THYROID AND PARATHYROID GLAND PATHOLOGY

Role of Imaging

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THYROID IMAGING

Lesions of the thyroid gland represent some of the most heterogeneous abnormalities in the head and neck. Depending on the clinical presentation and suspected abnormality, the clinician may order nuclear medicine scintigraphy, ultrasonography, computed tomography (CT), or magnetic resonance (MR) imaging as the first imaging modality. Clearly, the work-up for an infant with a midline cystic mass in the lower neck is entirely different from that for a 40-year-old male with a solitary palpable nodule in the thyroid gland. Therefore, it is important to consider lesions of the thyroid gland according to neoplastic, congenital, and inflammatory categories. Within each of these categories, imaging is discussed.

Neoplasms of the Thyroid Gland

To assist the clinician faced with a solitary nodule in the thyroid gland, imaging has a well-defined role. Invariably, unless the classic appearance of a benign condition is present, fine-needle aspiration or biopsy is required, because the appearance of most thyroid malignancies may
simulate benign processes, and vice versa. For example, calcification occurs in 13% of all thyroid lesions, including 17% of all malignancies and 11% of all benign processes. In a similar fashion, cystic components of a lesion occur in 24% of thyroid masses; 38% of malignancies and 62% of benign masses may be wholly or partly cystic. Most adenomas and carcinomas have solid components also. Hemorrhage may be found in papillary carcinomas, degenerated nodules, or goiters. It is difficult to pinpoint a specific histologic diagnosis despite these imaging findings.

Thyroid cancers are a mixed group of lesions. The most common histologic subtype, however, is papillary carcinoma, which occurs in 55% to 75% of thyroid malignancies. Mixed papillary-follicular carcinomas (follicular variant of papillary carcinomas) are generally placed in the papillary carcinoma category, because they behave clinically similarly to pure papillary carcinomas. Purely follicular carcinoma occurs in 10% to 15%, anaplastic carcinoma in 5% to 15%, and medullary carcinoma in 5% of cases. Anaplastic carcinoma and medullary carcinoma do not take up iodine usually, but may be thallium or gallium avid. Somatostatin receptor scintigraphy may also detect medullary carcinoma. Medullary carcinoma may present in association with the multiple endocrine neoplasia (MEN) syndromes and serologically may express calcitonin. Other histologic diagnoses to consider in thyroid malignancies are non-Hodgkin’s lymphoma and metastases.

The detection and characterization of a thyroid neoplasm is not the only role of imaging. Imaging should also evaluate for infiltration of adjacent soft tissue, paraspinal musculature, and adjacent vessels. The presence or absence of adenopathy is important both for its prognostic implications with thyroid cancer and for distinguishing benign from malignant processes. Papillary carcinoma is the lesion with the greatest likelihood of spread to lymph nodes, and the nodes may be tiny, cystic, hemorrhagic, or calcified. After the lymph nodes, papillary carcinomas may metastasize to the lungs, bone, or central nervous system (CNS). The coexistence of parathyroid abnormalities in patients who have neoplasms or masses of the thyroid gland is also important. Parathyroid adenomas or hyperplasia may accompany medullary carcinoma as part of the MEN IIa or MEN IIb complex (along with pheochromocytomas).

**Ultrasound**

Ultrasound, because of its accessibility, low cost, noninvasiveness, and ability to distinguish cystic from solid lesions, is often the first modality employed to evaluate a thyroid mass in the euthyroid patient. Good-quality ultrasound requires transducers with frequencies of 7.5 to 10 MHz. This allows excellent detail of the superficial gland and enough penetration to evaluate as deep as the spine.

When a solid lesion is hyperechoic, the likelihood of malignancy is only 4%. If a solid lesion is isoechoic, the likelihood of malignancy increases to 26%. If it is hypoechoic, the likelihood of malignancy is 63%. Papillary carcinoma most commonly presents as a solid hypoechoic (77%) rather than isoechoic (14%) lesion (Fig. 1). On the other hand, follicular
Figure 1. Unusual hyperechoic papillary carcinoma of the thyroid gland. This longitudinal view of the right thyroid gland demonstrates a well-defined hyperechoic mass (arrows). The lesion is echogenic compared with the surrounding thyroid tissue (T). Biopsy proved a papillary carcinoma.

carcinoma is solidly isoechoic in 52% and hypoechoic in 44% of cases. Anaplastic and medullary carcinomas and lymphoma are most commonly hypoechoic.\textsuperscript{12,15,53} Echogenic foci due to deposits of calcium may be seen in primary sites and metastatic lymph nodes of medullary carcinoma.\textsuperscript{15} A lesion with echogenic foci (calcifications) in a solid nodule protruding into a cyst suggests cystic papillary carcinoma.\textsuperscript{19}

If one looks at the margins of tumors on ultrasound, one finds that 16% of malignant lesions have sharply marginated, well-defined borders, and that irregular or ill-defined borders occur in approximately 60% of cancers.\textsuperscript{53} Unfortunately, irregular or ill-defined borders also occur in approximately 45% of benign lesions.\textsuperscript{53} A lesion surrounded by complete halo of echopenia makes it 12 times more likely to be benign than malignant (Fig. 2).\textsuperscript{53} If the halo is incomplete, however, a benign etiology is only 4 times more likely than a malignant cause.\textsuperscript{53}

Ultrasound is usually not as helpful as cross-sectional imaging techniques in the detection of soft tissue, esophageal, tracheal, and vascular infiltration. Lymph node metastases are also better imaged with other modalities.

