Audio Companion for SESAP® 16
ENDOCRINE — Category 6

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*The following faculty report no relevant financial interests:* Dr Dina M Elaraj.
Thyroid Nodules: Fine-Needle Aspiration Biopsy

The approach to a patient with a thyroid nodule has definitely changed. Currently, the only indication for a radioactive iodine scan is to determine whether hyperthyroidism is coming from an autonomously functioning nodule or from the entire thyroid gland. If a patient is euthyroid, we do not get radiiodine scans. Instead we rely very heavily on thyroid US and fine-needle aspiration (FNA) biopsy. Thyroid nodules are common, with a prevalence of ≤5% in children and up to 35% to 50% in adults. Because most thyroid nodules are benign, it is not practical to biopsy every nodule. However, the risk of malignancy is different in children versus adults. In children, the risk of malignancy is about 25%, so we must be more suspicious of a thyroid nodule in a child. These are more commonly diagnosed in adolescents. The risk of malignancy in an adult ranges from 5% to 15%. The American Thyroid Association just revised their guidelines for both the pediatric and adult populations that give us some guidance regarding which nodules to biopsy, which is really based on both size and sonographic pattern. The two main sonographic features associated with an increased risk of malignancy are hypochoegenicity and microcalcifications. The guidelines subdivide nodules into risk categories, and we choose nodules to be biopsied based on size plus appearance.

FNA Biopsy: At my institution, I do all my own FNA biopsies in the office. I chose the nodule for biopsy, give 1 mL of lidocaine as local anesthesia (some people do it without local anesthesia), and then I usually start with a 25-gauge needle and, under US guidance, can target the nodule. I apply a little suction to the syringe, and once I get a little flash in the needle hub, that is enough. I have a medical assistant who prepares the slides for me. Some people use a 27-gauge needle, which is fine, and some people have a cytopathologist on site that reviews the specimens for adequacy (are there enough cells to interpret the biopsy?). I do not do it that way because my unsatisfactory or inadequate rate is so low that it is not worth it (<5% unsatisfactory rate means no cytopathologist need be present). I submit three slides.

Thyroid Nodules: Indeterminate Nodules on FNA Biopsy

Sometimes FNA biopsy of a thyroid nodule comes back from the cytopathologist as “indeterminate.” If you consider “indeterminate” as the main title of the category, then three subcategories come under this heading.

AUS: The first subcategory is “atypia of undetermined significance” (AUS), which is also known as “follicular lesion of undetermined significance.” The risk of malignancy in this diagnostic category is approximately 15%. The cytopathologist is seeing some normal cells, but some cells are not normal or are arranged in an abnormal pattern, but not abnormal enough to be classified in a more worrisome diagnostic category. Generally, we just repeat the biopsy a couple of months later, which can sometimes put it into a more definitive diagnostic category. If we get two AUS diagnoses, then we talk to the patient about surgery for a definitive diagnosis.

Suspicious for Neoplasm: The second indeterminate subcategory is “follicular or Hürthle cell neoplasm” or “suspicious for neoplasm.” This subcategory causes a lot of confusion because some people think it means cancer, but it does not. Instead, it just means that the cytopathologist sees cells arranged in a microfollicular pattern. The risk of malignancy in this diagnostic category ranges from 20% to 30%. Malignancy is defined by capsular or vascular invasion, meaning a diagnostic thyroid lobectomy is required to make a definitive diagnosis.

Suspicious for Malignancy: The third indeterminate subcategory is “suspicious for malignancy,” by which they mean suspicious for papillary thyroid cancer. The risk of malignancy in this diagnostic category ranges from 50% to 75%. We take all of these patients to the operating room and do a hemithyroidectomy with a frozen section, and if cancer is diagnosed, then we do a total thyroidectomy.
Indeterminate Thyroid Nodules: Molecular Marker Tests

Most thyroid nodules classified as “indeterminate” on FNA biopsy are ultimately benign. Because of this, great interest is being shown in figuring out how to determine which nodules are benign without taking patients to the operating room. Multiple commercial tests broadly called “molecular testing” have become available for this purpose.

