Concepts in Thyroid, Parathyroid, and Adrenal Surgery

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Thyroid

Thyroid surgery was rarely performed in the mid-1800s, in part because the mortality rate exceeded 50%. In 1866, Samuel Gross a well-respected American surgeon wrote: "*if a surgeon should be so adventurous, or foolhardy, just to undertake thyroidectomy, I shall not envy him… Every step he takes will be in environed with difficulty, every stroke of his knife will be full by a torrent of blood, and lucky will it be for him if his victim lives long enough to enable him to finish his horrid butchery… No honest and sensible surgeon it seems to me, would ever engage in it.*" It took pioneer surgeons like Theodor Kocher to significantly decrease the operative mortality from this operation utilizing meticulous dissection, minimizing blood lost and protecting the parathyroid glands and the recurrent laryngeal nerve (RLN) by leaving some thyroid tissue behind. By the time Kocher retired in 1912, he had decreased the operative mortality from a thyroidectomy to <2%, teaching others to safely perform this operation worldwide.

Thyroid surgery is performed for both benign and malignant diseases. The major risk of this operation includes injury to the parathyroid glands and the recurrent laryngeal nerve (RLN), and a life-threatening postoperative neck hematoma. Although the standard "Kocher" cervical incision is the most common approach, endoscopic, robotic, and remote access techniques are increasingly performed worldwide. Adjuncts such as RLN monitoring, energy devices for vessel ligation, and hemostatic agents for hemostasis are commonly utilized. Regardless of the approach, thyroid surgery should carry a risk of RLN injury no greater than 2%, and permanent hypoparathyroidism less than 2% and no more than a 3% risk of neck hematoma. The extent of surgical resection is dependent on the disease. The minimal operation for thyroid disease should be a lobectomy including the pyramidal lobe and the isthmus as there is no role for enucleating a thyroid nodule.

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Benign Thyroid Disease

Hyperthyroidism

Overproduction of thyroid hormone results in thyrotoxicosis. Depending on the severity of the thyrotoxicosis, symptoms include nervousness, palpitations, fatigue, weight lost, heat intolerance, and sleep disruption. The most common causes of endogenous hyperthyroidism are Graves' disease, toxic multinodular goiter (TMG), toxic follicular adenoma, and thyroiditis. Endogenous hyperthyroidism can be treated medically, with radioactive iodine, or surgically, depending on the cause.

Graves' disease is the most common cause of endogenous hyperthyroidism, accounting for 75% of thyrotoxic patients. Immunoglobulin G autoantibodies (thyroid-stimulating immunoglobulin (TSI)) produced by B lymphocytes bind and activate the TSH receptor on the follicular cell causing a release of T3 and T4. Approximately 50% of Graves' patients will develop ophthalmopathy characterized by proptosis and periorbital edema. The diagnosis of Grave's disease is confirmed by the demonstration of a suppressed TSH, elevated serum T3 and T4 levels, and the presence of TSI. The thyroid gland is diffusely enlarged, and on I^{123} uptake, scan will demonstrate diffuse uptake as high as 80% in 24 hours.

The initial treatment of Graves' disease is directed at controlling the symptoms of hyperthyroidism and blocking the production of thyroid hormone. This is achieved with the antithyroid medication such as methimazole or propylthiouracil. Biochemical euthyroidism is usually achieved within 6–8 weeks. In addition, the utilization of beta-blocking agents on initial presentation can quickly reduce the beta-adrenergic symptoms. Complete long-lasting remission fol-

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lowing the administration of antithyroid medication can occur in up to 30% of patients. However, 70% of patients will require a more permeant solution to their hyperthyroidism. Radioiodine therapy (RAI) is the most frequently utilized treatment in North America. RAI will take several months to have an effect and may require multiple treatments. Contraindications to RAI include pregnancy, nursing mothers, significant ophthalmopathy, and large goitres.

Surgical management of Graves' disease is becoming more common not just for medical and RAI refractory patients. The advantages of a thyroidectomy include rapid onset of effect and a low recurrence rate. Preoperatively, the patient should be rendered clinically and biochemically euthyroid (normalization of T3 and T4) with antithyroid medication. The addition of Lugol's solution 5 days before the operation helps decrease the vascularity of the gland and the risk of developing thyroid storm perioperatively. The operation of choice is a near-total thyroidectomy. Some surgeons have advocated for a bilateral subtotal thyroidectomy to avoid the need for thyroid hormone replacement. This operation, however, has a greater risk of surgical failure and a higher incidence of recurrence than a total thyroidectomy. A Dunhill procedure (total lobectomy and contralateral subtotal thyroidectomy) is a reasonable alternative to avoid permeant hypoparathyroidism while minimizing the risk of recurrence.