One strong point of ultrasound is the ability to perform guided biopsies. Fine-needle aspirations have over 95% accuracy when directed by imaging. Ultrasound, because of its interactive real-time capability, is the
Figure 2. Echopenic halo signifying benign lesion on ultrasound. This longitudinal view of the thyroid gland demonstrates an echopenic halo (arrows) around a large thyroid mass. An intact, complete echopenic halo suggests a benign process.

study of choice in this regard. The needle tip can be followed ultrasonographically as it enters a suspicious abnormality. This advantage is especially useful in postoperative patients or in patients without palpable abnormalities.56

**Nuclear Medicine**

The agents used for thyroid imaging include iodine 123 (I 123), iodine 131 (I 131), technetium (Tc 99m) pertechnetate, and thallium 201 (Tl 201). The half-lives, whole-body doses of radiation and thyroid doses of radiation are listed in Table 1.41,67

Scanning is performed 15 minutes after administration of technetium

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pertechnetate, 4 hours (range 2 to 24 hours) after administration of I 123, and 24 to 72 hours after administration of I 131 agents. Scanning is performed 5 to 10 minutes after thallium 201 administration. Because the radiation energy of I 131 is so high (364 keV), it is the preferred agent to image substernal thyroid glands or to image the whole body after thyroid ablation in order to detect metastatic foci of thyroid cancer. The other agents have energies of 140 keV (Tc 99m), 159 keV (I 123), and 80 keV (Tl 201).47

A major role of scintigraphy in the evaluation of a thyroid mass is the determination whether the lesion is "hot" (more uptake than the normal thyroid gland), "warm" (some activity but not as much as the normal gland), or "cold" (hypofunctioning). The risk of cancer in a hot nodule is 1% to 4%, in a warm nodule 8% to 10%, and in a cold nodule 15% to 25%.41,44,45

By far the majority (90%) of solitary hot nodules on scintigraphy are benign in etiology, usually adenomas (Plummer's disease is hyperthyroidism due to a solitary hot nodule) or hyperplasias that are expressing thyroid hormone41 (Fig. 3). The difference between an autonomous and a hypertrophic, functional hot nodule depends on the response to a thyroid suppression test. After a diagnostic course of thyroid hormone administration, a lesion that is persistently hot on a Tc 99m pertechnetate scan is considered an autonomous lesion, whereas a previously hot lesion that is now cold is considered hypertrophic.44 Other sources of hot nodules are thyroiditis, normal variation in thyroid function, and ectopic tissue.44

A cold nodule is approached more aggressively because of the higher incidence of malignancy. A biopsy or aspiration is often in the diagnostic algorithm. In a patient who has a prior history of head and neck irradi-

Figure 3. Hot nodule on nuclear scintigraphy. This technetium 99m pertechnetate scan demonstrates a solitary mass (m) with high uptake in the right thyroid gland. Note that its increased activity leads to suppression of the remaining thyroid gland. A hyperfunctioning hot nodule with hyperthyroidism is suggestive of Plummer's syndrome.
ation, the risk of malignancy in a cold nodule doubles to 30% to 50%. Still, the majority of cold nodules are due to degenerated adenomas, nodular hemorrhage, cysts (goitrous or colloid cysts), inflammatory conditions (see later), or amyloid deposition (Fig. 4). Occasionally, one finds a cold adenoma that is responsive to thyroid-stimulating hormone (TSH) in a patient with Graves' disease. It appears as a cold nodule because the hyperthyroidism of Graves' disease suppresses the TSH, thereby suppressing the adenoma on a nuclear medicine study. This entity is called Marine-Lenhart syndrome.

When a lesion is cold on I 123 nuclear medicine scintigraphy but hot or warm on a technetium pertechnetate scan, the differential diagnosis includes malignancy, goiter, and follicular adenoma. Often a biopsy is required in this paradoxical situation.

Another role of nuclear medicine scintigraphy is to determine whether a patient has a multinodular goiter. A goiter is simply an enlarged thyroid gland, which may be seen with hyperthyroidism or hypothyroidism; in the United States, the common vernacular is to imply a nontoxic (no hyperthyroidism) goiter when the term is used. A euthyroid or hypothyroid goiter is the most common thyroid lesion in our country. Patients, usually older women, may present because of neck masses or tracheoesophageal compression. The incidence of carcinoma in a multinodular goiter is very low (less than 3%), and the characteristic appearance of multiple cold areas interspersed with hot areas in a large gland usually obviates the need for biopsy of a palpable nodule (Fig. 5). A large, dominant, hard, or growing mass amidst a goiter should probably undergo biopsy.

Figure 4. Cold nodule on nuclear scintigraphy. This technetium 99m pertechnetate scan reveals a cold nodule (n) with decreased radiotracer uptake in the lateral aspect of the left lobe of the thyroid gland. The lesion was biopsy-proven carcinoma; however, cysts, degenerating nodules, and areas of thyroiditis may appear similarly.
Figure 5. Multinodular goiter. A, Note the areas of decreased radiotracer uptake (arrows) and increased radiotracer uptake (arrowheads) in this enlarged inhomogeneous thyroid gland. The presence of heterogeneity with hot and cold regions suggests the diagnosis of a multinodular goiter. B, On ultrasound the presence of multiple cystic and solid nodules (arrows) in an enlarged thyroid gland suggests the diagnosis of a goiter.
Whole-body gallium scans occasionally identify a thyroid mass. Increased activity may be seen in cases of thyroid lymphoma, and other lymphoproliferative and granulomatous diseases may also be gallium avid.