**Afirma:** The gene expression classifier (GEC) test is made by a company called Veracyte® and the test is called the Afirma® Thyroid FNA Analysis. Cells gathered during FNA biopsy are saved in a DNA preservation solution and sent to the company, which runs the test on the cells from the nodule in question. The Afirma test runs the patient’s sample against an RNA expression array that contains 142 cDNA fragments. Because these fragments are all proprietary, the company does not tell us which genes are evaluated. The lab gives us either a benign result or a suspicious result. It is marketed as a “rule-out test” because the negative predictive value for a benign result is approximately 95%. The positive predictive value of a suspicious result is approximately 5% to 40%. Therefore, most nodules considered as “suspicious” by this test turn out being benign. This test’s main limitation is that, if a lot of Hürthle cells are present in the specimen (most commonly seen in Hashimoto thyroiditis), most of the results will be in a suspicious category because of the way the test was developed. Therefore, one may decide not to submit the specimen for this test if a lot of Hürthle cells are found in the specimen.

**ThyroSeq:** ThyroSeq® is a gene panel test made by CBLPath, Inc. This test is called “next generation sequencing” and looks at 14 cancer-related genes and 42 gene fusions known to be associated with papillary thyroid cancer. It also looks at multiple “hot spots” in these genes. The company tells us what genes they are evaluating. This test is marketed as a “rule-in test” because, if a mutation is discovered in a gene, then the risk of thyroid cancer is approximately 80% to 85%. The patient would need an operation for something like that. The negative predictive value is similar to that of Afirma.

**ThyraMIR:** The third test is ThyraMIR™ made by Interpace® Diagnostics. Like ThyroSeq, it is a gene panel test that looks at genes and gene mutations. It is also considered a “rule-in test.” The negative predictive value for ThyraMIR is not as good as that for ThyroSeq, and so this company has added a microRNA panel to improve the test’s negative predictive value. This test’s main limitation is that it was a retrospective study tested on FNAs of surgical specimens. I think we need more data to tell us the actual value of this test.

**Conclusions:** Use of these molecular marker tests is controversial. They can provide some information and they are very expensive. I do not believe they should be used reflexively.

**Thyroid Nodules: Positive, Negative for Malignancy Results for FNA**

Other than the indeterminate category, the results of FNA biopsy of thyroid nodules are either going to say “negative for malignancy” or “positive for malignancy.” We should know that a “negative for malignancy” result has a false-negative rate of 3% or 4%, depending on the institution. We tend to treat a “negative for malignancy” result as being a benign nodule, but these two are not exactly equivalent. Therefore, these patients all need follow-up US, and according to the American Thyroid Association (ATA), the follow-up US needs to be performed between 6 and 18 months after the initial biopsy.

A positive result (“positive for malignancy”) is only going to be positive for papillary thyroid cancer. Follicular thyroid cancer cannot be diagnosed based on FNA. Instead, the results come back in this follicular neoplasm category, and the false-positive rate of a positive follicular neoplasm result is <1% but it is not zero.

**US Follow-Up:** In my follow-up, I perform an US of the nodule. If there is no change in the size or sonographic characteristics of the nodule, I will then repeat the US every 3 to 5 years as recommended by the ATA.
Papillary Thyroid Cancer: Management

All papillary thyroid cancer (PTC) is not the same, but the vast majority of it is “classic PTC.” Rarely does FNA give us a subtype of PTC. The more aggressive variants of PTC are very rare. One is called the tall cell variant and another is the sclerosing variant, and these are usually diagnosed on the final pathology. Therefore, if a clinician gets a PTC result, we would treat it as classic PTC. We would stage the patient with neck US, which is the most sensitive and specific imaging modality. If there is bulky lymphadenopathy, if the cancer is large, or fixed, or offers any concern about substernal extension, then generally we get cross-sectional imaging like CT, but not routinely.

Surgical Therapy: 20 years ago, there was this debate about thyroid lobectomy versus total thyroidectomy. This debate went away, and everybody was doing total thyroidectomies. And the debate became, “Should we be doing prophylactic central neck dissections?” We currently think the answer is “no,” and this debate has kind of gone away. Now the debate has gone back to thyroid lobectomy versus total thyroidectomy for thyroid cancer. The most recent guidelines from the American Thyroid Association (ATA) were published in 2015 and they say that, if you have a cancer that is up to 4.0 cm with no evidence of extrathyroidal extension on US and no lymph nodes, then thyroid lobectomy could be considered adequate treatment. This is new change in practice in the last 6 to 12 months. For 2-cm nodules, I believe people are being swayed toward also performing a thyroid lobectomy. Obviously, the surgeon first needs to have a discussion with the patient regarding recurrence rates and pros and cons.

