Benign Thyroid Disease: What Is the Role of Nuclear Medicine?

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**Nuclear medicine is directly involved in both the diagnosis and treatment of benign thyroid disease, which requires an understanding of the pathophysiology and management of thyroid disorders in addition to expertise in nuclear methodology. Thyroid uptake and imaging, the principal nuclear tests in thyroid disease, may be used as follows: (1) Differential diagnosis of hyperthyroidism: A very low thyroid uptake suggests destructive ("subacute") thyroiditis, a self-limited disorder, whereas a normal or elevated uptake is consistent with toxic nodular goiter and Graves' disease. Scintigraphic characteristics also help differentiate between nodular and Graves' disease. (2) Function of thyroid nodules: Fine-needle aspiration biopsy with cytological examination (FNAB) is used routinely to assess for malignancy in thyroid nodules. Scintigraphy may be of assistance before FNAB. "Hot" nodules are generally benign and do not require FNAB, while "cold" nodules may be malignant. (3) Differential diagnosis of congenital hypothyroidism: Scintigraphy combined with ultrasound examination may be used to identify such conditions as thyroid agenesis, dyshormonogenesis, and incomplete thyroid descent. Treatment of Graves' disease and toxic nodular disease with ^{131}I may require greater clinical involvement and decision analysis compared with thyroid uptake and imaging. The following aspects of treatment are particularly important: (1) Risk: Radioiodine treatment may occasionally aggravate hyperthyroidism, Graves' ophthalmopathy, and airway obstruction caused by large, nodular goiters. Alternative treatments, including the temporary use of antithyroid drugs, and surgery for nodular goiters, may be considered. (2) Radioiodine dose: Cure of hyperthyroidism with a single ^{131}I treatment is desirable, though not always possible. Such factors as a large goiter, severe hyperthyroidism, and prior propylthiouracil therapy, may contribute to treatment failure. (3) Informed consent: A detailed discussion with the patient regarding the clinical risks, outcomes, and side effects of ^{131}I is a critical component of successful management.
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Nuclear thyroidology dates back to the 1930s when Saul Hertz, Arthur Roberts, Robley Evans, and Howard Means in Boston and Joseph Hamilton and Mayo Soley in Berkeley began studies of radioiodine physiology, paving the way for the first radioactive iodine (RAI) treatment of hyperthyroidism by Hertz and Roberts in 1941.[1] Today, thyroid applications are a major component of nuclear medicine, requiring a significant contribution from nuclear medicine professionals for both diagnosis and treatment. There are, however, substantial differences in the thyroid training of nuclear medicine physicians and, consequently, the extent of their involvement in thyroid disease. Although a few physicians are capable of providing total patient care on their own, most assume varying responsibilities in conjunction with a referring endocrinologist. In recent years, there has been an unfortunate trend toward greater dependence on the referring endocrinologist. At its extreme, nuclear medicine may take little responsibility for many important clinical functions, including evaluation of the appropriateness of RAI therapy, estimation of the therapeutic ^{131}I dose, and discussion with patients of the side effects of therapy. There is a failure to recognize that endocrinologists are not necessarily thyroidologists. A significant number may devote most of their time to nonthyroid specialties and have only limited clinical expertise in thyroid disease, let alone nuclear medicine procedures. Nuclear medicine professionals must also bear in mind that they are at least partially responsible for the

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Table 1 Causes of Hyperthyroidism

1. Destructive ("subacute") thyroiditis
2. Graves' disease
3. Toxic nodular disease
4. Jodbasedow (iodine-induced hyperthyroidism)
5. Iatrogenic
6. Gestational transient thyrotoxicosis (elevated hCG)
7. Pituitary adenoma (elevated TSH)
8. Metastases from differentiated thyroid cancer
9. Struma ovarii
10. Factitious

Table 3 Usual Range of 24-Hour Radioiodine Uptakes

Thyroid Condition	Uptake
Destructive thyroiditis	≤2%
Graves' disease	50-80%
Toxic nodular disease	20-40%
Jodbasedow	≤2%, N, or H

N, normal; H, high.

diagnostic and therapeutic use of radionuclides and, therefore, should be familiar with the pathophysiology and management of common thyroid disorders.

