Multimodality Imaging of the Thyroid and Parathyroid Glands

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Nuclear imaging of the thyroid and parathyroid glands has evolved from early radionuclide rectilinear thyroid scanning to the recently developed dual isotope subtraction technique for detecting parathyroid lesions. At the same time, x-ray fluorescent scanning, ultrasound, x-ray computed tomography, and magnetic resonance imaging have improved identification of these endocrine organs. The appropriate use and relative role of these imaging modalities in the investigation of patients with thyroid and parathyroid diseases is discussed.


Thyroid and parathyroid disorders affect a wide spectrum of the human population from the neonate to the elderly. Numerous imaging modalities including nuclear medicine, ultrasonography, x-ray fluorescent scanning, x-ray transmission computed tomography (CT) and, more recently, magnetic resonance imaging (MRI) have been used in an attempt to provide a diagnosis in patients with diseases of the thyroid and parathyroid glands. The purpose of this article is to evaluate the noninvasive imaging procedures currently available to diagnose thyroid and parathyroid disorders.

IMAGING PRINCIPLES

The imaging principles of nuclear medicine, x-ray fluorescence scanning, ultrasonography, and CT are well established. Nuclear medicine techniques provide the ability for assessment of thyroid and parathyroid size, location, and function at the time the study is performed through the use of chemical as well as imaging procedures. These techniques utilize the physiological processes of the glands and radiolabeling of chemicals taken up by the glands in order to perform the evaluations.

X-ray fluorescence scanning utilizes an external source of radiation to map the stable iodine that has been trapped and stored by the thyroid, in order to assess its past functional status. Ultrasonography utilizes reflected sound waves to identify and evaluate gland size, location, the presence of nodules, and to differentiate between cystic and solid lesions. X-ray computed tomography makes use of the attenuation of transmitted x-rays to provide high resolution images of neck anatomy.

Magnetic resonance imaging (MRI) is a relatively new imaging modality that makes use of magnetic fields and radiofrequency (RF) waves applied in specific pulse sequences to image selected slices in the body with image contrast determined by tissue characterization. The advantage of MRI and also one of its complexities is the fact that a multitude of different types of images can be produced by varying the RF pulse length and the sequence in which the pulses are applied. High resolution images of neck anatomy can be obtained using sequences that emphasize proton density. For the demonstration of pathologic lesions, either T1 or T2 dependent images are usually necessary.

The spin-lattice relaxation time (T1) measurement varies from tissue to tissue depending upon the relationship of the hydrogen atoms to their surrounding or molecular lattice. Short relaxation times exist where water (rich in hydrogen) is closely bound to proteins, such as in muscle or in fat. In general, malignant tissue has a longer T1 than its normal native tissue, as does edematous and infected tissue. The T1 parameter is the major constituent of inversion recovery images and produces images of high contrast. The appearance of inversion recovery images may be altered by varying the pulse sequence, a phenomenon that must be understood in order to interpret the images obtained. In addition, signal intensity decreases with increasing T1, a factor that may cause confusion in image interpretation. Calculated T1 images may be obtained using MRI techniques. However, care must be exercised in the use...
of T1 measurements in patients with thyroid nodules and parathyroid lesions because calibration of an MR imager must be continually performed to assure precise determination of T1 values. In addition, the absolute value of T1 is dependent upon the strength of the magnetic field utilized. Thus, comparison of values between instruments with different magnetic field strengths and resonant frequencies is complex.

Spin-spin relaxation times (T2) are often more sensitive to differences in tissue makeup and therefore T2 dependent images are important in MRI. T2 dependent images are acquired using a spin-echo technique with signal intensity increasing with increasing T2 values. T2 values also are determined by the environment in which the hydrogen protons exist. T2 dependent images tend to be of high spatial resolution and to have high contrast between areas of differing T2 values. Similar attention to the pulse sequence employed in the production of T2 images must be paid, as is necessary when viewing T1 dependent images.

The MRI technique may be applied in any plane and images are routinely produced from axial, coronal, and sagittal planes. An advantage of MRI over CT in the imaging of sagittal and coronal planes is that images are constructed from data acquired in the chosen image plane and not reconstructed from data acquired in another plane.