Monitoring Thyroglobulin: According to old lobectomy data, the long-term follow-up of those patients would say that the risk of cancer in that other lobe is extremely low. This is still believed today. Total thyroidectomy was advocated more because it facilities the patient’s follow-up so we can check thyroglobulin levels in a patient who has had a total thyroidectomy. But if they have a thyroid lobe still in place, thyroglobulin will always be detectable, so it cannot be used as a tumor marker. Total thyroidectomy also facilitates radioactive iodine administration, which you cannot give if someone still has a lobe in place. But the pendulum has swung in the direction of giving less radioactive iodine.

Follicular Thyroid Cancer: Management

Follicular thyroid cancer (FTC) cannot be diagnosed on FNA, but FNA can suggest a follicular neoplasm. Therefore, if FNA gives a follicular neoplasm result, the FTC should be in the differential diagnosis. The patient with the nodule that is follicular neoplasm should be taken to the operating room for a thyroid lobectomy. Unfortunately, the pathologists at most institutions cannot tell follicular cancer versus follicular adenoma on a frozen section in the operating room because that diagnosis requires the pathologist slicing the nodule into multiple sections to evaluate the capsule in 3 dimensions. Additionally, pathologists are evaluating for vascular invasion. Therefore, evaluating the specimen usually takes a few days. If a follicular cancer is diagnosed and it has minimal capsular invasion (into the capsule but not all the way through the capsule), we believe that thyroid lobectomy is adequate treatment. If the cancer has burst through the capsule, then that is a more aggressive tumor and we would ask the patient to come back for a completion thyroidectomy. If vascular invasion is discovered, we would also recommend completion thyroidectomy. I probably have to bring a patient back for a completion thyroidectomy from 15% to 20% of the time. A total thyroidectomy is recommended as the initial surgery in a few special circumstances. For example, if a patient has multiple nodules on the contralateral side, then total thyroidectomy is a reasonable up-front surgery. Obviously, we first discuss the pros and cons with the patient, but a total thyroidectomy would mean that the patient does not need lifelong surveillance for the nodules on the contralateral side. Another circumstance where patients may choose to have up-front total thyroidectomy is if they already have hypothyroidism and are taking levothyroxine. Because they are already taking thyroid hormones, they may just choose to have the whole thyroid removed because it is not going to change anything other than maybe the dose of their
levothyroxine. Most patients who have thyroid lobectomy with a preoperative normal TSH actually do not need thyroid hormone replacement after a thyroid lobectomy, and so most patients would want to just remove the lobe if that is what is needed to make a diagnosis.

**Differentiated Thyroid Cancer: Use of Postop RAI Treatment**

The use of radioactive iodine (RAI) treatment after surgery for papillary or follicular thyroid cancer is changing. The most recent guidelines from the American Thyroid Association subdivide patients with differentiated thyroid cancer into risk categories for recurrence: low-, intermediate-, and high-risk categories. Patients at low risk for recurrence have negative margins, no positive lymph nodes, and <5 positive central neck lymph nodes with micrometastases (metastasis <2.0 mm in largest dimension), no vascular invasion, and completely intrathyroidal. We do not recommend RAI for low-risk patients. Patients at intermediate- or high-risk for recurrence are patients who have extrathyroidal extension, aggressive histology, multiple positive lymph nodes (especially macrometastases), incomplete tumor resection, and distant metastases. These patients still definitely need RAI. The bottom line is that we are trying to be more thoughtful and sparing about using RAI and really only using it if we think it will impact the patient’s risk for recurrence.

**Medullary Thyroid Cancer: Diagnosis, Staging, Treatment, and Follow-Up**

Medullary thyroid cancers are sporadic in about 75% of cases and are familial in about 25%. The American Thyroid Association advocates genetic testing for everybody, so everybody gets RET tested. The concern is whether the patient has multiple endocrine neoplasia type 2 (MEN2). Then we ask, if the patient has MEN2, could a pheochromocytoma be a part of the diagnosis? Therefore, most of us will send plasma metanephrines to screen for pheochromocytoma just because that test comes back faster than the gene test, which usually takes several weeks to come back. If a patient has positive RET testing, then we also have to screen for primary hyperparathyroidism.

