before 5 years of age should have the surgery performed at an experienced tertiary care center to decrease the chance of recurrent laryngeal nerve or parathyroid injury. According to the ATA guidelines, central neck dissection is not indicated for FMTC patients undergoing prophylactic thyroidectomy at any age unless there is evidence of lymph node metastasis, thyroid nodules greater than 5 mm, or a basal serum calcitonin greater than 40 pg/mL.

Patients with suspected MTC should have a cervical neck ultrasound, serum CEA, serum calcium, and a serum calcitonin level preoperatively. If there is no evidence of local invasion by the primary tumor, and there is no evidence of lymph node metastasis, then the ATA task force recommends total thyroidectomy with prophylactic central neck dissection. If the serum calcitonin level is greater than 400 pg/mL or there is evidence of local lymph node metastasis, then a neck, chest, and three-phase liver computed tomography scan or MRI is indicated to rule out metastatic disease. If distant metastasis is evident, the degree of surgical resection should be determined on an individual basis. Less aggressive neck surgery may be considered to control locoregional disease, while maintaining parathyroid, swallowing and speech function.

If central neck disease is diagnosed or suspected in a FMTC patient with MTC, the patient should have a total thyroidectomy with central lymph node dissection. The role for prophylactic lateral neck dissection for patients without evidence of lateral neck disease is currently not established, and should be considered on an individual basis. However, if lateral neck disease is demonstrated preoperatively without evidence of distant metastasis, the task force recommends a central neck dissection and a compartment oriented lateral neck dissection (levels IIA, III, IV, V) on the affected side. If the parathyroid glands are removed or devascularized during surgery, they may be reimplanted in the neck if the genetic mutation is consistent with FMTC, or in the forearm in conjunction with cryopreservation, if the genetic defect is more consistent with MEN 2A.

Two to three months postoperatively, calcitonin and CEA levels should be measured. These tumor markers may be obtained every 6-12 months initially, and then annually depending on the patient. A neck ultrasound six months after surgical intervention may be used as a baseline. The ATA task force recommends thyroid replacement therapy rather than thyroid suppressive T4 therapy after
thyroidectomy. Radioactive iodine is not indicated for patients after thyroidectomy for MTC. If patients have undetectable serum tumor markers, they may be followed with serial laboratory testing. Patients who have detectable calcitonin levels less than 150 pg/mL should have a neck ultrasound to evaluate for additional disease, and additional imaging may be considered. Patients with calcitonin levels greater than 150 pg/mL should have additional imaging of the neck, chest, liver, and axial skeleton to rule out distant metastatic disease. Adjuvant chemotherapy and external beam radiation may be beneficial in some patients, such as those with unresectable disease or positive margins, and the use of these modalities should be individualized.

**Pendred Syndrome**

In 1896 Pendred syndrome was first described in an Irish family by Vaughan Pendred, an English physician. This autosomal recessive disorder is characterized by non-reversible bilateral sensorineural hearing loss and thyroid goiter (Box 5). In addition, this disease is thought to represent up to 10% of cases of hereditary deafness, which can be noted at birth or may progressively develop during childhood. The most common gene associated with Pendred syndrome, located on 7q31, produces pendrin, a protein involved with chloride and iodide transport. The loss of pendrin production leads to defective iodide organification, resulting in thyroid overgrowth and goiter. The diagnosis of Pendred syndrome is supported with the perchlorate discharge test, whereby affected individuals have less than 10% of radioactive discharge after administration of radioactive iodine. Affected individuals often develop thyroid goiters. Patients who have adequate iodine intake typically are euthyroid. However, approximately one-third of patients actually develop overt hypothyroidism, especially those with iodine deficiency. Treatment of Pendred syndrome consists of thyroid hormone replacement and surgery if the patient has compressive symptoms.

**Other Conditions Associated with Thyroid Goiter**

Iodide transport deficiency disease and iodotyrosine deiodinase defect disease comprise some of the syndromes characterized by hypothyroidism and the development of a goiter. Even though no chromosome has been linked to these syndromes, both seem to be inherited in an autosomal-recessive fashion. Like Pendred syndrome, these conditions should be treated with thyroid hormone replacement and surgery if patients have compressive symptoms.