Hyperthyroidism

Hyperthyroid patients generally comprise the majority of thyroid referrals to nuclear medicine. At the initial encounter, the nuclear medicine physician should address the following questions: (1) Are recent thyroid function tests available? (2) What is the cause of hyperthyroidism? (3) Is an alternative to ^{131}I treatment indicated? (4) How long should antithyroid drug treatment be stopped before ^{131}I therapy? (5) How much ^{131}I should be administered? (6) What instructions should be given to the patient regarding the outcome and side effects of ^{131}I therapy? These questions are considered in detail in the following sections.

Are Recent Thyroid Function Tests Available?

A recent set of thyroid function tests is required for 2 reasons. First, in hyperthyroidism related to a destructive thyroiditis, thyroid hormone levels normalize spontaneously, and ^{131}I therapy is not needed.[2-4] Second, in those with Graves' hyperthyroidism, the decision to proceed with therapy as well as the ^{131}I dose may depend on the severity of the disease as judged by recent thyroid function tests. Patients who require prompt control of hyperthyroidism, including those with severe hyperthyroidism or serious coexisting medical conditions, may be treated initially with an antithyroid drug to lower thyroid hormone levels more rapidly. [131]I treatment may be administered after the patient has been stabilized. Severe hyperthyroidism tends to be resistant to RAI treatment and generally requires larger ^{131}I doses.[5] These concepts are elaborated in later sections on RAI treatment.

What is the Cause of Hyperthyroidism?

Hyperthyroidism may be related to a wide variety of causes, of which destructive thyroiditis, Graves' disease, and toxic nodular disease are the most common (Table 1). Thyroid uptake and imaging using radioiodine or technetium pertechnetate (Table 2) may assist in identifying the cause. The scintigraphic techniques and patient preparation are discussed in the section "Thyroid Nodule." The uptake is normal or elevated in Graves'/nodular disease but very low (generally 2% or less) in destructive ("subacute") thyroiditis (Table 3).[6,7] The image characteristics are also helpful in differentiating Graves' disease from toxic nodular disease. The clinical and scintigraphic features of these common hyperthyroid conditions are discussed below.

Destructive (Subacute) Thyroiditis

Destructive thyroiditis is caused frequently by viral infection and autoimmune thyroid disease (Table 4).[2-4,8-11] Hyperthyroidism results from disruption of thyroid follicles and release of excessive amounts of thyroid hormone, without a concomitant increase in hormone synthesis. The disorder is self-limited, typically with restoration of euthyroidism in 3 to 12 months. Treatment consists of β-adrenergic blockers and analgesics. Glucocorticoids may be used in painful and protracted thyroiditis. Antithyroid drugs (methimazole, PTU) and RAI are not needed.

What are the diagnostic characteristics of viral and autoimmune thyroiditis? Viral thyroiditis generally is associated with a painful goiter, flu-like symptoms, and increased erythrocyte sedimentation rate and C-reactive protein levels. Permanent hypothyroidism is infrequent after viral thyroiditis. Autoimmune thyroiditis typically is associated with a painless goiter, increased thyroid peroxidase antibody levels, and a high incidence of permanent hypothyroidism at long-term follow-up. It occurs most commonly in postpartum women because of immune rebound following pregnancy, and frequently reoccurs after a subsequent pregnancy. Usually, thyroid peroxidase antibodies are also elevated during pregnancy.[12] Hyperthyroidism caused by thyroiditis may be dis-

Table 2 Radiotracers for Thyroid Uptake and Imaging

Radiotracer	Administered Activity
Iodine-123	200-400 μCi (7.4-14.8 MBq)
Iodine-131	5 μCi (0.19 MBq)*
[99m]Tc-pertechnetate	5-10 mCi (185-370 MBq)

*Iodine-131 is used only for uptake measurement. Higher activity needed for imaging is associated with a high thyroidal absorbed radiation dose.