**Staging:** Then we do our staging evaluation. Patients should have a blood test to measure their serum calcitonin as well as the CEA. Not everybody knows that CEA is also part of medullary thyroid cancer, in addition to colon cancer, but it is part of the staging. Patients also need a comprehensive neck US. The need for additional imaging depends on the patient’s calcitonin level. If calcitonin is <400, then neck US is all that is required. If calcitonin is >400, then we do cross-sectional imaging of the entire body (neck, chest, abdomen, and pelvis) looking for distant metastases.

**Treatment:** There is no adjuvant therapy for medullary thyroid cancer. I like to think of this as a purely surgical disease, and so surgical therapy is more aggressive. Therefore, the standard therapy for a patient with medullary thyroid cancer is a total thyroidectomy with a prophylactic bilateral central neck dissection.

**Clarification:** Even if the patient is RET-negative and pheo-negative, we still obtain a calcitonin level. The calcitonin is for the medullary thyroid cancer. The gene testing and the pheochromocytoma testing are just to make sure the patient does not have a pheochromocytoma. If so, it would have to be addressed first to make sure that the patient does not have a hypertensive crisis on the table from an undiagnosed pheochromocytoma.

**Follow-Up:** After total thyroidectomy with bilateral central node dissection, follow-up consists of calcitonin levels and CEA levels. If calcitonin and CEA are undetectable after surgery, we continue to check that annually. If calcitonin and CEA are detectable, then we must do radiographic surveillance. The metastasis is usually in the neck, so a high-resolution neck US is required. If we cannot find anything, we continue to follow up the calcitonin level. We may do a PET scan, but that depends on the calcitonin level and how worried we are that the patient may have a distant metastasis. Follow-up is lifelong.
Anaplastic Thyroid Cancer

There are no new developments to improve the outcome of anaplastic thyroid cancer. Anaplastic thyroid cancer is a terrible, terrible disease. It is not resectable in the vast majority of cases. The medical oncologists try chemotherapy and external beam radiation therapy. These can help for a little bit, but ultimately patients do succumb to this cancer.

Hyperthyroidism: Diagnosis and Treatment

The hyperthyroid condition is generally easy to identify. Patients routinely get TSH levels measured as part of their annual physical exam. If a patient has a suppressed TSH, then the physician orders a T4 with or without a T3, so hyperthyroidism (HT) is generally very easy to identify. Some patients can present with asymptomatic HT (subclinical HT), which has a pattern of suppressed TSH but normal T3 and T4 levels. These patients require only follow-up. Patients with overt HT have symptoms such as anxiety, tremor, weight loss, heat intolerance, and diarrhea, so it is easy to check the TSH and go from there. HT treatment now mostly resides in the realm of the endocrinologist, but not completely. **Treatment:** HT can be caused either by an autonomously functioning nodule (“hot nodule” on radioactive iodine [RAI] scan) or by Graves disease, an autoimmune condition in which an antibody binds to and stimulates the TSH receptor. HT has three treatment options: (1) antithyroid drugs, such as methimazole or propylthiouracil, (2) RAI, and (3) surgery. In the 1990s, a randomized trial compared these three therapies for the treatment of Graves disease. When patients were asked if they would recommend their assigned treatment to a friend or family member, they all answered yes to the same degree. Generally, when I see a patient with HT, I give them the pros and cons of each approach. Medical therapy is noninvasive but the remission rate is approximately 20% at 1 year, and the medications can have serious side effects. RAI is noninvasive, but it involves radiation exposure. Patients of childbearing age should not get pregnant or make someone pregnant for a year after RAI. Some patients have an aversion to radiation exposures, so surgery would treat a hot nodule or Graves disease, with recurrence rates approaching zero. In the United States, RAI is the most common treatment for HT, probably because most patients are treated by an endocrinologist. Most endocrinologists do not discuss surgery as a treatment option. Patients who end up in a surgeon’s office are members of a skewed population who have decided they do not want RAI. For example, one contraindication to RAI is the orbitopathy of Graves disease because RAI makes that worse. **Preop Management:** The preoperative management of patient scheduled to undergo surgery for HT consists of beta blockade and antithyroid drugs. These patients receive methimazole or propylthiouracil. We try to get T3 and T4 somewhere close to normal. The TSH will not be normal because it always lags behind what we do to T3 or T4. Then we give them iodine for about 10 days before the operation for Graves disease, which also decreases thyroid hormone production. **Surgery:** The operation for Graves disease HT is total thyroidectomy. Subtotal thyroidectomy was the old operation, but it had high recurrence rates. Postoperatively, patients receive replacement therapy for thyroid hormone.