**PARATHYROID ENDOCRINOPATHIES**

**Hereditary Hyperparathyroidism Jaw-Tumor Syndrome**

Hereditary hyperparathyroidism jaw-tumor syndrome is a rare autosomal dominant disorder with incomplete penetrance associated with the gene \( \text{HRPT2} \) (also known as CDC73), which is thought to be a tumor suppressor gene located on 1q25-32. This syndrome is characterized by renal cysts or solid tumors, ossifying fibromas of the mandible or maxilla (Fig. 2), uterine fibromas, and PTH-mediated

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<td>Bilateral sensorineural hearing loss</td>
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hypercalcemia (Box 6). Approximately 80% of patients with this disease develop hyperparathyroidism. Moreover, 15% of patients may develop parathyroid carcinoma. Patients with hereditary hyperparathyroidism jaw-tumor syndrome should be followed closely with annual screening of serum calcium and intact parathyroid hormone levels. If biochemical testing is elevated, cervical ultrasonography should be used. Surgical resection should involve excision of enlarged parathyroid adenomas. In the case of suspected parathyroid carcinoma, an en bloc resection should be performed with an ipsilateral thyroid lobectomy and any involved adjacent structures.

Familial Isolated Hyperparathyroidism

It has been postulated that familial isolated hyperparathyroidism is a genetic variant of hereditary hyperparathyroidism jaw-tumor syndrome or MEN with incomplete penetrance. However, currently the diagnosis of familial isolated hyperparathyroidism requires that the patient and at least one relative be diagnosed with primary hyperparathyroidism associated with abnormal histology, but without the clinical manifestations of MEN or hereditary hyperparathyroidism jaw-tumor syndrome. To date, this disease has been linked to an area on chromosome 2p14, and it has been associated with mutations of the HRPT2 (CDC73) gene, the MEN1 gene, and the CASR gene. Genetic testing should be considered to definitively rule out MEN, because patients may have incomplete penetrance. However, genetic testing is low-yield for patients who do not have early-onset, multiglandular, cystic, atypical, or malignant parathyroid glands. Also, CASR testing is of little utility except to distinguish familial isolated hyperparathyroidism from primary hyperparathyroidism. The surgical management of familial hypercalcemic hypocalciuria should be the same as for

Box 6
Hereditary hyperparathyroidism jaw-tumor syndrome

- Primary hyperparathyroidism
- Parathyroid carcinoma
- Ossifying fibromas of the jaw
- Renal cysts
- Renal solid tumors
- Uterine fibromas
hyperparathyroidism: uniglandular resection for single-gland disease and subtotal parathyroidectomy for multiglandular disease.\textsuperscript{48}

ADRENAL ENDOCRINOPATHIES

Adrenocortical Tumors

Beckwith-Wiedemann syndrome

Usually recognized at birth, Beckwith-Wiedemann syndrome is a congenital overgrowth syndrome that presents in an autosomal dominant pattern with variable expressivity (15% of cases) or in a sporadic form (85% of cases).\textsuperscript{54} John Bruce Beckwith, an American pediatric pathologist, first reported this syndrome from autopsy findings of 3 affected children.\textsuperscript{55} German pediatrician Hans-Rudolf Wiedemann further described this syndrome among 3 siblings in 1964.\textsuperscript{56} Linked to the 11p15 chromosomal locus, this disorder is characterized by omphalocele, macroglossia, macrosomia, hemihypertrophy, hypoglycemia, visceromegaly, and renal abnormalities in the neonate (Box 7).\textsuperscript{53,57} Multiple genes have been linked to this syndrome, such as \textit{IGF-2}, \textit{KCNQ10T1}, \textit{H19}, \textit{CDKN1C}, and \textit{KCNQ1}.\textsuperscript{58} Among patients with this syndrome, 5% to 10% develop childhood embryonal tumors, such as Wilms tumor (5%), adrenocortical tumors (3%), or less commonly, hepatoblastoma, neuroblastoma, pancreatoblastoma, and rhabdomyosarcoma.\textsuperscript{59}