**Computed Tomography**

CT scanning had been the mainstay of cross-sectional techniques in the evaluation of thyroid lesions until the advent of MR imaging. As stated previously, the presence of calcification, cysts, hemorrhage, or hypodensity or hyperdensity of a solitary mass on CT does not exclude or specify a carcinoma (Fig. 6). Multiplicity of nodules in an enlarged thyroid gland suggests a benign process, whereas the presence of lymphadenopathy or infiltration of adjacent tissues suggests malignancy. The lymph nodes of thyroid papillary carcinoma may also show calcification, cyst formation, hemorrhage, and necrosis. Any lymph node seen in a patient with papillary carcinoma is suspected of being malignant, regardless of size, because of the disease's relatively high rate of lymphatic spread.

Thyroid lymphoma may present as a solitary mass (80% of the time) or as multiple nodules (20%). An antecedent history of Hashimoto's thyroiditis in an elderly female patient with a rapidly enlarging, compressive, and infiltrative mass suggests lymphoma. The tumor is hypodense on unenhanced and enhanced studies and shows necrosis or calcification in only 7% of cases. Invasion into the carotid sheath and involvement of the lymph nodes are not uncommon.

**Magnetic Resonance Imaging**

The role of MR imaging of thyroid lesions has benefited in recent years from the development of appropriate surface coils. Using a surface coil with small fields of view allows greater signal-to-noise ratios and higher resolution than the standard body or head coil. In one of the earliest articles on the subject of MR imaging of this gland, thyroid nodules as small as 4 to 5 mm were identified. Follicular adenomas appeared as well-circumscribed nodules with heterogeneous intensity, bright on T1-weighted examinations. On the other hand, colloid cysts and hemorrhagic cysts were characterized by homogeneous high signal on T1-weighted examinations. The tumor is hypodense on unenhanced and enhanced studies and shows necrosis or calcification in only 7% of cases. Invasion into the carotid sheath and involvement of the lymph nodes are not uncommon.
Figure 6. Calcification and cyst formation in thyroid masses. A, In this patient the CT scan shows an area of calcification (arrow) in the left thyroid lobe and cyst formation (arrowhead) in the posterior right thyroid gland. The diffuse enlargement of the gland with narrowing of the trachea is compatible with a multinodular goiter. B, On ultrasound, the demonstration of increased through transmission (arrowheads) and the well-defined back wall of a lesion signifies a cyst. C, Acoustic shadowing (arrows) from an echogenic focus (arrowhead) suggests calcification.
Figure 7. Colloid cyst. A hyperintense mass (c) on this T1-weighted coronal MR scan in the right lobe of the thyroid gland was due to a colloid cyst. Colloid, hemorrhage, hyperproteinaceous secretions, melanin, and occasionally calcification may be hyperintense on T1-weighted imaging.

Figure 8. Multinodular goiter on MR image. This T1-weighted axial MR scan demonstrates subtle masses (g) in both lobes of the thyroid gland. The single void (arrowhead) anteriorly on the left side did not represent a blood vessel, but instead was due to calcification.
Lymphoma is usually homogeneously bright in intensity on T₂-weighted MR images. Although some have found Hashimoto's thyroiditis to be low in intensity on T₂-weighted images and distinguishable from lymphoma (bright on T₂-weighted images), most have found the signal intensities to overlap.

Colloid cysts are often found to have high intensity on T₁-weighted MR images. This finding is not specific to colloid cysts, because areas of subacute or chronic hemorrhage, also bright on T₁-weighted images, can be seen in goiters, hemorrhagic adenomas, and traumatized cysts. Even thyroglossal duct cysts (see later) may be hyperintense owing to high protein content.

Magnetic resonance imaging is thought to be superior to CT scanning in detecting early esophageal and tracheal invasion. It also has fewer problems with shoulder artifacts than CT in tracing thyroid lesions (goiters and cancers) into the thoracic cavity and anterior mediastinum.

Postoperatively, thyroid carcinoma recurrences are usually of medium to high intensity on T₂-weighted images, whereas scar in the operative bed is usually of low intensity. Postoperative edema, infection, or bleeding may simulate recurrent tumor. MR imaging has been recommended in conjunction with I 131 radioisotope scanning for confusing postoperative cases.

**Congenital Lesions**

Two of the most common congenital abnormalities associated with the thyroid gland are thyroglossal duct cysts and the lingual thyroid gland. *Thyroglossal duct cyst* is a congenital lesion in which the tract of migration of the thyroid gland from the foramen cecum of the tongue (located in the midline at the circumvallate papillae level) to its normal position is persistent. Whenever an epithelium-lined tract has the potential for obstruction, a cyst may occur because of retained secretions. In the case of the thyroglossal duct cyst, one may identify a midline cystic mass located at the infrahyoid level in 65%, hyoid level in 15%, and suprahypoid level in 20% of cases. Although the lesion is typically midline, it occurs in a paramedian position in 25% of cases, usually in the infrahyoid compartment. The classic locations for a thyroglossal duct cyst are (1) embedded in the strap muscles below the hyoid bone, (2) in the midline in the tongue base, and (3) in the hyoid bone above the strap muscle insertions.

Because the fluid in the thyroglossal duct cyst may have a high protein content, it may appear cystic with some internal echoes on ultrasonography. On CT scanning the noninfected thyroglossal duct cyst varies in intensity from markedly hypodense (with low protein content) to slightly hyperdense (with high protein content or hemorrhage). On MR images, the thyroglossal duct cyst may be either dark or bright on T₁-weighted images but is typically hyperintense on T₂-weighted images (Fig. 9). Enhancement is uncommon in thyroglossal duct cyst unless the lesion has been traumatized or infected. In these cases, peripheral rim enhancement may occur.
Figure 9. Thyroglossal duct cyst. A. A midline cystic mass (c) is seen in the inferior floor of the mouth on this axial CT scan. The majority of thyroglossal duct cysts are infrahyoid in location, but may extend anywhere from the foramen cecum to anterior mediastinum. B. Twenty-five percent of thyroglossal duct cysts are off the midline. The presence of this cyst (C) embedded in the strap muscles anterior to the larynx is virtually pathognomonic of a thyroglossal duct cyst.
Ectopic thyroid tissue is found in roughly 25% of thyroglossal duct cysts. The incidence of carcinoma within the thyroid tissue of a thyroglossal duct cyst is less than 1%. When cancer coexists, it is usually papillary carcinoma (Fig. 10).