Toxic multinodular goiter (TMG) is most prevalent in areas of endemic goiter and iodine deficiency. Iodine deficiency results in low thyroid hormone production leading to an increase in TSH. This chronic TSH stimulus leads to nodular formation and eventually, the development of autonomously secreting nodules. These patients tend to be older, and many patients present insidiously with cardiac manifestations such as heart failure, atrial fibrillation, tachycardia, and insomnia. In contrast to Graves' disease, the I123 uptake scan will demonstrate patchy uptake in a background of a multinodular goiter. RAI can be utilized in elderly, poor surgical candidates; however, unlike Graves's disease, TMG is relatively RAI refractory and as such, commonly requires surgical intervention. Ideally, the patient should be blocked and rendered euthyroid preoperatively.

With the increased use of amiodarone for refractory ventricular and supraventricular arrhythmias, amiodarone-associated thyrotoxicosis (AAT) has become more prevalent worldwide. The incidence of AAT has been reported between 2 and 18% of patients on this drug. There are two proposed mechanisms for AAT. Type 1 is an iodine-induced phenomenon caused by the excess iodine load from amiodarone in patients with a preexisting goiter. Type 2 AAT is due to the direct toxic effects of the drug on the thyroid, causing follicular destruction and a chemically induced thyroiditis. Patients with AAT demonstrate very poor uptake on radioactive iodine scans, thereby precluding treatment with RAI. Medical management of AAT involves the discontinuation of amiodarone (if possible) and the utilization of antithyroid medication. Unfortunately, because of the long half-life of amiodarone (107 days), it can take several months before a clinical effect is achieved. Steroids have been shown to be beneficial in AAT type 2. Many of these patients cannot tolerate the stoppage of the amiodarone, and also require a prompt resolution of their thyrotoxic state. Total thyroidectomy has been shown to be an effective treatment of AAT, despite the significant perioperative comorbidities these patients have.

A toxic follicular adenoma is benign discrete nodule that secretes thyroid hormone independent of TSH control. A suppressed TSH and a thyroid scan demonstrating a hot autonomous nodule with suppression of the reminding thyroid gland confirm the diagnosis. These lesions are rarely malignant (<1%), and fine-needle aspiration (FNA) is not recommended as it may be misleading (often demonstrating cellular atypia). The natural history of these lesions follows the "rule of thirds." One-third of these nodules will involute, one-third will demonstrate no change in size or hormone production and one-third will progress. Although RAI can be utilized in these patients, thyroid lobectomy results in complete cure and rarely do these patients require thyroid hormone supplementation postoperatively.

Multinodular Goiter

Multinodular goiter (MNG) is an enlarged thyroid gland containing multiple colloid and hyperplastic nodules. MNG is one of the most common endocrine disorders worldwide affecting up to 600 million people. The etiology appears to be multifactorial. Causes include iodine deficiency, goitrogens (substances that induce thyroid enlargement), and genetic predisposition. Surgical indications for multinodular goiter are as follows: 1) suspicious or confirmed thyroid cancer, 2) toxic multinodular goiter (as discussed above), 3) compressive symptoms, 4) documented growth, and 5) a significant retrosternal component. Signs and symptoms of compression of the trachea, esophagus, the vascular structures, or the RLN may occur; and these should all be included in the initial assessment. A history looking for difficulty in lying flat, disrupted sleep, and an audible stridor all suggest tracheal compression. The physical finding of a positive Pemberton sign (venous congestion of the face when both arms are raised over the head) is used to detect compression at the thoracic inlet by the goiter. Although exceedingly rare, a direct laryngoscopy should be done to assess function of the RLN. Cross-sectional imaging has facilitated the assessment of tracheal compression, retrosternal extension not adequately assessed with physical exam, and the documentation of significant growth.

When indicated, total thyroidectomy has become the operation of choice for MNG.

Thyroid Carcinoma

Thyroid cancer is the ninth most commonly diagnosed cancer and comprised of approximately 4% of all new cancers in North America. The majority (90%) are well-differentiated thyroid cancer (WDTC) derived from the follicular epithelial cells. The histological subtypes of WDTC include papillary (80%), follicular (5–8%), and Hurthle or oncocytic carcinomas (5%). Exposure to ionizing radiation, particularly in the pediatric population, and high iodine intake have each been associated with an increased risk of developing WDTC. Although most WDTC are sporadic, familial forms associated with familial adenomatous polyposis, Carney's complex, and Cowden's syndrome are well recognized.

Medullary thyroid cancer (MTC) (5%) arises from the parafollicular C cells and is both clinically and genetically distinct from WDTC. Most MTC are caused by an activating mutation in the RET protooncogene, and 25% carry a germline mutation.