Hypothyroidism

Patients with hypothyroidism do not necessarily present with a clear-cut profile. Because patients routinely get the TSH levels measured as part of their routine annual physical exam, hypothyroidism is usually diagnosed at an early stage. Symptoms of hypothyroidism would be weight gain, cold intolerance, fatigue, etc. Unfortunately, because of the large number of overweight and obese individuals in the United States, the physician cannot look at a patient’s weight and immediately suspect hypothyroidism.
The final diagnosis of hypothyroidism is based on an abnormal TSH, followed by testing of T3 and T4. For patients with a hypothyroid diagnosis, we do not need to worry much about them needing either elective or emergency general surgical procedures. These patients are taking levothyroxine (thyroid hormone) and their thyroid levels are either normal or near normal. Cases of subclinical hypothyroidism (high TSH, normal T3 and T4) do not need thyroid hormone treatment. Because the half-life of thyroid hormone is 1 week, missing a few doses has no major impact on the patient.

**Primary Hyperparathyroidism and Familial Hypercalcemic Hypocalciuria**

The diagnosis of primary hyperparathyroidism (PHPT) is completely a biochemical diagnosis (no FNA biopsy). PHPT is most commonly diagnosed because hypercalcemia is found on routine labs. Next, the parathyroid hormone (PTH) levels are checked. If elevated, PHPT is suspected. In some PHPT cases, PTH can be in the normal range, making the diagnosis somewhat challenging. Nonetheless, if the patient has an elevated calcium and a PTH that is in the mid to upper end of the normal range, that is not normal. These patients probably have PHPT.

**FHH:** For the patient with hypercalcemia and inappropriately elevated PTH, the other main component of the differential diagnosis is familial hypercalcemic hypocalciuria (FHH), which is due to a germline mutation in the calcium-sensing receptor. Patients with FHH have lifelong elevations of calcium and PTH. Therefore, patients who have been normocalcemic their entire lives and then they become hypercalcemic do not have FHH — these patients have PHPT. If we do not have access to old labs, then we must ask patients to do a 24-hour urine collection for calcium and creatinine in order to rule out FHH. Urine calcium is either normal or elevated in PHPT and is low in FHH.

**Pathology:** Generally, PHPT is a single-gland disease in 80% to 85% of patients that is caused by a parathyroid adenoma. PHPT is a four-gland disease in 10% to 15% of patients. Double or triple adenomas are very rare.

**Asymptomatic PHPT:** In cases of asymptomatic PHPT (asymptomatic hypercalcemia plus elevated PTH), the need of surgery is controversial. Cases with kidney stones, pathologic fractures, or hypercalcemic crisis are NOT asymptomatic: these cases require surgery. However, if symptoms are difficult to quantify, such as debilitating fatigue, bone pain, or depression, these cases are considered to be asymptomatic by the National Institutes of Health’s definition of asymptomatic. However, studies have shown that if you systematically question patients, fewer than 5% or 10% are truly asymptomatic when using the word “asymptomatic” as defined in the English language. Should asymptomatic patients with PHPT have surgery? Much of this decision depends on how they feel. We order bone density scans, because those with osteoporosis should have surgery. Long-term studies have shown that asymptomatic patients who are observed will have a decline in their bone density with time. Those starting out with severe osteopenia at diagnosis want surgery because they will then regain some of that bone density after the operation. In PHPT patients, the bone density loss is really in cortical bone, which puts them at risk for pathologic fractures.

**Primary Hyperparathyroidism: Parathyroidectomy and Four-Gland Explorations**

In patients with PHPT, localization of the hyperfunctioning parathyroid gland is essential to a minimal surgical approach to the disease. I start by performing an in-office neck US. Generally if I see something on neck US, that’s all the imaging that I do. If not, then I order a parathyroid sestamibi scan. Recently, I have been doing more four-gland explorations, so if something is seen on US or a sestamibi, then that is the side that we start on in the OR. I generally will do a unilateral neck exploration, looking at both parathyroid glands on that side. If one is normal and one is abnormal, I resect the abnormal one and then check the intraoperative PTH levels. If they fall appropriately (>50% decrease from highest baseline
level), then we are done. If the intraoperative PTH levels do not drop, then I go to the other side, check to see what those two parathyroid glands look like, resect whatever looks abnormal, and then check the PTH values again.