Recurrence rates of approximately 4% are seen after attempted removal of thyroglossal duct cysts. The surgery removes the entire tract of the duct, the midportion of the hyoid bone, and a portion of the base of the tongue, including the foramen cecum (Sistrunk procedure).

The lingual thyroid gland represents arrest of migration of the thyroid tissue within the tongue, usually in the midline between the circumvallate papillae and the epiglottis. Arrest may be complete or incomplete, and the primary role of imaging is to identify whether or not there is normal thyroidal tissue in the lower neck, so that complete excision or transplantation of the lingual thyroid tissue may be contemplated. Otherwise, the patient is doomed to thyroid replacement therapy for life, in the event of total resection of a lingual thyroid gland. Lingual thyroid tissue occurs in 1 in 3000 patients who have thyroid disease and represents the most common form of functioning ectopic thyroid tissue. Lingual thyroid glands are associated with absence of thyroid tissue in the neck in 70% of cases and are much more commonly seen in women. A nuclear medicine study to determine whether a lingual mass represents thyroid tissue, as well as to search for other (ectopic) thyroid tissue, is the primary way to evaluate this lesion (Fig. 11). The thyroidal tissue within the tongue can also be identified by its high attenuation on CT scanning, due to iodine accumulation, or its avid contrast enhancement. In a similar fashion, MR imaging demonstrates tissue isointense to thyroid gland that avidly enhances in the tongue.

**Inflammatory Lesions**

There are no specific scintigraphic, sonographic, CT, or MR imaging appearances to differentiate one inflammatory process involving the thyroid gland from another. The most useful study may be the nuclear medicine thyroid scan (performed with Tc 99m pertechnetate) or radioactive iodine (I 123 or I 131), which will determine the activity of the thyroid gland. The imaging studies’ value, however, pales in comparison with that of serology for distinguishing the various inflammatory lesions of the thyroid gland. If, however, imaging is to be used as a map for surgical correction or resection of the thyroid gland, MR imaging and ultrasound seem to be of particular benefit. One must be cautious regarding the administration of iodinated compounds for enhanced CT of the thyroid gland, because they will interfere with iodine function tests for up to 6 weeks. Additionally, in some instances, the administration of iodine might precipitate thyroid storm.

Acute suppurative thyroiditis manifests as abrupt onset of pain and swelling in the thyroid gland associated with fever, odynophagia, and dysphagia. The role of imaging is to exclude a piriform sinus fistula as an etiology for the acute suppurative thyroiditis; this entity occurs in
Figure 10. Carcinoma in a thyroglossal duct cyst. This T1-weighted axial MR scan reveals solid masses (m) within hyperintense cysts (c). Histopathologically, the diagnosis was papillary carcinoma within a multiloculated thyroglossal duct cyst, a very rare occurrence.

Figure 11. Understanding this thyroid scan requires the identification of the sternal notch marker (arrow) and realizing that there is no thyroid gland tissue in the expected location in the neck. Instead, there is increased uptake in the region of the tongue (t) where a lingual thyroid gland is present.
association with a fourth branchial cleft anomaly and has a left-sided pre-
dominance. Imaging may identify leakage from the piriform sinus to the
lateral neck–thyroid location. Acute suppurative thyroiditis is the rarest
form of thyroiditis but has the most fulminant clinical presentation.

Most of the other forms of thyroiditis are chronic diseases. Hashi-
moto’s (lymphocytic) thyroiditis is the most common of the chronic thy-
roiditides, being five to ten times more frequent than subacute thyroidi-
tis. It is the most common thyroiditis in children. The diagnosis is based
on serology, because the disease is an autoimmune process with antigenic
stimulation to thyroglobulin, colloid, and other thyroid cell antigens.
Women are affected nearly 20 times more frequently than men. The gland
is enlarged and shows heterogeneously increased or decreased uptake of
radiotracers. The disease imparts no greater risk for carcinoma but may
predispose to non–Hodgkin’s lymphoma. Hashimoto’s thyroiditis in the
presence of thyroid lymphoma is seen in 25% to 67% of cases.

On imaging, the thyroid gland is symmetrically enlarged but may
contain nodules. Early in the disease, there may be increased uptake of
iodine on nuclear medicine studies, but the usual response is diminished
or normal thyroid uptake on imaging. Increased signal intensity, some-
times with linear low intensity bands, seen on T₂-weighted MR images is
thought to represent fibrosis.

Riedel’s thyroiditis (struma thyroiditis) is an uncommon chronic in-
flammatory lesion of the thyroid gland. The disease may be bilateral or
unilateral and is more common in women than men. Patients present with
evidence of mass effect, with compression of the trachea, hoarseness, and
difficulty in swallowing. Usually they are hypothyroid. On imaging, Rie-
del’s thyroiditis is homogeneously hypoechoic on ultrasound and is usu-
ally hypodense to normal thyroid tissue on CT. The lesion may be
isodense to muscle on unenhanced CT. The characteristic finding on MR
imaging is hypointensity on both T₁- and T₂-weighted sequences with
infiltration of adjacent structures of the neck. The low intensity on MR
imaging is thought to be due to the chronic fibrosis associated with Rie-
del’s thyroiditis. This lesion may be associated with retroperitoneal fibro-
sis, mediastinal fibrosis, sclerosing cholangitis, and orbital pseudotumor.
It is distinguished from Hashimoto’s thyroiditis, which shows typically
increased intensity on T₂-weighted MR images.