Most, but not all patients with Beckwith-Wiedemann syndrome who develop adrenocortical abnormalities have symptoms resulting from the overproduction of steroids associated with these tumors.\textsuperscript{50} It is currently recommended that all patients with Beckwith-Wiedemann syndrome undergo routine screening with annual serum and urine cortisol levels, a-fetoprotein levels, and adrenal ultrasound until 9 years of age.\textsuperscript{60} Laparoscopic adrenalectomy is contraindicated in the setting of suspected adrenal cortical carcinoma because of its association with peritoneal carcinomatosis.\textsuperscript{61} Therefore, open adrenalectomy is the treatment of choice for adrenocortical carcinomas, even for patients with isolated metastatic disease.\textsuperscript{57,61}

Li-Fraumeni syndrome

First described in 1969 by American cancer epidemiologist and internist Joseph F. Fraumeni, Li-Fraumeni syndrome is an autosomal dominant disorder classically characterized by multiple cancers, including sarcoma, breast cancer, leukemia, brain tumors, and adrenocortical tumors (Box 8).\textsuperscript{62} This syndrome has been associated with germ-line mutations of the \textit{p53} gene.\textsuperscript{63,64} Three percent of patients with this disease actually develop adrenal cortical carcinoma, usually during childhood.\textsuperscript{64,65} \textit{En bloc} surgical resection is the treatment of choice for adrenocortical carcinomas,
even when isolated metastatic disease is present. Adjuvant chemotherapy with mitotane, one of the most commonly used chemotherapy drugs administered after radical resection for adrenal cortical carcinoma, has been reported to have different responses at different centers. The authors’ experience at The University of Texas M. D. Anderson Cancer Center has been that although adjuvant mitotane may not improve overall survival compared with other chemotherapy drugs, the time to progression of disease is prolonged with the use of mitotane alone. The authors have also found that patients with recurrent disease who regress or have stable disease with the use of mitotane have a better overall prognosis.

**Pheochromocytoma**

**Neurofibromatosis 1 (von Recklinghausen disease)**

Von Recklinghausen disease, also known as neurofibromatosis 1 (NF1), is the most common autosomal dominant disorder. Named after the German histopathologist Friedrich Daniel von Recklinghausen, von Recklinghausen disease affects 1 in 3000 to 4000 individuals, with variable presentation. Identified in 1990, the NF1 gene is a tumor suppressor gene located at the 17q11.2 chromosome locus that encodes neurofibrin, a GTPase-activating protein, which affects the production pathway of the Ras oncoprotein. Approximately 50% of affected patients have de novo mutations. This condition is characterized by neurofibromas, skin pigmentations (eg, café-au-lait macules, freckling in non-sun–exposed areas), optic gliomas, Lisch nodules, bony lesions, short stature, learning disabilities, and macrocephaly (Box 9). Approximately 25% of patients with NF1 have intestinal fibromas that may result in bleeding. NF1 is often identified during childhood when patients are noted to have 6 or more café-au-lait spots, or during the late teens and early twenties with the identification of Lisch nodules.
A 1999 literature review of 148 patients with NF1 found the incidence of pheochromocytomas to be 0.1% to 5.7%, with a mean age of 42 years at presentation. Among these patients, 84% had unilateral disease, 9.6% had bilateral disease, and 6.1% had extra-adrenal paragangliomas. The percentage of these patients who had tumors with metastatic disease or local invasion was 12%. Moreover, 78% of patients had symptoms of hypertension. Patients with a known diagnosis of NF1 may be followed with plasma metanephrine levels, especially if they have hypertension.

The surgical management of patients with hereditary pheochromocytoma and NF1 is dependent on the presence of bilaterality. Patients who have uniglandular disease should undergo complete open or laparoscopic adrenalectomy. When bilateral disease is involved, the potential morbidity of an acute Addisonian crisis associated with total bilateral adrenalectomy needs to be considered. The authors recommend bilateral cortical-sparing adrenalectomy for patients with bilateral pheochromocytoma associated with NF1, because the risk of metastatic and recurrent disease is low, and the necessity of lifelong steroid dependence is avoided. However, when bilateral cortical-sparing adrenalectomy is performed, lifelong surveillance of the remnant glands and annual biochemical screening studies are imperative to monitor for recurrent disease.