Anaplastic thyroid cancer is exceedingly rare and comprises of <1% of all thyroid cancers.

Ultrasound, Fine-Needle Aspiration, and Molecular Testing

Over the last two decades, the incidence of WDTC has been increasing at a rate of 6% per year. This increase is in part related to the increase in detection of small subclinical thyroid cancers by widespread use of neck ultrasounds (US) and fine-needle aspirations (FNA). Since most thyroid nodules are benign, stratification with ultrasound and, ultimately, FNA has significantly reduced the need for thyroid surgery. Standardized thyroid ultrasound reporting, developed in 2015, by the American College of Radiology (ACR) has become the expectation of clinicians in their diagnostic workup. The American Thyroid Association (ATA) recently stratified these sonographic patterns of thyroid nodules and their potential risk of malignancy, developing an algorithm for ultrasound-directed FNA. Solid, hypoechoic nodules with irregular borders, microcalcifications, taller than wider, and with evidence of extrathyroid extension are highly suspicious features of malignancy and require FNA. In contrast smooth cystic or spongiform lesions rarely require FNA. Thyroid FNA cytology should be reported using the diagnostic categories outlined by the Bethesda reporting system in 2007. Each of the six diagnostic categories have a calculated risk of malignancy, allowing for a more informed and educated discussion with the patient regarding the need for thyroid surgery. Bethesda 5 (suspicious for malignancy) or Bethesda 6 (malignant) have an estimated cancer risk of 60–75% and 97–99% respectively. As such, surgical intervention is recommended. Benign lesions, Bethesda 2, have only a 0–3% chance of malignancy and, therefore, can be safely observed.

It is the Bethesda 3, atypia or follicular lesion of undetermined significance (AUS or FLUS), and Bethesda 4, the follicular neoplasm, that continue to be a challenge for both the surgeon and the patient. The estimated risk of cancer for an AUS/FLUS lesion is 5–15% and 15–30% for a Bethesda 4 lesion. As a general rule, a repeat FNA is recommended for AUS/FLUS lesions as a more definite diagnosis occurs >70% of the time. For the Bethesda 4 lesion, a diagnostic lobectomy is recommended.

More recently, the development of molecular testing has focused on these two indeterminate groups in the hopes of avoiding unnecessary surgery and decreasing the need for completion thyroidectomy. Molecular testing on thyroid lesions can be categorized into two groups, a "rule out" test and a "rule in" test. The ideal "rule out" test would have a negative predictive value (NPV) similar to the Bethesda 2 category (3%) and a "rule in" test would carry a positive predictive value similar to Bethesda 6 (98%). A 167 gene expression classifier has been proposed as a "rule out" test due to its relatively high NPV of 93%. It, therefore, can be utilized in those patients with AUS/FLUS lesions in whom non-surgical management or active surveillance is considered. Mutations in *BRAF, RET/PTC*, or *RAS* have been seen in over 70% of papillary thyroid cancer, and *PAX8/PPAR* gamma mutations are found in 80% of follicular cancers. Identifying point mutations, deletions, and gene re-arrangements of these genes with a next-generation sequencing panel is now commercially available. Proponents of this molecular test have illustrated its utilization as a "rule in" test with a sensitivity of 90% in predicting cancer in the cytological follicular neoplasm Bethesda 4. The Pittsburg group utilizes this test to rule in malignancy in a follicular neoplasm, allowing the surgeon to go directly to a total thyroidectomy instead of a diagnostic lobectomy at the initial procedure. However, with the current ATA guidelines suggesting that some low-risk WDTC no longer require a total thyroidectomy, it is unclear how gene panel molecular testing will be utilized in the future. The use of molecular testing on indeterminate FNA specimens is involving. Currently molecular testing of FNAs is utilized to help stratify treatment options for the patient, either surgical intervention or active surveillance At the present time, these tests should not replace clinical judgment or the clinical findings on physical exam and/or sonographic evaluation.

Surgical Treatment of Thyroid Cancer

Well-Differentiated Thyroid Cancer

The extent of surgery for WDTC is currently under considerable debate with the publication of the 2015 ATA guidelines. In the past, most centers performed a total thyroidectomy for

WDTC ≥1 cm, as it allowed for the ease of postoperative surveillance with thyroglobulin and the administration of RAI when deemed necessary. Recently, retrospective evidence from large institutional databases have demonstrated that, in low-risk WDTC (solitary lesions <4 cm with no extrathyroidal extension or lymph node involvement), the extent of the initial operation had little effect on disease-specific survival. In addition, it appears that salvage surgery is effective in the few patients who do reoccur following thyroid lobectomy alone. For these reasons, the 2015 ATA guidelines have recommended a thyroid lobectomy in low-risk WDTC. Completion thyroidectomy is recommended in those patients who on final pathology are upstaged to an intermediate- or high-risk category. For all WDTC ≥4 cm, total thyroidectomy remains the treatment of choice. It is however, too early to evaluate what the impact of performing a lesser operation will have on the long-term survival of these patients.