De Quervain’s thyroiditis (subacute granulomatous thyroiditis) is a
disease of middle age occurring most commonly in women after an upper
respiratory infection. Subacute thyroiditis may manifest early (50% of
cases) with acute toxic hyperthyroidism and conversion to a euthyroid
state after 1 to 2 months. Hypothyroidism occurs approximately 2 to 4
months after onset, and typically, by 6 months after the acute event, the
patient returns to a euthyroid state. Patients are treated medically
because the prognosis is good for return of normal thyroid function.
Subacute thyroiditis is hypoechoic on ultrasound, and there may be
atrophy of thyroidal tissue with time. Nuclear medicine studies show
heterogeneous uptake that varies in extent with the stage of the disease
(Fig. 12).
Metabolic Diseases of the Thyroid Gland

Thyrotoxicosis

Graves' disease is the most common cause of diffuse toxic goiter. Other causes of thyrotoxicosis are toxic multinodular goiter and single toxic adenoma. On rare occasions, ectopic thyroid tissue (lingual or ovarian) may cause hyperthyroidism. Again, blood tests usually are able to make the diagnosis of Graves' disease because of the autoimmune phenomenon associated with the disorder. Thyroid-stimulating immunoglobulins such as long-acting thyroid stimulator (LATS) simulate the function of TSH and cause hyperthyroidism. On iodine scans, there is markedly elevated iodine uptake within a diffusely, homogeneously enlarged thyroid gland. Toxic multinodular goiter and toxic adenomas have less uptake than Graves' disease, and the uptake may be more focal.

In a patient who is hyperthyroid, scintigraphy may be very useful in distinguishing Graves' disease, which shows homogeneous diffuse intense uptake (70% to 85%), from the thyroiditides (Fig. 13). Thyroiditis is less homogeneous, and the uptake may be normal, high, or low, depending on the state of the inflammatory process. Because some thyroiditides may revert to euthyroid activity with time (see earlier), the implications for therapy are important. Graves' disease requires antithyroid medication, radioactive iodine obliteration of the gland, or surgery.
Figure 13. Graves' disease. This patient has a very enlarged thyroid gland with increased radiotracer uptake (80%). Analysis of the thyroid scan for Graves' disease requires not only an assessment of the size and degree of uptake but also thyroid function.

**Hypothyroidism**

Hashimoto's thyroiditis is the most common cause of hypothyroidism in the United States (see earlier). Additional etiologies are the other chronic thyroiditides and dysbormogenesis (organification defects). Postoperative and post-radiotherapy (be it with I 131 or external beam irradiation) patients also account for a great number of these cases. It is common for patients treated with radioactive iodine for hyperthyroidism to become hypothyroid after several years.

**PARATHYROID IMAGING**

Hyperparathyroidism has an incidence of 0.037% in the United States. Patients may present with the classic findings of "stones" (renal calculi), "groans" (abdominal pain), "bones" (demineralization or arthritis), or "moans" (psychiatric disturbances). Primary hyperparathyroidism is caused by a solitary parathyroid adenoma in 80% to 85% of cases. Hyperplastic parathyroid glands (12% to 15%), multiple adenomas (2% to 3%), and parathyroid carcinoma (<1%) account for the remaining 15% to 20%. Parathyroid adenomas may be ectopic (not around the thyroid bed) in 10% of cases.
Parathyroid imaging is controversial, not only from the standpoint of the indications for imaging but also in terms of the studies of choice. In most institutions, preoperative localization of the parathyroid glands by imaging is not performed. This practice stems from the early surgical literature that suggested that neither operative time nor operative morbidity or mortality is significantly influenced by preoperative localization of parathyroid adenomas for hyperparathyroidism. The surgical exploration in these centers consists of bilateral dissection in the perithyroidal region, emphasizing the inferior poles, where most parathyroid adenomas occur. In experienced hands, the surgical procedure can be performed quickly and accurately with success rates of over 90%. Thompson states that the best localization procedure one can obtain for parathyroid adenomas is to "locate an experienced parathyroid surgeon."

The case for preoperative localization of parathyroid adenomas is based on (1) the ease of unilateral dissections when an adenoma is evident on imaging, (2) identifying ectopic adenomas preoperatively, and (3) detecting other head and neck masses that may require treatment at the same time (e.g., thyroid masses). The proponents of preoperative imaging believe that unilateral neck dissections decrease operating room time as well as the risk of damage to recurrent laryngeal nerves and normal parathyroid glands. In the experience reported by Russell and colleagues, the difference between mean operating times of unilateral (71 minutes) and bilateral (97 minutes) explorations justified the preoperative imaging. Uden and associates also noted that the time for surgery and anesthesia decreased with preoperative imaging, but when results were analyzed in a cost-benefit scheme, these authors found the cost of the imaging procedure to outweigh its benefit. Some surgeons perform unilateral neck dissections if imaging studies are definitive but choose bilateral surgery if (1) imaging is equivocal or shows multifocal abnormality, (2) enlarged glands are identified at surgery, (3) the patient has a multiple endocrine neoplasia syndrome (often associated with parathyroid hyperplasia), or (4) a unilateral exploration is unrevealing. In any case, less experienced surgeons and those who have had a less successful track record may opt for preoperative localization of parathyroid adenomas.

When a parathyroid adenoma is not identified in a stereotypical perithyroidal location, the surgeon may explore the anterior mediastinum or the upper neck region. The yield of surgery in this scenario is much lower than that expected for those adenomas in a perithyroidal location. Ectopic parathyroid adenomas also may rarely be located intrathyroidally (0.2% to 3.5% of cases); these are difficult to distinguish from thyroid adenomas. In fact, thyroidal abnormalities occur in 40% to 48% of patients with hyperparathyroidism.