CLINICAL APPLICATION

Thyroid

Radionuclide imaging plays an important role in the investigation of patients with thyroid disorders, especially those with solitary thyroid nodules. It serves to confirm the presence of a nodule within the thyroid, identifies the functional characteristics of the nodule, and may demonstrate the presence of multiple nodules. A variety of radiopharmaceuticals have been and are currently employed for this purpose.

Technetium-99m (99mTc) pertechnetate is the most readily available radionuclide employed for thyroid imaging. Pertechnetate ions (TcO₄⁻) are trapped by the thyroid in the same manner as iodine through an active transport mechanism but not organified (1–5). Iodine-123 (123I) is both trapped and organified by the thyroid gland, allowing overall assessment of thyroid function. Iodine-123 is cyclotron-produced, significantly reducing its availability and increasing its cost. Also, 123I has a relatively short half-life of 13.6 hr and, therefore, long-term storage is a problem; thus, advance notice is usually necessary prior to imaging with this radionuclide. Iodine-131 (131I), although frequently used in thyroid imaging in the past, now plays a role mainly in the study of metastatic thyroid cancer, due to the high thyroid and total-body radiation dose from beta emission.

The choice of radionuclide for routine imaging of the thyroid gland therefore lies between 99mTc and 123I. A disadvantage of imaging with pertechnetate is that it is only trapped and not organified in the follicles. In addition, early imaging following intravenous administration is associated with high background activity. Imaging with 99mTc, however, frequently provides enough information to serve as an acceptable alternative to 123I. In those instances where it is thought essential to assess both organification and trapping, 123I scanning can be subsequently performed.

Normal thyroid gland. The normal thyroid gland and anatomic variants can be visualized by numerous imaging modalities including scintigraphy, ultrasound and computed tomography. MRI is capable of providing excellent anatomic detail of the thyroid gland using proton density imaging (Fig. 1).

Multinodular goiter. The pathophysiology of multinodular goiter is thought to be the consequence of cycling periods of hyperstimulation, followed by involution of the stimulated areas in most instances. In some patients the hyperplastic tissue fails to return to normal. Hormonal synthesis is maintained even though some of the stimulated thyroid follicles may be unable to mobilize colloid, the net effect of which is an imbalance between synthesis and mobilization, resulting in both an increase in size and occasional rupture of the follicle. The rupture and release of colloid from the follicles may result in areas of fibrosis within the thyroid gland. If these fibrotic areas are scattered irregularly throughout the gland, a typical multinodular colloid goiter may develop. The importance of identifying a multinodular goiter relates to the lower incidence of malignancy in these patients (1% to 6%) compared with a higher incidence in patients with a single “cold” nodule (15% to 25%).

The scintigraphic appearance of a multinodular goiter is that of multiple nonfunctioning cold areas inter-

![FIGURE 1](Transverse MRI through a normal thyroid gland using a spin echo 3000/32 (T2 weighting). Thyroid isthmus (I), right lobe (Rt), left lobe (Lt), carotid artery (Ca), and jugular vein (Jv).)
dispersed between focal areas of increased activity in an asymmetrically enlarged thyroid gland. Ultrasound is also an excellent imaging modality for identifying multinodular goiter. High-resolution, realtime sonography allows the visualization of adenomas of 2 to 3 mm in size, increasing the detection of multinodular goiter when only a solitary thyroid nodule was detected by clinical palpation (6). Since current available data on the incidence of malignancy in a multinodular goiter is related to clinically palpable goiters, the significance of small nonpalpable nodules detected by real time sonography remains uncertain. Multinodular goiters are easily identifiable by MRI on the basis of their anatomic appearance (Figs. 2A-E).

Thyroid nodules. The investigation of a solitary thyroid nodule should be performed in a logical sequence. It is important to identify those patients with functioning thyroid nodules and further differentiate this group into hypertrophic versus autonomous nodules which have the potential to become toxic. The recent move to make thyroid biopsy the only investigative procedure in patients with solitary thyroid nodules may prevent the diagnosis of a functioning autonomous thyroid nodule (7).