The extent of lymph node dissection in the clinical negative patient has also undergone considerable debate. Regional microscopic lymph node disease is found in approximately 50% of PTC patients. The ability to assess level VI disease with US or by inspection had proven to be inaccurate. This led many surgeons to perform prophylactic central lymph node dissections (pCND) without evidence that it changed survival. Prophylactic CND did, however, upstage 30–50% of patients, likely resulting in a greater utilization of RAI therapy. The jury is still out as to the benefit of pCND in low-risk patients. It may be beneficial in T3 or T4 tumors to help guide postoperative management. However, there is an increased risk of injury to the RLN and parathyroids with CND. Therapeutic compartmental neck dissections should be done in patients with clinically proven metastatic disease for local/regional control. Lateral lymph node mapping with US should be done to aid in the preoperative planning.

Follicular WDTC rarely spreads via the lymphatics and as such regional nodal disease is found in only 5% of patients. Small, encapsulated follicular carcinomas can be adequately treated with a lobectomy. However, total thyroidectomy allows for the assessment of occult distant metastatic disease with RAI and is advocated by many for the treatment of follicular carcinoma. In contrast, Hurthle cell carcinoma can spread to both the lymph nodes (30%) and hematogenously. Preoperative lymph node assessment should be done in all Hurthle cell carcinomas and a therapeutic compartmental neck dissection included with the total thyroidectomy in those with suspicious nodal disease.

Papillary thyroid cancer less than 1 cm in size (MicroPTC) is becoming a growing health-care problem for both patients and clinicians. With the increased utilization of head and neck US, MicroPTC are incidentally discovered with increasing frequency. The concern as to whether all these lesions require surgical removal has been raised. The Japanese have been successfully following MicroPTC with only 8% demonstrating progression at long-term follow-up. Although MicroPTC can metastasize, most have an indolent biological behavior and most surgeons agree that a unilateral lobectomy, if undertaken, is all that is required when confined to the thyroid.

Medullary Thyroid Cancer

Most MTC are sporadic (75%) presenting with a solitary lesion, while hereditary MTC are usually bilateral and multicentric. Involvement of both the central and lateral nodal compartments is common in both sporadic and hereditary MTC (50–80%). Cytopathology can usually distinguish MTC from WDTC. Most of these cancers secrete calcitonin and CEA, although they can also secrete vasoactive peptide and ACTH. All patients diagnosed with MTC should undergo genetic testing. Multiple endocrine neoplasia (MEN) types IIa and IIb have other associated tumors that need to be assessed prior to surgical intervention on the thyroid. Screening for a pheochromocytoma and hyperparathyroidism is essential as the adrenal disease should always be treated prior to the MTC. Familial MTC (FMTC) is a hereditary form of MTC that is not associated with the other endocrine neoplasms of MEN II. Specific codon mutations of the *RET* gene have identified the particular phenotype of FMTC versus MEN IIa and MEN IIb. The ATA has developed a stratification system correlating genotype with the risk of aggressiveness of the MTC. This has helped define when to initiate screening of the at-risk patients and when to perform prophylactic thyroidectomy to avoid the development of MTC.

Serum calcitonin and CEA levels should be done preoperatively. Lymph node mapping with neck US and/or cross-sectional imaging of the neck and mediastinum is required. Additional metastatic workup for distant disease should be included in patients with lymph node disease or calcitonin levels >400 pg/ml. The appropriate surgical management of MTC includes a total thyroidectomy and bilateral central neck dissection. Lateral neck dissection should be included when clinically concerning lateral nodal disease is detected or in patients with calcitonin levels >400 pg/ml.