The preoperative management of patients with pheochromocytoma is important in minimizing complications in the perioperative setting. The primary goal is to control hypertension and heart rate, restore volume depletion, and prevent the patient from having a surgical catecholamine-induced storm. Therapy should begin at least 1 to 2 weeks before surgery with α-adrenergic blockade to normalize blood pressure to 130/80 mm Hg while sitting and 100 mm Hg systolic when standing. Likewise, the target heart rate should range from 60 to 70 beats per minute (bpm) while sitting and 70 to 80 bpm while standing. Phenoxybenzamine, the most common α-antagonist used, can be started at a dose of 10 mg twice a day and increased until the clinical manifestations of the disease are controlled. β-blockers are indicated to help control catecholamine or α-blocker induced tachycardia. β-Blockers must always be used in conjunction with an α-antagonist because the use of β-blockers alone could exacerbate hypertension in these patients. β-1 blockers are preferred, such as atenolol in doses of 12.5 or 25 mg 2 to 3 times a day or metoprolol in doses of 25 to 50 mg 3 to 4 times a day. In addition, preoperative coordination with essential personnel, including a dedicated anesthesiologist, endocrinologist, surgeon, internist, and cardiologist, ensures the best preparation for surgery while minimizing the risks of complications in the perioperative setting.

The surgical approach to pheochromocytoma or other benign adrenal tumors can be performed by open or laparoscopic surgery. The authors recommend the posterior retroperitoneoscopic adrenalectomy as a minimally invasive approach. Performed in the prone jackknife position, this technique avoids mobilization of intra-abdominal solid organs. Trocars are placed in the retroperitoneal space, followed by separation of the adrenal gland from the kidney using blunt and sharp dissection. The adrenal vein is identified, clipped, and divided. Next, the adrenal gland is completely mobilized and placed into an endocatch device. Posterior retroperitoneoscopic adrenalectomy is useful for bilateral adrenalectomies because repositioning the patient is avoided.

**Von Hippel-Lindau disease**

Von Hippel-Lindau disease (VHL) occurs in approximately 1 in 36,000 births and is associated with hemangioblastomas of the nervous system, retinal angiomas, clear cell renal carcinoma, pheochromocytomas, pancreatic neuroendocrine cell tumors,
and endolymphatic sac tumors (Box 10). In 1895 Eugen von Hippel was the first to report retinal angiomas associated with this disease. Many years later in 1926, Swedish pathologist, Arvid Lindau, recognized the coexistence of cerebellar tumors and other cystic tumors involved in VHL. Other findings associated with this disease include pancreatic, renal, epididymal, and broad ligament cysts, and cystadenomas. VHL has been associated with mutations of the von Hippel-Lindau gene (VHL gene, autosomal dominant), a tumor suppressor gene located on chromosome 3p25 that regulates hypoxia-induced cell proliferation and angiogenesis. Type I VHL families have a low risk of developing a pheochromocytoma, and type II families have a high risk of pheochromocytoma. Type II families can be further subdivided into type IIA (low risk of renal cell carcinoma), type IIB (high risk of renal cell carcinoma), and type IIC (pheochromocytoma with no other characteristics of VHL). Screening for this disease should begin in childhood with a yearly eye examination to detect retinal angiomas, analysis of urinary or plasma metanephrine levels, abdominal ultrasound, and magnetic resonance imaging. When plasma metanephrine levels are analyzed patients should withhold the use of acetaminophen, because this drug may cause a false-positive result. In addition, tricyclic antidepressants, phenoxybenzamine, diuretics, and β-blockers also interfere with norepinephrine responses to the clonidine suppression test, another modality occasionally used in the diagnosis of pheochromocytoma.

All patients who are diagnosed with familial, early-onset, or multiple pheochromocytomas should be offered genetic testing, because 5% to 11% of patients diagnosed with pheochromocytoma have germ-line mutations of the VHL gene. Approximately 20% of patients with VHL develop a pheochromocytoma at a mean age at diagnosis of 20 years. Cortical-sparing adrenalectomy is the favored approach for resection rather than total adrenalectomy because pheochromocytomas are malignant only 3.3% of the time, and are frequently bilateral. The benefit of this approach lies in avoidance of long-term steroid dependence as well as the risk of an Addisonian crisis. Furthermore, the risk of recurrence of pheochromocytomas for these patients is only 10%. These patients also often require multiple treatments and surgical procedures whereby having adrenocortical function may be of substantial benefit. Patients must be treated with α- and, possibly, β-blockade at least 2 weeks before surgery.