**Four-Gland Exploration:** Recent reports are swaying me toward doing more four-gland explorations. Some selection bias is seen in the literature that reports the results of minimally invasive parathyroidectomy. We only know if a patient really had single-gland disease when they undergo long-term follow-up. We get the most information regarding the prevalence of single-gland versus multigland disease from studies that have patients who had bilateral neck explorations and four-gland explorations. Recently, studies with long-term follow-up of >10 to 15 years have been published, and we are finding that patients who had surgery for presumed single-gland disease are now recurring. Perhaps these patients did not truly have single-gland disease at the time of their operation. Because of the recurrence, they now need reoperation, which is more challenging because it is in a reoperative field and the surgical risks are higher. Therefore, I have been transitioning toward doing more four-gland explorations, especially if the intraoperative PTH values are not dropping appropriately. According to the literature, if intraoperative PTH drops by >50%, then I should be fine. However, if the final number is higher than expected or higher than I would like, I have a very low threshold for doing a bilateral neck exploration.

**Hypercalcemic Crisis**

Generally, we manage hypercalcemic crisis via aggressive hydration. Once we are certain that the patient is hydrated, we give him/her a loop diuretic to promote calciuresis. This approach generally works. Another agent that can be used to treat hypercalcemic crisis is a bisphosphonate, which works by blocking bone reabsorption by the osteoclasts. The osteoclast actually ingests the drug, which causes them to undergo apoptosis. Therefore, bisphosphonates can be used as an adjunct to hydration and loop diuretics. Calcitonin is another drug that I have seen used, but it does not work very well. Calcitonin also inhibits osteoclast function, so it takes a little longer to work but can also help if the calcium is super high, such as 17 mg/dL. Mithramycin is a drug that is not used much anymore for this indication. Denosumab is an antibody that targets the RANK ligand and also works at the level of the osteoclasts. It is used for patients who have hypercalcemia malignancy. Because its onset of action requires some added time, it is not a good choice in the emergency department. After using hydration and loop diuretics to get through the crisis, then determining the cause of the hypercalcemic crisis comes next. If the cause is hypercalcemia malignancy, then bisphosphonates and denosumab medication definitely have a role as oncologists try to do something to treat the primary tumor. Most patients with hypercalcemic crisis do not need an urgent parathyroidectomy.

**Secondary Hyperparathyroidism**

Secondary hyperparathyroidism (SHPT) occurs most commonly in patients who have chronic renal failure and are on dialysis. The parathyroid glands are stimulated by what they perceive as hypocalcemia, although the patient’s calcium is usually normal. As a result, four-gland hyperplasia develops. The primary treatment of SHPT is medical: the nephrologists treat this with phosphate binders (high phosphate is part of SHPT’s pathophysiology) and with vitamin D analogs. Sometimes they administer cinacalcet, which is a calcimimetic agent that attempts to suppress PTH production by making the parathyroid cell think that the calcium is higher than it is.

**Surgical Indications:** Very few patients get referred for surgery for SHPT because medical treatment is usually able to treat this condition. Hard indications for parathyroidectomy in SHPT would be if a patient develops calciphylaxis, which consists of very painful skin lesions due to microvascular ischemia in the vessels in the skin and subcutaneous tissues. Patients with calciphylaxis develop these painful
black eschars. Other hard indications for parathyroidectomy are the development of extraskeletal calcifications and/or severe osteoporosis.

**Surgery:** The usual surgical approach for SHPT is either a subtotal parathyroidectomy or a total parathyroidectomy with an autotransplant of a fragment of a parathyroid gland into the brachioradialis muscles. All patients with SHPT have four-gland hyperplasia. The parathyroid glands are just responding normally to what they perceive as hypocalcemia, so all glands are involved. Each approach has pros and cons, and the final decision boils down to surgeon preference. The main advantage to doing a subtotal parathyroidectomy (leave a remnant in the neck) is that the PTH is not zero after surgery, making patients easier to manage medically. They all have tremendous bone hunger after surgery and are, in fact, usually in the ICU on continuous calcium infusion for about 24 hours while we give them high doses of oral calcium and calcitriol and try to stabilize them on an oral regimen. In patients who have had a total parathyroidectomy with an autotransplant, their PTH is zero after surgery. These patients are much more difficult to control on an oral regimen while waiting for that autotransplant to take effect, which generally takes about 6 to 8 weeks.