Nonfunctioning ("cold") nodules, identified by thyroid scintigraphy, are regions that do not concentrate radioisotopes relative to the rest of the thyroid gland. Although thyroid malignancies do not effectively concentrate radioisotopes, only ~20% or less of "cold" nodules are caused by cancerous lesions (8). The remaining 80% of "cold" nodules arise from thyroid adenomas, colloid nodules, degenerative nodules, nodular hemorrhage, cysts, inflammatory nodules (including Hashimoto's thyroiditis or de Quervain's thyroiditis), infiltrative disorders (including amyloid or hemachromatosis), or nonthyroid neoplasms. A functioning TSH-dependent adenoma may appear as a cold nodule in patients with Graves' disease where impaired radionuclide uptake by the nodule is secondary to low TSH levels. This entity is known as the Marine-Lenhart syndrome. Confirmation of the diagnosis can be made by TSH stimulation.

The detection of extrathyroidal activity on a routine thyroid scan in a patient with palpable lymph nodes and a solitary thyroid nodule, although rare, most likely indicates metastatic thyroid cancer. Although frequently used in thyroid imaging, there are no specific signs using ultrasonography that permit the differentiation of benign from malignant nodules (6,9,10). Quantitative x-ray fluorescent scanning is useful in predicting benignancy of solitary cold thyroid nodules with a sensitivity of 63% and a specificity of 99% (11).

In vitro magnetic resonance studies on thyroid biopsy specimens performed by de Certaines and co-workers revealed abnormal T1 and T2 values in both benign and malignant lesions with no clear differentiation possible (12). Nodules showing increased radionuclide uptake showed a marked degree of variability in T1 values with nine out of ten having significantly increased T2 values compared with normal extranodular tissue. Solitary benign cold nodules (n = 9) all showed increased T1 and T2 values. T1 and T2 values showed considerable variation in four patients with thyroid carcinoma. An increase in T1 was observed in two patients and a decrease in one. T1 was not measured in the fourth patient. T2 values were increased in two cases and decreased in two. There was no significant difference in the relaxation times between nodular and extranodular tissue in patients with multinodular goiter.

The in vivo differentiation between benign and malignant thyroid lesions does not at present appear to be possible on the basis of T1 and T2 measurements alone (Figs. 3, 4). Benign and malignant thyroid tissue may, in part, be distinguished using MRI by the degree of disruption of thyroid anatomy, and the invasion of normal thyroid tissue and surrounding structures. Colloid cysts exhibit greatly prolonged T1 values characteristic of simple fluids. Hemorrhage into a cyst should lower the T1 value. Adenomas exhibit a wide range of T1 values, although generally prolonged, encompassing those of thyroid carcinomas. The ability of magnetic resonance in vivo spectroscopy to differentiate benign versus malignant thyroid nodules awaits further investigation.

Hyperthyroidism. Hyperthyroidism, a chemical syndrome that results from supraphysiologica levels of thyroid hormones, may occur as a consequence of numerous diseases (Table 1). Clinical history and physical examination, combined with thyroid scintigraphy, thyroid uptake and thyroid antibodies, allows identification and differentiation of the various disease processes.

Patients with Graves' disease exhibit prolonged T1 values; the physiologic basis of which remains unexplained (Fig. 5). MRI of patients with Graves' disease, however, is of limited value when compared to the numerous modalities currently available to diagnose this disorder and differentiate it from other causes of hyperthyroidism.

Retrosternal goiter. Although substernal aberrant thyroid goiter accounts for only 10% of all mediastinal masses, it remains one of the major diagnostic considerations in the assessment of mediastinal abnormalities (13).

The preoperative diagnosis of a thyroid mediastinal mass frequently requires the use of sophisticated imaging techniques including, either alone or in combination, radionuclide thyroid scintigraphy, computed tomography, and MRI (14,15).

Radionuclide imaging has been the standard method for evaluating whether or not a mediastinal mass represents functioning thyroid tissue. False-negative thy-
FIGURE 2
A: Patient with large multinodular goiter presenting with neck discomfort without symptoms of superior mediastinal obstruction. B: Chest x-ray reveals a large right-sided chest mass. C: Iodine-131 thyroid scintigram shows a large diffuse multinodular goiter with retrosternal extension (white arrow). D: Sagittal MRI 500/32 pulse sequence shows large goiter with anterior and posterior mediastinal extension (white arrows). E: Sagittal MRI 2,000/160 pulse sequence (T2 weighting) shows diffuse increase in signal intensity in most areas of multinodular goiter most likely related to colloid and hemorrhage.
TABLE 1
Classification of Hyperthyroidism