Table 4 Causes of Destructive (Subacute) Thyroiditis

1. Viral infection
2. Autoimmune
   Postpartum, sporadic
   Interferon-alpha
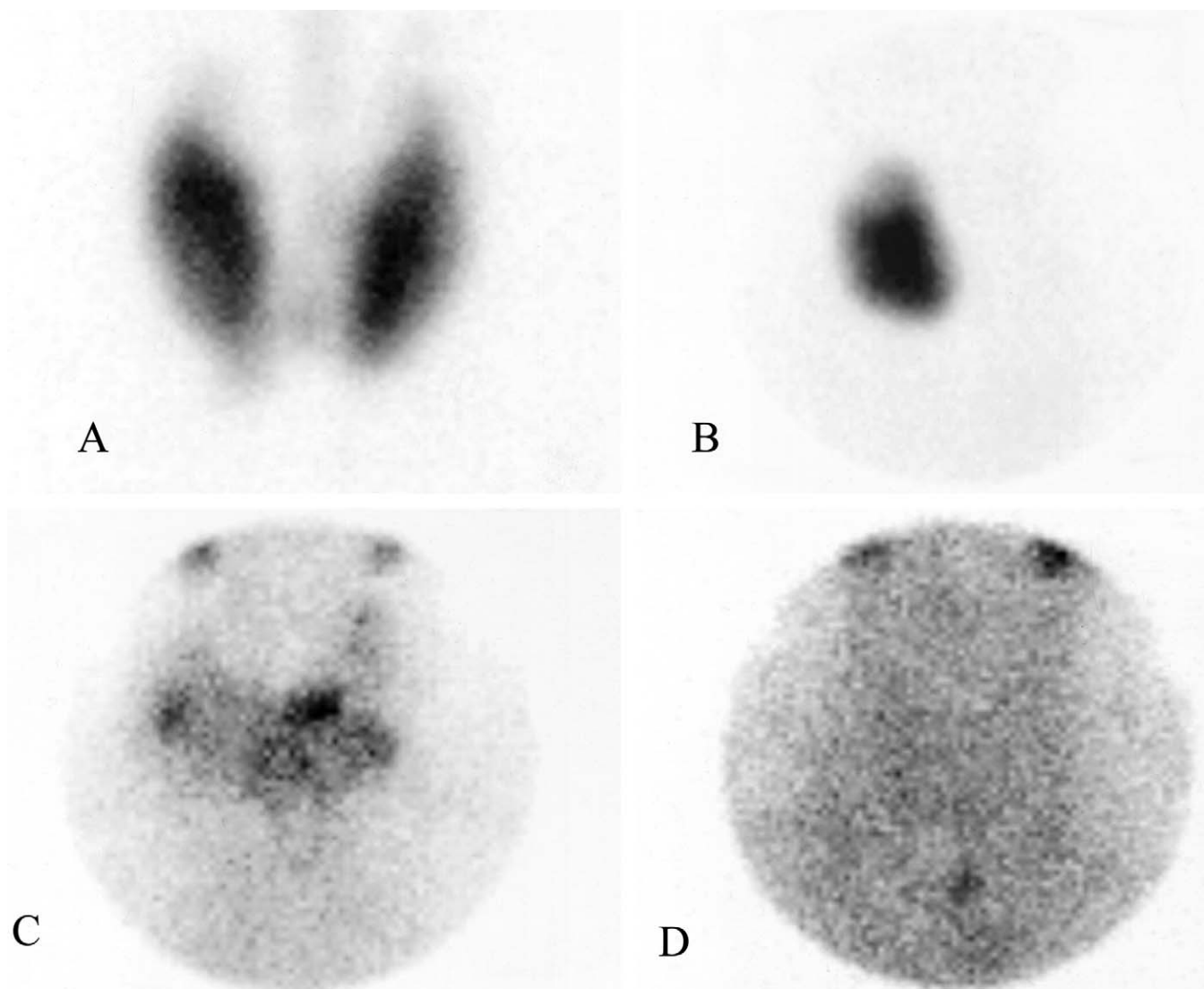   Interleukin-2
   Lithium
3. Amiodarone

Figure 1 (A) Graves' disease; (B) solitary toxic right lobe nodule; (C) toxic multinodular goiter; (D) subacute thyroiditis (salivary glands at top of image)

tinguished from Graves' disease with the help of a thyroid uptake and scan.[6,7] The thyroid uptake of RAI and [99mTc]-pertechnetate is very low in thyroiditis, but high in Graves' disease (Table 3, Fig. 1).