Parathyroid

Calcium is essential for a variety of physiological functions, including cellular signaling, muscle contraction, nerve conduction, and skeletal maintenance. Parathyroid hormone (PTH) is the key hormone responsible for calcium homeostasis. PTH is produced by the parathyroid glands in response to a low ionized serum calcium. This 84 amino acid peptide has a very short half-life (2–4 minutes) allowing for minute-by-minute regulation of serum calcium. PTH stimulates calcium reabsorption in the distal nephron of the kidney, causes reab-

sorption of bone, and indirectly increases the absorption of calcium from the gastrointestinal tract via vitamin D. Hyperparathyroidism (HPT) is an inappropriate production of PTH from hyperfunctioning parathyroid gland(s). There are three types of hyperparathyroidism. Primary hyperparathyroidism (PHPT) is defined as an inappropriate autonomous production of PTH from a parathyroid adenoma (80–85%), diffuse parathyroid hyperplasia, or multiple adenomas (15–20%), or parathyroid carcinoma (1%). Secondary hyperparathyroidism (SHPT) is an adaptive response of the parathyroid glands to chronic hypocalcemia and/or hyperphosphatemia. Chronic renal failure is the most common cause of secondary HPT; however, other causes such as malabsorption syndromes, vitamin D deficiency, chronic lithium therapy, liver disease, and juvenile rickets also result in chronically low ionized calcium levels. In tertiary hyperparathyroidism (THPT), one or more parathyroid glands function autonomously and, thus, inappropriately secrete PTH. It typically occurs after prolonged SHPT, despite the correction of the underlying cause of the low ionized calcium state such as a renal transplant. Each of these conditions is considered in greater detail in the sections which follow.

Primary Hyperparathyroidism

Primary HPT is the third most common endocrine disorder, with a prevalence of 1% in the adult population. It occurs more commonly in women with the incidence increasing drastically after the age of 55. Approximately 95% of all cases of PHPT are sporadic. When first described in the late 1920s, the clinical manifestations of this disease were the result of the end-organ effects from prolonged untreated HPT such as osteitis fibrosis cystica, nephrolithiasis, and significant myopathies. Today these clinical manifestations are rarely seen with only 5% of patients presenting with osteitis fibrosis cystica and 15–20% with nephrolithiasis. Most patients are diagnosed on routine laboratory evaluation demonstrating an elevated serum calcium. Many symptoms associated with PHPT are vague and nonspecific including weakness, difficulty in concentrating, polyuria, and irritability. The vague nature of these symptoms has made it difficult to quantify preoperatively, leading some to believe that the majority of patients are asymptomatic. There are, however, many prospective studies that have documented an improvement in these vague nonspecific symptoms following successful parathyroidectomy, illustrating that these symptoms are true manifestations of the disease.

The diagnosis of HPT is biochemical. An elevated serum calcium level, low-normal serum phosphate, with an inappropriately elevated PTH level in the absence of hypocaluria confirms the diagnosis. Serum Vitamin D 25(OH) and creatinine levels should also be included to rule out secondary HPT. Multiple endocrine neoplasia type I and type IIa, hyperparathyroidism-jaw tumor syndrome, and familial isolated HPT comprise the familial forms of PHPT. Hereditary HPT syndromes are more likely due to multigland disease and are associated with additional endocrine and nonendocrine tumors. It is, therefore, important to obtain a family history and consideration for genetic screening in young patients preoperatively.

Once the diagnosis is established, assessment of end-organ disease is sought. Bone mineral density (BMD), an ultrasound of the kidney looking for occult kidney stones, 24-hour urinary calcium, and a creatinine clearance complete the assessment. Preoperative imaging is not diagnostic and should only be utilized for surgical planning. The indications for surgery include all symptomatic patients, patients <50 years of age, those with t-scores ≥ -2.5 at any site on BMD, or documented fragility fracture, nephrolithiasis, and high urinary calcium. Most patients with the diagnosis of PHPT should have a surgical assessment to discuss the risk versus benefit of a parathyroidectomy regardless of whether they meet the guideline criteria outlined above.

Preoperative imaging is recommended in all surgical candidates as it can help focus on the operation, provides insight into the possibility of the disease being multigland or ectopic, and allows for assessment of concomitant thyroid nodules prior to surgical exploration. Cervical ultrasound (US), technetium-99 m sestamibi scan (MIBI), and 4D-CT scans are the most commonly utilized modalities. Single-photon emission computed tomography (SPECT) MIBI has a distinct advantage over planar imaging as it allows for more anatomical detail on the functional scan. Unfortunately, MIBI scans are poor at distinguishing single- from multigland disease and ultrasounds are operator dependent, demonstrating that positive imaging is no substitute for an experienced parathyroid surgeon. Nonlocalizing MIBI scans can be seen in up to 40% of patients with PHPT and should not be a deterrent for parathyroid exploration by an experienced surgeon. The sensitivity and positive predictive value in patients with a solitary adenoma have been reported to be 76% and 93% for US, 79% and 91% for MIBI, and 89% and 94% for 4D-CT.