**Syndromes Associated with Cortisol Hypersecretion**

**Carney complex**
The median age of diagnosis of patients with Carney complex is 20 years-old. Cases are often associated with a mutation of the tumor suppressor gene, PRKAR1A

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<th>Box 10</th>
<th>Von Hippel-Lindau disease</th>
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<tbody>
<tr>
<td>Pheochromocytoma</td>
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<td>Pancreatic neuroendocrine tumors</td>
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<td>Pancreatic and renal cysts</td>
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<td>Clear cell renal carcinoma</td>
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<td>Retinal angiomas</td>
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<td>Hemangioblastomas of the nervous system</td>
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<td>Endolymphatic sac tumors of the inner ear</td>
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<td>Cystadenomas of the pancreas, epididymis, and round ligament</td>
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on chromosome 17, or another gene at 2p16, with a 97% penetrance.\textsuperscript{90,91} Patients with this disease have a shortened life span, most often because of cardiac problems associated with cardiac myxomas.\textsuperscript{91,92}

Clinical manifestations of Carney complex begin during the first few years of life, with the identification of abnormal spotty skin pigmentation, and cardiac and cutaneous myxomas.\textsuperscript{91} Testicular tumors, most commonly large-cell calcifying Sertoli cell tumors, and thyroid adenomas or carcinomas (discussed earlier), often develop within the first 10 years of life.\textsuperscript{91} The characteristic lentigines, or spotty skin pigmentation, are often not apparent until puberty and may fade after the fourth decade of life.\textsuperscript{91} Growth hormone secreting pituitary adenomas are most commonly identified during the third and fourth decades of life.\textsuperscript{91} Additional manifestations include mammary myxoid fibroadenoma, epithelioid blue nevus, psammomatous melanotic schwannomas, and osteochondromyxoma.\textsuperscript{91} Diagnosis requires that the patient have 2 or more manifestations of the disease, or 1 manifestation plus a first-degree relative with the diagnosis or an inactivating mutation of the $PRKAR1A$ gene.\textsuperscript{91}

Screening recommendations for postpubertal patients who are diagnosed with Carney complex include annual echocardiograms, urinary cortisol and serum IGF-I levels, and testicular ultrasound for men.\textsuperscript{93} Thyroid ultrasound examinations should be obtained at the time of diagnosis and repeated as needed.\textsuperscript{93} Pediatric patients should undergo annual echocardiograms as well as testicular ultrasound examinations.\textsuperscript{93,94} Routine screening for endocrinopathies in the prepubescent population is not recommended because most of these conditions manifest later in life, although Cushing syndrome can present earlier.\textsuperscript{93,94}

Approximately one-fourth of patients with Carney complex have been diagnosed with primary pigmented nodular adrenocortical disease (PPNAD) (Fig. 3) and can present with corticotrophin-independent Cushing syndrome.\textsuperscript{95} This fraction could be an underestimation of the number of patients with PPNAD, as many have subclinical disease. Moreover, the histologic presence of PPNAD has been found in almost every autopsy of deceased patients.\textsuperscript{96} Patients with subclinical or periodic forms of PPNAD can be identified with the dexamethasone stimulation test.\textsuperscript{96} Symptomatic PPNAD can be cured with bilateral laparoscopic adrenalectomy, as previously described.\textsuperscript{60}

**PANCREATIC ENDOCRINOPATHIES**

**Beckwith-Wiedemann Syndrome**

Fifty percent of children diagnosed with Beckwith-Wiedemann syndrome have hypoglycemia.\textsuperscript{94,96} The hypoglycemia usually resolves after the first few days of life, but in 5% of patients it persists beyond the neonatal period.\textsuperscript{96,97} Persistent hypoglycemia can be severe and may even result in brain damage.\textsuperscript{96} Management primarily involves continuous feeding, but can involve partial pancreatectomy when hypoglycemia cannot be controlled medically.\textsuperscript{96} The etiology of the hyperinsulinemia is unclear, but has been linked to overexpression of a mutated insulinlike growth factor (IGF2) gene.\textsuperscript{96,98}