Treatment with amiodarone, a drug used for cardiac arrhythmia, is another cause of destructive thyroiditis.[13,14] This type of thyroiditis is similar to viral and autoimmune thyroiditis in scintigraphic appearance but tends to last longer because of the long biologic half-life of amiodarone and its metabolite. Amiodarone may cause hyperthyroidism by another mechanism. It has a high iodine content, which may induce increased synthesis of thyroid hormone. This phenomenon, known as jodbasedow, tends to occur in nodular thyroid glands and is more common in endemic goiter areas.[15] Scintigraphic distinction of jodbasedow from thyroiditis is difficult because a very low uptake frequently is seen in both (Table 3), and the 2 conditions may occasionally coexist. However, an uptake that is low normal or higher is suggestive of jodbasedow. Jodbasedow is treated with drugs that

decrease hormone synthesis, namely propylthiouracil (PTU) or methimazole, which may be combined with potassium perchlorate to decrease thyroidal iodine content.[13] Resistant cases may be treated with ^{131}I if the thyroid uptake is adequate. If the cause of amiodarone-induced hyperthyroidism is uncertain, antithyroid drugs may be combined with glucocorticoid treatment for thyroiditis.

Graves' Disease and Toxic Nodular Disease

Graves' disease is an autoimmune thyroid disorder characterized by elevated levels of stimulating thyroid-stimulating hormone (TSH)-receptor antibodies (also known as thyroid-stimulating antibodies or thyroid-stimulating immunoglobulins), with increased thyroid uptake of iodine, and increased hormone synthesis and release.[16,17] The cardiovascular manifestations are most pronounced, and some patients may have a characteristic ophthalmopathy.[18-20] The diagnosis is based on the clinical presentation, thyroid uptake and scan and, in equivocal cases, the thyroid-stimulating antibody levels. The

thyroid scan typically shows uniform uptake in a diffusely enlarged thyroid gland, and the 24-hour uptake is elevated (Table 3, Fig. 1). Atypical thyroid images may result when Graves' disease is superimposed on a nodular thyroid gland.

Nodular disease is believed to result from the rapid proliferation of cells with a growth advantage.[21] Growth in the early stages is aided by (intermittent) TSH stimulation, which results from decreased hormone synthesis due to iodine deficiency, occasionally in combination with a goitrogen.[21,22] Also important in the pathogenesis are "gain-of-function" mutations, usually of the TSH receptor, that have the same effect as chronic TSH stimulation.[21] At thyroid scintigraphy (Fig. 1), toxic multinodular disease shows heterogeneous distribution of radiotracer with or without discrete "hot" nodules, and single toxic nodules are frequently associated with decreased uptake in the remainder of the gland. On images showing solitary or multiple hot foci, the areas of decreased uptake may consist of suppressed normal tissue and/or autonomous micro- and macro-nodules with relatively less function than the dominant toxic nodule.[22] The 24-hour thyroid uptake in toxic nodular disease is often normal or only mildly elevated in contrast to Graves' disease, where the uptake is generally high (Table 3).