Secondary and Tertiary Hyperparathyroidism

Secondary HPT is an adaptive response of the parathyroid glands to chronic hypocalcemia and/or hyperphosphatemia, most commonly seen in chronic renal failure. As the renal failure progresses, so does the SHPT moving from an adaptive process to a pathological one. Medical management of dialysis patients directed at lowering the phosphate levels with phosphate binders, or calcium and vitamin D, or with calcimimetic drugs has delayed the need for surgical inter-

vention in these patients. Operative indications for progressive SHPT include: failure of medical management to control hypercalcemia and/or hyperphosphatemia, PTH > 500 pg/ml, calciphylaxis, progressive myopathy, and a decreasing BMD. There is also a growing body of literature that recommends surgery for severe progressive SHPT prior to renal transplant to avoid significant hypercalcemia postoperatively.

Long-standing SHPT causes parathyroid gland hyperplasia, and failure of hyperplastic glands to involute following renal transplant leads to autonomous function. Tertiary HPT is typically diagnosed 6 months following a renal transplant and has a similar biochemical profile to that of PHPT. The incidence of THPT following transplantation is approximately 10% (5–30%). Indications for surgery include persistent symptomatic hypercalcemia, declining graft function, nephrocalcinosis, pancreatitis, pathologic bone fracture, pruritus, musculoskeletal pains, or markedly increased PTH levels. In contrast to progressive SHPT, where all four glands are involved, recent literature suggests that approximately 20% of posttransplant THPT patients will have involuted some of their parathyroid glands, allowing for a limited resection following bilateral neck exploration.

Parathyroidectomy

There are three operations for HPT: bilateral neck exploration (BNE), unilateral exploration, and a focused, imaged-directed procedure. Each procedure has advantages and disadvantages, and the surgeon must appropriately select the best operation for each patient. Bilateral neck exploration is the gold standard operation. All four parathyroid glands are visualized and the abnormal one(s) removed. This operation does not require preoperative imaging, however, most surgeons would perform a cervical ultrasound; or does BNE require intraoperative PTH (iPTH) to tell the surgeon if he/she is dealing with single- or multigland disease as the morphological appearance of the glands in experienced hands usually is adequate to achieve a > 98% success rate. BNE is indicated in patients known or suspected to have multigland disease (familial HPT, SHPT, and THTP), failure of iPTH to fall during a more limited approach, and in many cases of nonlocalizing preoperative imaging.

Unilateral exploration is a morphological assessment of both parathyroid glands on the same side. This procedure, first described in 1976, was developed long before preoperative imaging was available. Given the fact is that >80% of patients with PHPT will have a solitary adenoma, if one abnormal and one normal parathyroid glands were found on the first side explored, then the operation was terminated as diffuse hyperplasia was ruled out. This approach in experienced hands resulted in a 95% cure rate, albeit with a 50% conversion to the contralateral side when unilateral criteria were not met. Today, even with preoperative imaging, up to 35% of patients will still require conversion to the contralateral side due to inability to find the ipsilateral normal gland, false-positive imaging, or multigland disease was found. Many surgeons use this approach with the additional adjunct of iPTH to direct when a bilateral exploration due to asymmetrical hyperplasia or double adenoma is warranted; thus, minimizing the exploration while achieving >97% success rate.

The third surgical approach is an imaged-directed or minimally invasive parathyroidectomy. This is a focused exploration, visualizing and removing only the parathyroid abnormality seen on preoperative imaging. To avoid failure resulting from undiagnosed multigland disease, many surgeons utilize iPTH. Although recently there have been concerns raised about the longevity of this operation compared to the bilateral procedure, it does appear to be successful in correcting the hypercalcemia in over 95% of patients for at least 8–10 years. This procedure does rely on the accuracy of preoperative imaging and is appropriate in approximately 60% of patients with sporadic PHPT. Minimally invasive parathyroidectomy can be performed in a variety of ways; from a focused open approach under regional block to an endoscopic or remote access exploration.

Adrenal

The layers of the adrenal gland, the cortex and the medulla, have distinct embryological development explaining the diverse physiological functions of these paired organs. The outer cortex derived from the mesoderm has three distinct layers: the zona glomerulosa, fasciculata, and reticularis. These layers are responsible for the production of aldosterone, cortisol, and sex steroids, respectively. The inner medulla develops from neural crest cells from the spinal ganglia. Ectopic adrenal tissue can be found along the path of embryologic migration; in the gonads, within or adjacent to the paraaortic sympathetic chain, or at the aortic bifurcation.