**Tertiary Hyperparathyroidism and Calciphylaxis**

Tertiary hyperparathyroidism (THPT) refers to persistent hyperparathyroidism after correction of a secondary cause. The most common scenario is a patient who has secondary hyperparathyroidism (SHPT) from chronic renal failure who then gets a kidney transplant. Once the kidney transplant is done and it starts working, then the calcium is normal, the phosphorus is normal, and so the hyperplastic parathyroid glands that had developed during SHPT should go back to normal. However, sometimes they do not go all the way back to normal. So if a patient has persistent hyperparathyroidism after the renal transplant, particularly if it starts to cause hypercalcemia, then the nephrologist will generally refer the patient for surgery. Because the initial four-gland hyperplasia associated with the SHPT was asymmetric, sometimes patients with tertiary hypercalcemia do not have all four parathyroid glands involved. They all need a four-gland exploration, but they do not all necessarily need to have a subtotal parathyroidectomy, it just depends on the intraoperative findings.

**Calciphylaxis:** Calciphylaxis is a poorly understood, uncommon disease in which calcium accumulates in small blood vessels of the fat and skin tissues, causing painful skin ulcers and potentially serious infections that can lead to death. Calciphylaxis is generally associated with kidney failure and dialysis, although it can occur in patients without kidney disease. This is a horrible condition. Unfortunately, there are no treatment tricks for this condition. The patient needs a parathyroidectomy as soon as possible. This is followed by local wound care, including debridement and perhaps some skin grafting, depending on how it looks. Pain control is a big part of managing calciphylaxis.

**Incidental Adrenal Masses: Diagnostic Management**

Patients are getting abdominal CT imaging with increasing frequency. Incidental adrenal masses are common, occurring in about 5% of people. Most incidental adrenal masses (60% to 80%) are benign, nonfunctional, adrenal corticoadenomas. The initial approach is to test patients for hormones that can have subclinical hyperfunction. Generally we test for hypercortisolism, hyperaldosteronism, and pheochromocytoma. If testing is negative, then we generally repeat the imaging in about 6 months to determine if the adenoma’s size changes. If it is stable, then clinical practice guidelines advocate monitoring annually for 5 years with both imaging and repeat hormonal testing. Patients who are initially negative but become hormonally active with time are usually subclinical hypercortisolism patients.

**Differential:** The differential diagnosis is functional versus nonfunctional tumor, primary versus metastatic tumor, and benign versus malignant adrenal tumor.
Metastatic? To rule-out metastatic disease, I generally ask screening questions based on risk factors and age. Make sure that women aged >40 years are getting annual mammograms, that patients aged >50 years are getting colonoscopies, and that smokers have at least a chest x-ray. I also ask patients about prior skin cancers, especially about melanomas because patients sometimes forget about the melanoma that they had resected 5 years ago.

Benign? To determine if the tumor is benign, imaging is helpful. Adrenal cortical cancers are usually large at presentation, although some can be smaller. The decision to biopsy is based on the size plus appearance. Most of us use a size threshold of 4.0 cm. A noncontrast CT with Hounsfield units <10 is indicative of an adenoma. An adrenal protocol CT scan (noncontrast CT followed by IV contrast, then washout is measured) with >50% washout at 10 to 15 minutes is indicative of an adenoma. On MRI, if signal drop is seen on out-of-phase images, then this is indicative of adenoma. Therefore, if a radiologist says it is an adenoma, the size is 4.0 cm, the appearance is innocuous, and it is nonfunctional, then it is probably okay to watch that patient. In contrast, for the smaller adrenal mass (example: 3.0 cm) that is irregular and heterogeneous and maybe has a calcification, surgery would be recommended to definitively exclude an adrenocortical cancer that we could potentially catch early.

More Imaging? Usually the CT scan for incidentally discovered adrenal masses is usually done only with IV contrast (usually no noncontrast CT). Therefore, we do not know the noncontrast Hounsfield units and the washout characteristics. As a result, the initial scan is usually nondiagnostic for an adenoma. In these cases, if the hormonal evaluation is negative and I am planning on watching the patient, then the scan that I get 6 months later is either an adrenal protocol CT or an MRI. I usually explain the pros and cons of the 2 imaging procedures to patients and let them choose between CT and MRI.