**Imaging Techniques**

The options for imaging the parathyroid glands are many; they include ultrasonography, CT, MR imaging, angiography, and a multitude
of nuclear medicine studies. The options for scintigraphic localization of parathyroid adenomas include Tc 99m pertechnetate–thallium 201 subtraction scanning, thallium 201 scanning alone, Tc 99m sestamibi imaging alone, Tc 99m sestamibi imaging with I 123 or thallium 201 subtraction, and Tc 99m sestamibi and Tc 99m pertechnetate subtraction scanning. In the patient for whom surgery for parathyroid adenoma has failed, imaging is much more difficult. Scar tissue in and around the thyroid glands as well as postoperative inflammation causing lymphadenopathy may lead to inaccurate localization of parathyroid adenomas by ultrasound or cross-sectional imaging techniques.

The advantages and disadvantages of each of the imaging modalities described here are summarized in Table 2. Suffice it to say that ultrasound, because it does not require intravenous injections of any compounds, is the least invasive of the imaging modalities. Unfortunately, its accuracy is less than that of the other modalities, mainly because of the difficulty in identifying ectopic parathyroid adenomas, which may occur throughout the neck, behind air-filled structures, or in the anterior mediastinum, where acoustic impedance by bone prevents adequate imaging. Nonetheless, for parathyroid adenomas located in a perithyroidal location, ultrasound is an excellent imaging choice. Parathyroid adenomas appear sonographically as oval, oblong, or bulbous lesions with echogenicity less than that of the thyroid glanda'. (Fig. 14). In this location, the only difficulty with ultrasound is discriminating an eccentric pedunculated thyroid adenoma from a perithyroid lymph node from a parathyroid ade-

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<td>Computed tomography</td>
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<td>Easy detection of calcification</td>
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<td>Excellent soft tissue discrimination</td>
<td>Reasonable cost</td>
</tr>
<tr>
<td>Nuclear medicine scintigraphy</td>
<td>Examines head and neck well</td>
<td>Lower yield for ectopic glands, especially in chest</td>
</tr>
<tr>
<td></td>
<td>Functional, not morphologic imaging</td>
<td>Intrathyroidal masses indistinguishable from adenomas</td>
</tr>
<tr>
<td></td>
<td>Distinguishes nodes from adenomas</td>
<td>Smaller lesions easily missed</td>
</tr>
<tr>
<td></td>
<td>Reasonable cost</td>
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<tr>
<td>Ultrasound</td>
<td>Examines neck well</td>
<td>Lower yield for ectopic glands, especially in chest</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>Cannot differentiate nodes and adenomas</td>
</tr>
<tr>
<td></td>
<td>Noninvasive</td>
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<tr>
<td></td>
<td>Realtime images, biopsy capable</td>
<td>Lower sensitivity</td>
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Hyperplastic lymph nodes, unfortunately, look identical to adenomas on all nonscintigraphic imaging studies. Computed tomography offers the benefit of cross-sectional imaging for parathyroid adenoma localization. Because one is able to scan the entire neck from skull base to anterior mediastinum with CT, the possibility of detecting ectopic parathyroid adenomas is increased. The difficulty in distinguishing lymphadenopathy from parathyroid adenomas is also encountered with computed tomography. The other disadvantage of using CT is the need to administer iodinated intravenous contrast agents. These agents are essential for distinguishing blood vessels from adenomas or lymphadenopathy, but their use prevents subsequent imaging with iodine-based nuclear medicine studies, because of the uptake of contrast by the thyroid gland. Contrast enhancement is not the solution to parathyroid imaging—only 25% of parathyroid adenomas demonstrate noticeable enhancement.57 False results of CT scanning may occur in the setting of poor-quality studies because of broad shoulder artifacts.

Magnetic resonance imaging with gadolinium enhancement is another useful study for evaluating the patient with hyperparathyroidism. On T₂-weighted images and post-gadolinium enhancement T₁-weighted images performed with fat suppression, parathyroid adenomas are bright against a dark background17, 23-25, 46, 56 (Fig. 15). MR imaging is limited by the distribution and coverage of the surface coil used to detect parathyroid adenomas as well as by any motion artifact that may occur during imaging. Nonetheless, with the appropriate surface coil or body coil and
Figure 15. Parathyroid adenoma on MR image. A. This axial T2-weighted MR scan reveals a hyperintense mass (*) below the left thyroid gland. In a patient with hypercalcemia, this mass should be highly suspicious for a parathyroid adenoma. B. Note that the lesion enhances on post-gadolinium axial T1-weighted fat-suppressed image.

proper instructions to the patient, MR imaging is able to adequately evaluate the entire neck and anterior mediastinum. As with the other modalities listed, the potential for misdiagnosing lymph nodes as parathyroid adenomas is present with MR imaging.

The wealth of options for nuclear medicine scanning for parathyroid adenomas stems from the fact that no agents are specifically taken up by the parathyroid glands. Therefore, one must subtract agents that are taken up by parathyroid adenomas and the thyroid glands from the agents that are taken up only by the thyroid glands, thereby allowing visualization of abnormal uptake by parathyroid adenomas. Thallium 201, a potassium analog, is localized to the normal thyroid gland and parathyroid adenomas. Because thallium 201 emits low-energy 80-keV photons, it requires prolonged patient immobilization and produces scans with relatively low signal-to-noise ratio. Thallium 201 uptake appears to correlate with the
number of mitochondria or oxyphil cells in the thyroid gland and lesions.\(^{45}\)

For Tc\(^{99m}\) pertechnetate–thallium 201 subtraction scanning, the technetium pertechnetate is injected first, followed 10 minutes later by the thallium 201. Five minutes after the thallium is injected, one subtracts technetium scans from the thallium scans, in order to detect a parathyroid adenoma (Fig. 16). Technetium (as noted previously) is a nuclear medicine agent that admits gamma rays at 140 keV and is taken up by the thyroid gland but not by parathyroid adenomas. Iodine 123 thyroid images can also be subtracted from thallium 201 scans to detect parathyroid adenomas.