Primary tumors arising from the adrenal gland should be classified as either benign or malignant and screened for overt function. Screening for function includes a detailed history and physical exam, aldosterone:renin ratio in hypertensive patients, either a 24-hour urinary free cortisol or a 1 mg overnight dexamethasone suppression test, and a serum DHEA-S if androgen function is suspected. To rule out catecholamine excess, either 24-hour urinary metanephrines or plasma free metanephrines should be done. As a rule, all functioning adrenal tumors should be removed. Small, benign nonfunctioning adrenal lesions can be safely observed, whereas indeterminate lesions regardless of size may require resection for diagnosis. Larger lesions (> 6 cm)

have an increased risk of being adrenal cortical carcinomas (ACC) and should be assessed for surgical resection. The adrenal gland is a common site for metastases from such malignancies as renal cell, breast, and melanoma. These secondary adrenal lesions are found in 5% (0–18%) of series that include all patients with an adrenal mass. In highly selected patients, resection of an isolated adrenal metastases maybe indicated.

Adrenal Incidentalomas

An adrenal incidentaloma is an asymptomatic adrenal mass detected on imaging performed for nonadrenal indications. The widespread use of cross-sectional imaging has resulted in the increased discovery of asymptomatic adrenal lesions in medical practice. From autopsy series, the prevalence of clinically inapparent adrenal masses ranges from 1 to 9% (mean of 2%). This prevalence increases with age, as adrenal lesions are rarely seen in patients under the age of 20, yet approaches 10% in those over the age of 70. Most adrenal incidentalomas are nonfunctioning (75%). From mostly surgical series, 12% of these lesions will ultimately prove to be producing cortisol, 3% aldosterone, and 7% will be catecholamine-secreting pheochromocytomas. Approximately, 8% of incidentally found lesions will be ACC. In patients with a known malignancy, the likelihood of the incidentaloma being a metastatic lesion is approximately 25–36%, whereas the prevalence is less than 0.5% in patients with no previous history of cancer. In a recent review, however, Cawood suggested that the prevalence of functioning and malignant lesions has likely been overestimated given most of the reported series in the literature are either surgical- or oncology-based series.

The diagnostic workup of an adrenal incidentaloma includes functional screening and an assessment on cross-sectional imaging. Adrenal myelolipomas, adrenal hemorrhage, and simple adrenal cysts have classic characteristic findings on computed tomography (CT) or magnetic resonate imaging (MRI). Benign adrenal cortical adenomas contain a variable amount of cytoplasmic lipid, which enables the use of Hounsfield units (HU) on CT or chemical shifts on MRI to characterize these lesions as benign. Nonenhanced lesions that are <10 HU are benign, as are those lesions that have a relative washout of contrast of >50% utilizing an "adrenal protocol" CT. Dual gradient-echo sequence MRI can also characterize the lesion as a benign adenoma if there is a loss of signal compared to in-phase imaging. Most surgical guidelines utilize the cutoff for resection at 4 cm, although the risk of malignancy is only 10%. Large lesions >6 cm have a higher likelihood of being an ACC (25%) and should be considered for surgical resection in appropriately selected patients. Radiographically intermediate lesions between 2 and 4 cm need to be assessed by a multidisciplinary team for consideration of resection, further imaging with an alternative modality or close observation. Recent evidence suggests that the utilization of FDG-PET scans can help in this scenario as positive uptake likely reflects a malignant process.

Primary Aldosteronism

Primary aldosteronism (PA) is the most common cause of secondary hypertension. The prevalence of this disease in the hypertensive population is approximately 10%, and 25% in those patients with refractory hypertension. PA is characterized by autonomous secretion of aldosterone resulting in the suppression of plasma renin. Historically, hypokalemia was utilized as a screening tool for the diagnosis of PA. It is now recognized that less than 38% of patients with PA will present with hypokalemia. The diagnostic screening modality utilized today is an aldosterone:plasma renin activity greater than 30. Several authors recommend a confirmatory salt-loading suppression test to be done prior to anatomical cross-sectional imaging. PA can be caused by a unilateral functioning adenoma (Conn's syndrome) or by adrenal hyperplasia (either bilateral (BAH) or, rarely, unilateral). Older series stated that only 33% of PA patients have a unilateral adenoma, while recent series from hypertensive centers that routinely perform adrenal vein sampling (AVS) have demonstrated that 60% of PA patients have a unilateral source for their disease, suggesting a significant underdiagnosis rate of Conn's syndrome.

Identifying appropriate candidates for surgical intervention can be challenging. The mean size of an aldosteronoma is estimated to be 1.7 cm with 17% of adenomas less than 1 cm. As such a CT scan may not detect these small lesions. In addition, the incidence of nonfunctioning adenomas increases with age. This has led many authors to recommend the routine use of AVS in all surgical candidates with PA. Comparison of cross-sectional imaging to AVS has demonstrated that 20% of patients would not be offered surgical correction of unilateral disease based on CT findings alone. In 4% of patients, the CT findings would incorrectly identify the side of autonomous aldosterone production, and up to 15% of patients, if CT alone was utilized, would have failed surgical intervention as AVS demonstrated BAH. However, AVS is not readily accessible to all surgeons and if done poorly is of limited value. Bilateral canalization of both adrenal veins is paramount to the procedure and the success rate in the literature ranges from 60% to 97%.