<table>
<thead>
<tr>
<th>Thyroid gland (±95%)</th>
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<tr>
<td>Diffuse toxic goiter (Graves’ disease)</td>
</tr>
<tr>
<td>Toxic nodular goiter</td>
</tr>
<tr>
<td>Multinodular (Plummer’s disease)</td>
</tr>
<tr>
<td>Solitary nodule</td>
</tr>
<tr>
<td>Thyroiditis (subacute)</td>
</tr>
<tr>
<td>Exogenous thyroid hormone/jodine (±4%)</td>
</tr>
<tr>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Factitious</td>
</tr>
<tr>
<td>Iodine-induced (Jod-Basedow)</td>
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<tr>
<td>Rarely encountered causes (±1%)</td>
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Rarely encountered causes (±1%)

Hypothalamic-pituitary neoplasms
Struma ovarii
Excessive HCG production by trophoblastic tissue
Metastatic thyroid carcinoma

Intravenous contrast more than likely represents the vascularity of the mass rather than significant trapping and organification of iodine by the thyroid gland (18).

MRI is an excellent modality to image the mediastinum, producing high resolution tomographic or three-dimensional images without the use of ionizing radiation (Figs. 2D, E). MRI of the mediastinum also differentiates vascular structures from solid hilar or mediastinal masses without the use of contrast agents (19). Volume calculations of thyroid mediastinal masses are possible with MRI permitting quantitative assessment of the response of the mass to TSH suppression.

Parathyroid

There has been an increase in the incidence of the number of patients reported with primary hyperparathyroidism during the past decade (20). This increase has been attributed to the routine determination of serum calcium and phosphorus by new automated methods and the development of sensitive radioimmunoassay techniques for the detection of parathyroid hormone. The routine screening of serum calcium has had a significant influence on the clinical presentation of patients with primary hyperparathyroidism.
For example, the incidence of urolithiasis has fallen to <10% of its former rate and three times as many patients now have no obvious symptoms or adverse effects of the disease.

Numerous imaging modalities including technetium-99m/thallium-201 (\(^{99m}\)Tc/\(^{201}\)TI) subtraction, realtime ultrasound, dynamic computerized tomography, angiography, and more recently MRI are now being used in an attempt to improve both the sensitivity and the specificity of diagnosing parathyroid tumors.

**NUCLEAR MEDICINE**

Selenomethionine-75 (\(^{75}\)Se) was introduced as a non-invasive technique to localize parathyroid adenomas; however, in spite of numerous attempts to improve both the sensitivity and specificity of this technique, it has now been abandoned (21).

The successful utilization of combined \(^{99m}\)Tc/\(^{201}\)TI subtraction imaging has recently been described for the localization of parathyroid adenomas in patients with primary localization of parathyroid adenomas in patients with primary hyperparathyroidism (22–24). The \(^{99m}\)Tc/\(^{201}\)TI subtraction technique is based on the fact that the thyroid traps \(^{99m}\)Tc and \(^{201}\)TI. In addition, it has been shown that parathyroid adenomas also take up \(^{201}\)TI. The accumulation of \(^{201}\)TI in a parathyroid adenoma is nonspecific and is most likely related to the cellularity or vascularity of the lesion. Technetium-99m is administered to identify only the thyroid. The thyroid may then be subtracted out of the combined image by subtracting the \(^{99m}\)Tc image from the \(^{201}\)TI image. Any remaining areas of \(^{201}\)TI concentration are probably markers for identification of parathyroid adenomas (Fig. 6A).

There are several advantages of \(^{99m}\)Tc/\(^{201}\)TI subtraction for the detection of parathyroid adenomas. It is a noninvasive technique and has a high sensitivity and specificity for the detection of parathyroid adenomas. In addition, it has the potential to identify both aberrant and ectopic glands. The disadvantages of this technique are its inability to determine adenoma depth, its inability to determine the relationship of the adenoma to adjacent structures, and its inability to detect four gland hyperplasia and tumors <0.3 g in size with any degree of accuracy (22–25). False-positive results have been reported in patients with thyroid nodules including hypertrophic (23,24,26) and malignant nodules (27), multinodular goiter (28), sarcoid lymph nodes (23), and metastases to the neck.