**Tuberous Sclerosis**

Tuberous sclerosis, an autosomal dominant disorder occurring in approximately 1 in 6700 births, is associated with hamartomas of any organ, but most commonly the brain, skin, kidney, and heart.\textsuperscript{94,99} Other manifestations of the disease include kidney cysts and angiomyolipomas.\textsuperscript{94} Fifty percent to 70% of patients present with sporadic forms of this disease, whereas the remaining 30% to 50% of cases are familial.
Tuberous sclerosis has been linked to the TSC1 gene on the 9q34 chromosome and the TSC2 gene on the 16p13.3 chromosome. Tuberin, a TSC2 gene product associated with cell growth and proliferation, has been linked to the development of malignant pancreatic neuroendocrine tumors associated with tuberous sclerosis. Pancreatic neuroendocrine tumors in these patients can be both nonfunctional and functional. Because of the possible malignant potential of these tumors, surgical resection should be considered.

**Von Hippel-Lindau Disease**

The percentage of patients with VHL who have pancreatic involvement is 20% to 75%. Pancreatic lesions associated with VHL may be the only abdominal finding associated with the disease and may precede other manifestations by several years. Most of the patients with pancreatic involvement have pancreatic cysts, and 10% to 17% of patients are diagnosed with pancreatic neuroendocrine tumors (PNET). One study of 158 patients with VHL showed that among patients with pancreatic involvement 91% had pancreatic cysts, 12.3% had serous cystadenomas, 12.3% had PNET, and 11.5% had combined lesions. Although pancreatic cysts are typically asymptomatic, these lesions can have local compressive effects, require treatment, and thus should be closely monitored. Patients with VHL who are diagnosed with PNET are diagnosed at a younger age (mean, 29 to 38 years) than their sporadic counterparts. In addition, PNETs among patients with VHL can be multiple in nature and are located throughout the pancreas. As many as 60% of PNETs associated with VHL have a clear cell morphology. Patients with PNET

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**Fig. 3.** PPNAD associated with Carney complex. Approximately one-fourth of patients with Carney complex have been diagnosed with PPNAD. Patients with subclinical or periodic forms of PPNAD can be identified with the dexamethasone stimulation test.
involvement require surgical resection because of the malignant potential of these tumors.83,91,100

Patients with VHL should be screened for pancreatic lesions starting at age 12 years.101 Lesions should be resected if there is no evidence of metastatic disease, the lesion is larger than 2 cm if located in the head of the pancreas, and the lesion is larger than 3 cm when located elsewhere in the pancreas.101 In addition, resecting PNETs should be carefully considered if the patient is having an exploratory laparotomy for another manifestation of VHL.101

**Neurofibromatosis 1 (Von Recklinghausen Disease)**

Even though pheochromocytomas are the most common endocrine malignancy associated with NF1, other tumors, such as pancreatic insulinomas (only a few case reports) and duodenal somatostatinomas, have been associated with NF1.66 Patients with duodenal somatostatinomas may present with hyperglycemia, cholelithiasis, and malabsorption, but more commonly complain of nonspecific symptoms, such as weight loss, abdominal pain, or change in bowel habits.75 To date, only 34 patients with both NF1 and duodenal somatostatinomas have been reported in the literature.75 Among these patients, 56% of the tumors measured less than 2 cm.74 Sixty percent of the patients underwent a pancreaticoduodenectomy, whereas the remaining patients had local excision.102 The optimal surgical treatment of duodenal somatostatinomas is unclear at this time.102 Some experts advocate local excision for tumors smaller than 2 cm, and total excision for tumors larger than 2 cm.102 However, given that as many as 70% of surgical cases are associated with regional or portal metastasis, an aggressive surgical approach is indicated.86,100

**SUMMARY**

The development of genetic testing has allowed the identification of patients with familial endocrine diseases. The importance of this technological advancement cannot be underestimated, as some of these inheritable diseases have significant malignant potential. For instance, locating high-risk patients may improve overall survival when prophylactic surgery is warranted, as in familial medullary carcinoma of the thyroid. Similarly, appropriate screening in patients with inheritable diseases will help clinicians recognize specific malignancies early in their course in attempts to achieve the best potential cure. As technology continues to progress, the knowledge base of familial endocrinopathies will continue to expand.

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**REFERENCES**