BAH should be treated medically, whereas unilateral disease is best treated with an endoscopic adrenalectomy. Surgical resection for Conn's syndrome will lead to resolution of hypokalemia almost 100% of the time, cure of hypertension 35–45% of the time, improvement in blood pressure

control or decrease in antihypertensive medication in 50–60%, and failure to change the hypertensive state in 5% of patients.

Cushing's Syndrome

Endogenous Cushing's syndrome is a result of overproduction of cortisol from the adrenal glands. This is further classified into adrenocorticotropic hormone (ACTH)-dependent (80%) and ACTH-independent (20%) Cushing's syndrome. ACTH-dependent Cushing's syndrome is most commonly caused by an anterior pituitary adenoma (Cushing's disease) or rarely from ectopic ACTH production from small-cell lung carcinomas, and neuroendocrine tumors including gastrinomas, pheochromcytomas, and MTC. ACTH-independent Cushing's syndrome is caused by unilateral adrenal tumors (benign cortical adenomas in 10%), ACC (8%), or bilateral micro- or macronodular hyperplasia (2%).

Establishing the diagnosis of cortisol excess is the first step in the diagnostic / treatment algorithm. A 24-hour urinary free cortisol, a 1 mg overnight dexamethasone suppression test, or a midnight salivary cortisol can be utilized to diagnosis hypercortisolism. Once confirmed, an ACTH measurement will delineate whether it is ACTH independent or not. If ACTH is elevated, then a pituitary MRI should be ordered; and if negative, consideration of an ectopic source should be explored. If the ACTH level is suppressed, then cross-sectional imaging of the adrenal glands is warranted. Patients with unilateral adrenal lesions should be considered for adrenalectomy. Perioperative coverage with steroids is required as the contralateral adrenal gland is usually suppressed and return of the normal hypothalamic pituitary adrenal axis can take up to 2 years to resolve.

Pheochromocytoma/Paraganglioma

Pheochromocytoma is a tumor arising from the adrenal medulla, whereas a paraganglioma refers to a similar tumor arising from the extraadrenal sympathetic and parasympathetic ganglia. Pheochromocytomas and paragangliomas arising from the sympathetic ganglia secrete excess catecholamines. Paragangliomos arising from the parasympathetic chain are usually nonfunctional. These excess catecholamines cause episodic, paroxysmal hypertension, headaches, palpations, and diaphoresis. The old "rule of 10" (10% are genetic, 10% are malignant, 10% are bilateral, and 10% are found in children) no longer applies. It is now estimated that over 25% of these tumors have a germline mutation; these are associated with far more bilateral tumors, and the identification of more tumors in children. Most guidelines recommend that all patients presenting with a pheochromocytoma/paraganglioma be genetically screened for the known susceptible genes. To date, these include: RET proto-oncogene associated with MEN 2 [RET], von Hippel-Lindau [vHL], type 1 neurofibromatosis [NF1], and succinate dehydrogenase subunits [SDH – A, B, C, and D] associated with familial paraganglioma syndromes, MAX and TMEN127.

Diagnosis is established with either 24-hour urinary fractionated metanephrines or plasma free metanephrines. Urinary metanephrines have a high specificity (93–98%) and reasonable sensitivity (77–90%). Plasma free metanephrines when collected appropriately have a higher sensitivity (96–100%) but lower specificity of 85–89%. Surgical resection should be undertaken for all functioning pheochromcytomas and paragangliomas. Preoperative alpha-blockade and adequate volume resuscitation are recommended prior to resection to minimize the operative fluctuations in blood pressure.

Surgical Approaches to the Adrenal Gland

The advent of endoscopic approaches to the adrenal gland has greatly improved the surgical care of these patients. Endoscopic approaches have resulted in earlier mobilization, shorter length of stay, decrease analgesic requirements, and fewer postoperative complications compared to open adrenalectomy. The adrenal can be approached either anteriorly via a laparoscopic approach, or endoscopically via a posterior retroperitoneal approach (PRA). The PRA is an ideal operation for tumors less than 6 cm or in patients with previous abdominal surgery. The anterior laparoscopic adrenalectomy is a great approach for larger benign adrenal tumors. Open adrenalectomy is recommended for ACC or large tumors (>10 cm) highly suspicious for ACC. Thus, the adrenal surgeon must master both open and endoscopic approaches to the adrenal gland and appropriately select the surgical approach based on the patient and the tumor's imaging characteristics.

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