Technetium \(^{99m}\) sestamibi Cardiolite is a recently developed agent with a high ratio of parathyroid adenoma uptake to thyroid uptake.\(^{37}\) Sestamibi appears to concentrate in tissue with high mitochondrial content and therefore is reasonably well suited to parathyroid adenoma imaging (Fig. 16). In order to increase the efficacy of parathyroid scintigraphy with Tc\(^{99m}\) sestamibi, one can use technetium pertechnetate or I\(^{123}\) to subtract thyroid tissue from the initial Tc\(^{99m}\) sestamibi image. The subtraction optimizes the differentiation of thyroid from parathyroid tissue.

At most centers, Tc\(^{99m}\) sestamibi imaging is done without subtraction. Because the agent washes out of the thyroid gland rapidly but is retained by parathyroid (and thyroid) adenomas, delayed images are all that is necessary for good localization. The higher-keV photons emitted by technetium compared with thallium 201 allow higher signal-to-noise ratios and better penetration, particularly for substernal adenomas. Furthermore, the difficult task of patient immobilization and accurate superimposition of subtracted images required by Tc\(^{99m}\) pertechnetate–thallium 201 studies is obviated with delayed sestamibi imaging. Computer processing is required to enhance accuracy with subtraction techniques.\(^{3}\) Finally, one need not sacrifice accuracy with the simpler sestamibi study. The overall sensitivity of \(^{99m}\) pertechnetate–thallium 201 subtraction scintigraphy for parathyroid adenoma detection\(^{2,36}\) is substantially less than that of Tc\(^{99m}\) sestamibi, which is 88% to 100%\(^{,36,37,59}\). No adenomas that were positive on thallium 201 scanning have been negative on Tc\(^{99m}\) sestamibi scanning. Unfortunately, the high rate of thyroid abnormalities (40% to 48%) coexistent with parathyroid adenomas may lead to false-positive scintigrams because thyroid lesions may concentrate radiotracers to the same extent as parathyroid adenomas.\(^{30,36,37,59}\)

**Imaging Results**

**Nonoperated Patients**

High-resolution ultrasound was performed in 165 patients with hyperparathyroidism in a study by Reading et al.\(^{42}\) The authors found a sensitivity of 64% and a specificity of 94% using ultrasound for adenomas and hyperplastic glands. For those glands greater than 1 g in size, ultra-
Figure 16. Parathyroid adenoma demonstrated on nuclear scintigraphy. A. A technetium-thallium subtraction nuclear scan is demonstrated. On the upper left one sees a thallium scan showing thyroid uptake without clear evidence of a parathyroid adenoma; to the right is a technetium scan showing normal thyroid uptake. As one performs sequential subtraction of the technetium thyroid scan from the thallium scan in the lower rows, one is able to detect persistent thallium uptake (arrows) below the thyroid gland representing a parathyroid adenoma. B. Using technetium-99m sestamibi, an early scan shows both normal left thyroid gland (arrow) and parathyroid adenoma (arrowhead) uptake. C. With delayed sestamibi imaging, the thyroid uptake is washed out, leaving only the parathyroid adenoma (arrowhead). This parathyroid adenoma was ectopically located in the superoanterior mediastinum.
sound had a detection rate of 95%. When Stark and associates\(^5\) compared the accuracy of high-resolution CT and ultrasonography, they found a sensitivity of 70% and a specificity of 90% for CT, and a sensitivity of 60% and a specificity of 96% for ultrasound. CT had a sensitivity of 88% for hyperplastic glands, compared with 69% for ultrasound.\(^5\) Sommer and colleagues\(^5\) also found CT to be more accurate than ultrasound by over 10%; combined, the studies have a detection rate of 89% in patients without surgery.\(^5\) When ultrasound was compared with thallium 201–Tc 99m pertechnetate scintigraphy, the studies showed similar detection rates for adenomas (70% to 78%) and hyperplastic glands (65%) in nonoperated patients.\(^5\) Edmonson et al\(^1\) noted that a parathyroid carcinoma may have the same sonographic appearance as a benign large adenoma (hypoechoic with or without heterogeneity)—only the presence of local invasion into the thyroid gland, muscles, or vessels or nodal metastases would suggest this diagnosis.\(^1\)

The study by Spritzer et al\(^56\) was one of the first to report on the accuracy of MR imaging in detecting parathyroid lesions. In this study, 17 patients had adenomas, 3 had hyperplasia, and 2 had carcinomas. MR imaging correctly identified 14 of 17 adenomas (82.3%), both cancers, and five of eight hyperplastic glands. Two false-positive and three false-negative studies for adenomas were reported; given the possibility of 72 glands, this accuracy of MR imaging was 92% for adenomas. At nearly the same time, Kier and associates\(^2\) reported accuracy rates of 86%.

In a comparative study of nonoperated patients, Kneeland and colleagues\(^2\) found scintigraphy to have higher sensitivity (82%) than MR imaging (74%), CT (74%), and ultrasound (59%). The differences were statistically significant only between thallium-technetium scintigraphy and ultrasound.