Pheochromocytoma

Currently, pheochromocytomas (pheos) are associated with 13 known susceptibility genes, and we believe that 30% to 40% of pheos are hereditary. Young patients (age <50 years) with a pheo should be referred for genetic testing. Commercially available gene panels test for several genes at the same time, thus obviating the need for genetic counseling for most patients. Because some susceptibility genes are more often associated with malignancy than are others, treatment is based on the gene that tested positive. For most surgeons, genetic test results are not back by the time that we do the operation. Because pheos are usually picked up as an incidental adrenal mass, we identify them when we do hormonal testing. Most pheos are unilateral intra-abdominal masses not associated with a gene. Therefore, it is perfectly reasonable to block the patient, operate on them, and wait for the genetic test results to come back to see if we need to look for anything else. Some susceptibility genes are associated with other findings. For example, the VHL pathogenic variant linked to von Hippel-Lindau syndrome is associated with renal cell carcinoma and pancreatic masses, which we could see on the abdominal CT scan. The results of genetic testing can help us avoid doing an exhaustive workup looking for other lesions in every single patient who has a pheo.

Preop: To prepare patients with pheos for surgery, α- and β-blockade are routine. I do it 2 ways depending on the tumor’s size. The classic α-blocking agent is phenoxybenzamine (PBZ). This drug is very expensive because it only exists as a brand name medication (Dibenzyline®). However, PBZ provides excellent blockade because it is noncompetitive α-blocker, thus blocking all α receptors. I use PBZ for the patient who has a larger tumor. I start with α-blockade, and then I add the β-blocker 7 to 10 days later if they become tachycardic or develop extrasystoles. My end point is orthostatic hypotension. I check their vital signs every few days and increase the dose as needed. For the patient with a smaller tumor, I use doxazosin, a competitive α-blocker. I am just starting to use this drug, but it has worked relatively well for the handful of patients on whom I have used it. Doxazosin is definitely less expensive than PBZ and is available as a generic drug.
Surgery: The operation for pheos depends on each tumor’s size. Generally, we do these laparoscopically. Tumors >6.0 cm are technically difficult to remove laparoscopically, although I think it is worth a try. Most pheos are not malignant, and if you can remove one laparoscopically, this makes a big difference in the recovery. The approach can be transabdominal or through the retroperitoneum based on surgeon preference. Generally, for tumors >4.0 cm or so, the surgery cannot be done through the back, it should be done transabdominally.

Hyperaldosteronism: Venous Sampling

Case: A patient is referred to you with severe hypertension, elevated aldosterone level, enlarged right adrenal gland, and a normal left adrenal gland. Do you need any further testing in that patient? Recommendations: This patient needs venous sampling, which has been a debated topic during the last 10 to 15 years. Venous sampling is controversial because adrenal vein sampling requires some technical expertise and not all institutions have someone who can do it. Therefore, great interest has developed in trying to determine whether some patients can forego venous sampling. Papers published during the last 10 to 15 years demonstrated that imaging could be misleading in up to 20% of patients. By misleading, I mean that (1) patients may have a unilateral adrenal mass but their problem is really the normal-looking contralateral adrenal gland or (2) patients may have bilateral adrenal masses but they actually have a unilateral cause of their hyperaldosteronism. As a result, we advocate adrenal vein sampling. This may not be necessary in patients aged <35 years. The development of adrenal nodules happens with age, so adrenal nodules are more common in older people and are less common in younger people. Therefore, in a young person with a biochemical diagnosis of hyperaldosteronism and a unilateral adrenal mass >1 cm, that unilateral adrenal mass is causing the problem.

Perioperative Stress-Dose Steroids

Do patients on chronic glucocorticoid replacement need stress-dose steroids as part of their perioperative care? I think they do. But as things change in medicine, it seems like the endocrinology community has gone away from routine stress-dose steroids, at least at the higher doses that we had been using. Traditionally we used 100 mg of hydrocortisone preoperatively and then every 8 hours postoperatively followed by a taper. However, we probably do not need much more than 50 mg of hydrocortisone if we are going to administer stress-dose steroids preoperatively to someone who has been on chronic steroids. Some endocrinologists feel that patients do not need it at all. Therefore, whether you administer stress-dose steroids in the perioperative period depends on your comfort level with not doing it at all: if the patient develops signs of adrenal insufficiency, such as hypotension, then steroids could be administered at that time. Giving a reduce dose of hydrocortisone compared to the dose that was traditionally used is a nice intermediate and is generally what I have done for patients who are on chronic steroids. Giving 50 mg of hydrocortisone instead of 100 mg has been working relatively well for my patients. At our institution, the use of stress steroids is very surgeon-dependent. In my experience with the anesthesiologists, they usually just defer to what the surgeon wants for that.