Modifications to improve the sensitivity include taking oblique views (29), administration of oral phosphates (1 g per day in divided doses for 3 wk) (30), and \(^{123}\)I/\(^{201}\)TI subtraction. A disadvantage of \(^{123}\)I/\(^{201}\)TI subtraction is that salivary glands will routinely appear positive since iodine does not accumulate significantly in the salivary gland, while \(^{201}\)TI does (24).

**Ultrasound**

Sonographic imaging of the parathyroid glands has assumed increased clinical importance with the availability of high resolution, realtime ultrasound. Although normal parathyroids can only occasionally be imaged, abnormally enlarged parathyroids can be readily visualized with currently available scanners (31). Adenomatous, hyperplastic and neoplastic glands are less echogenic than surrounding normal tissue (Fig. 6B) (32). False negative studies may occur when the abnor-
mal gland is retroesophageal, substernal or mediastinal in position.

Computed Tomography
The accuracy of CT in the detection of a parathyroid adenoma is largely dependent on tumor size (33,34). The use of specially designed positioning maneuvers, bolus contrast administration, and dynamic CT scanning has improved the ability of this modality to detect parathyroid lesions. The use of intravenous contrast material is necessary to distinguish vessels from adjacent soft-tissue structures and parathyroid masses. Stark and colleagues have demonstrated contrast enhancement in 25 percent of parathyroid tumors and noted that large adenomas were more likely to enhance than small adenomas and that large hyperplastic glands were more likely to enhance than small hyperplastic glands (33). Disadvantages of high resolution CT scanning include the use of ionizing radiation, requirement for contrast enhancement, and anatomical distortion from scarring and metal clips in those patients who have a history of previous thyroid or parathyroid surgery. The major advantage of CT is its ability to locate parathyroid tumors that may be situated in either the retrosternal or retroclavicular position.

MAGNETIC RESONANCE IMAGING
Although the spatial resolution of MRI is currently a limiting factor, the use of specialized surface coils provides the ability to image superficial structures such as the parathyroid glands with sharp detail (Fig. 6C) (35). A variety of parathyroid lesions have been identified using MRI, all of which were >1 cm in size. While lesions can be separated from adjacent structures, it is not possible to reliably distinguish between parathyroid and thyroid tumors.

The development of paramagnetic contrast agents, which could provide greater tissue discrimination on the basis of vascularity, is still in its initial stages (36). Paramagnetic metal ion chelates may potentially be linked to more site specific ligands, providing the chemical basis for tissue specific contrast agents (37). Development of this class of compounds could have an impact, especially upon imaging of the thyroid and parathyroid glands by MRI and differentiation between benign and malignant disease.

Optimization of pulse sequence techniques to provide the greatest contrast between tissue structures could significantly improve MRI of both the thyroid and parathyroid glands. Determination of tissue T2 values and in vivo spectroscopy, in addition to T1 measurements, may further improve the diagnostic ability of MRI. Future comparative studies will define the role of MRI in the diagnosis of thyroid and parathyroid diseases. Cost effectiveness may limit its application, despite the ability of MRI to display both anatomic and functional information with high resolution and excellent quality.

SUMMARY
Technetium-99m/thallium-201 subtraction imaging has proven to be an accurate, noninvasive procedure for the detection of parathyroid adenomas. The sensitivity and specificity of dual subtraction parathyroid scintigraphy is equal to or better than that of other noninvasive imaging modalities. Technetium-99m/thallium-201 subtraction should be the investigative modality of choice in both the pre- and postoperative localization of parathyroid tissue. Ultrasound and CT, within limitations, should be used as complementary procedures to help identify those adenomas missed by radionuclide subtraction imaging, allowing for increased diagnostic accuracy. Angiography, because of its invasiveness, should be reserved for finding recurrence of ectopic adenomas not detected by the previously mentioned modalities following failed initial surgery. The role of MRI in the routine preoperative evaluation of patients with suspected hyperparathyroidism still remains to be established.

COMMENTS
The continued development of high technology in the rapidly expanding field of computer based imaging has had a significant impact on the areas of diagnostic imaging. The introduction of diagnostically related groups (DRGs) and the problem of rising medical costs emphasize the importance of reaching a diagnosis by the most straightforward and cost effective method while providing minimal patient discomfort. This responsibility to the patient and the medical care system rests with the physician. It is therefore essential that both imaging and referring physicians have a broad background of information regarding the potential limitations and relative merits of both old and new technologies available to patients with thyroid and parathyroid disorders.

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