All of the comparative studies described employed Tc 99m pertechnetate. O'Doherty and associates\(^3\) more recently compared parathyroid imaging using Tc 99m sestamibi with that using Tc 99m pertechnetate–thallium 201 subtraction (thallium subtraction). The sensitivity of thallium subtraction for the detection of parathyroid adenomas was 90%, whereas that for Tc 99m sestamibi was 98%.\(^3\) In a similar vein, parathyroid hyperplasia was detected in 47% of cases with thallium subtraction but in 55% with Tc 99m sestamibi. The authors noted that, with the tenfold decrease in total body dose radiation to the patient with the use of Tc 99m sestamibi compared with thallium scanning, there is strong reason to use the former for identification of parathyroid adenomas apart from its greater sensitivity.\(^3\) A consensus is growing in support of the use of Tc 99m sestamibi as the optimal agent for parathyroid adenoma localization.\(^3, 37, 59\)

Previously Operated Patients

As reported by Miller and colleagues,\(^3\) 30% to 75% of abnormal glands in reoperated cases are perithyroidal but were missed at the time of initial operation. Between 20% and 38% of parathyroid adenomas in patients with failed initial operations are located in the anterior medias-
Posterior mediastinal ectopic adenomas are one fifth as common as anterior ones. In patients who undergo reoperation, the risk of vocal cord injury through damage to the recurrent laryngeal nerve or vagus nerve is approximately 7%, compared with 13% for the initial operation. When imaging is not performed prior to reoperation for hyperparathyroidism, surgery is approximately 60% successful; when imaging is performed prior to reoperation, the success rate increases to 80% to 90%.

In the 1983 series of 19 patients reported by Stark et al., CT was shown to be more sensitive (63%) than ultrasound (47%) in detecting adenomas in postoperative patients. A study of 53 patients reoperated for persistent hyperparathyroidism found that MR imaging (50%) and CT (47%) were more sensitive than ultrasound (36%) and Tc 99m-thallium 201 scintigraphy (26%). CT had the lowest false-positive rate (2%). Combining ultrasound, CT, and scintigraphy increased the sensitivity to 78%. False-negative results tended to occur with adenomas in the thymus or parathryoid operative beds. Another study found CT and ultrasound to be superior to scintigraphy and MR imaging. In the second part of their study, Miller and colleagues performed invasive procedures in the same patient population. The authors found parathyroid venous sampling (80%), intraoperative ultrasound (78%), and arteriography (49% to 60%) to have higher sensitivities than the noninvasive studies. The expense and technical difficulty of performing these invasive studies preclude their routine utilization, but they may be held in abeyance for cases with equivocal or nonrevealing results of noninvasive studies.

In comparing scintigraphy and MR in the same 23 patients, Peck and associates found MR imaging to be prospectively (73%) and retrospectively (91%) more sensitive than thallium subtraction scintigraphy (64% prospectively and 64% retrospectively) in previously operated patients. MR imaging was performed without gadolinium enhancement. Hamilton et al. also looked at patients who had previous surgery for parathyroid adenomas and found the sensitivity of MR imaging (50% to 90%) superior to that of nuclear medicine (26% to 68%), ultrasound (36% to 76%) and CT (46% to 55%). In a study reported by Kang et al., abnormal parathyroid glands in the anterior mediastinum were correctly identified in 23 of 25 cases with MR imaging but in just 11 of 19 cases by nuclear medicine and 3 of 24 cases by ultrasound. Again, the potential for false-positive results due to lymphadenopathy, which has a similar MR imaging appearance to that of parathyroid adenomas, was addressed. The incidence of false-positive results is lowest with nuclear medicine studies, followed in order by MR imaging, ultrasound, and CT, according to Miller and colleagues.

Obviously, with all of these contradictory studies, there is no consensus in the literature regarding the most accurate test for detection of parathyroid adenomas. Expertise within a department may determine the best approach. When Price reviewed the entire literature to date in 1993 (from 243 to 1785 cases), however, he found that MR imaging had the highest sensitivity for the detection of adenoma (74%), followed by nuclear medicine studies (72%), CT (65%), and ultrasound (63%). Nonetheless, the false-positive rate for nuclear medicine (11%) was lowest compared with
MR imaging (14%), CT (16%), and ultrasound (18%). For hyperplasia, CT was more sensitive (45%) than nuclear medicine (43%), MR imaging (40%), and ultrasound (30%). Price's review of the literature also showed that at reoperation, MR imaging is found to have the highest sensitivity (66%) compared with ultrasound (60%), CT (48%), and nuclear medicine (45%).

Many surgeons approach evaluation of the patient who is being reoperated for hyperparathyroidism by using the simplest and least expensive study first. This means that ultrasound, despite its intermediate sensitivity and false-positive rate in reoperated cases, is usually the first imaging modality employed. It may identify a mass in the perithyroidal bed, where 75% of missed adenomas reside. When ultrasound results are either ambiguous or nonrevealing, either MR imaging or nuclear medicine is employed. Because the Tc 99m sestamibi study is very accurate and costs 30% to 40% less than MR imaging, it may be the second-line exam. The idea of using a morphologic test (ultrasound or MR imaging) as well as a functional test (Tc 99m sestamibi) is appealing, because MR imaging and ultrasound may not be able to differentiate nodes from adenomas. Using this algorithm increases the surgical success rate by over 30%.

Therapeutic Techniques

Ethanol ablation of parathyroid adenomas has been performed under ultrasound guidance by percutaneous injection of absolute ethanol. This technique may be employed in patients with primary or secondary hyperparathyroidism who are not surgical candidates because of medical illnesses. Approximately 0.5 to 1 ml of ethanol (95%) may be injected with a 22-gauge needle multifocally into the adenoma, until the patient is normocalcemic.

References


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