Differentiating Graves' Disease From Toxic Multinodular Disease

An attempt should be made to distinguish Graves' disease from nodular disease because of important differences in management: (1) Graves' disease usually is treated with RAI, but a few patients may go into a remission after long-term treatment with methimazole or PTU.[23] The remission is probably related in part to the immunosuppressive effect of antithyroid drugs. Nodular disease does not go into remission with antithyroid drug treatment. (2) Surgery is an alternative to RAI for treating a solitary hyperfunctioning nodule and is an option in low-risk patients with multinodular goiter, in whom a subtotal thyroidectomy generally accomplishes the required reduction in goiter volume (see the section "Is Radioactive Iodine Treatment Appropriate?"). Surgical cure of Graves' disease, however, requires a total thyroidectomy, which may be associated with significant complications, and is rarely done today. (3) On average, Graves' disease requires a lower ^{131}I dose than does multinodular goiter. (4) Most patients with Graves' disease develop early hypothyroidism, usually within 4 to 6 months of RAI treatment. Hypothyroidism is less frequent in nodular disease and, on average, takes much longer to develop (see later).

Is RAI Treatment Appropriate?

Determining the appropriateness of RAI treatment is the responsibility of both the referring and nuclear medicine physicians. Not all patients referred to nuclear medicine are ideally suited for RAI treatment, which may be associated with increased risk or decreased efficacy in the following situations: (1) Treatment with RAI does not afford prompt relief of hyperthyroidism. Moreover, radioiodine-induced thyroiditis occasionally may increase circulating thyroid hormone levels, which has the potential to exacerbate hyperthyroidism,

or complicate coexisting illnesses such as cardiovascular disease.[24] Severely hyperthyroid patients and those with serious medical conditions, therefore, may need stabilization with methimazole or PTU before radioiodine treatment. (3) Moderate-to-marked Graves' ophthalmopathy may be aggravated by RAI treatment and may require glucocorticoid prophylaxis.[20,25,26] Alternatively, treatment with RAI may be delayed until the eyes have improved. (4) Treatment with RAI may not be very effective in reducing the volume of large, nodular goiters because of heterogeneous distribution of activity and low 24-hour uptake (see "How Much [131]I Is Appropriate?"). Surgery may be an alternative, particularly if the operative risk is low. (5) Treatment with RAI is usually successful in curing hyperthyroidism associated with a solitary toxic nodule. However, the nodule itself may not be entirely eliminated, which may have cosmetic implications for some patients, and surgical resection may be offered as an alternative.

How Long Should Antithyroid Drugs Be Stopped Before RAI Treatment?

As noted previously, patients with severe hyperthyroidism or serious coexisting illnesses may be pretreated with methimazole or PTU. These drugs are routinely stopped before RAI treatment, usually for 4 to 6 days, and they may be restarted afterward. Patients with uncontrolled hyperthyroidism in particular should be closely monitored after stopping the antithyroid drug because of the potential for a sharp increase in thyroid hormone levels.[27,28] If needed, the withdrawal period may be shortened. Although not widely used, lithium treatment has been proposed as a means of preventing a rapid increase in hormone levels following antithyroid drug withdrawal.[29]

How Much [131]I Is Appropriate for Treatment?

The administered ^{131}I activity for Graves' disease continues to vary over a wide range, albeit with an upward trend because of a change in the perceived goal of ^{131}I therapy.[5,30-33] The traditional use of small radioiodine doses to obtain a euthyroid state currently is out of favor for a number of reasons. Euthyroidism after radioiodine treatment is usually temporary, progressing subsequently to hypothyroidism, or in some instances to recurrent hyperthyroidism. A rare patient may remain euthyroid for an extended period of time, but this outcome can be neither engineered nor predicted. Moreover, small doses tend to prolong the hyperthyroid state at increased expense and morbidity. Longstanding hyperthyroidism, both overt and subclinical, may have potential health risks.[18,19,34-37]

After RAI treatment of Graves' disease, the development of overt hypothyroidism, which is then treated with thyroid hormone, may well be the best outcome. It simplifies management, decreases cost, and as noted earlier, reduces potential health risks of persistent hyperthyroidism. Some patients may develop subclinical hypothyroidism, which may not be an ideal outcome. Because of uncertainty regarding the subsequent course of the disease, patients are often monitored

without treatment for long periods of time. Although the risk of prolonged subclinical hypothyroidism is debatable, detrimental cardiovascular effects have been reported.[18,37-40] A recent study of hyperthyroid patients treated with RAI showed a lower mortality among those who became overtly hypothyroid and were placed on thyroid hormone supplements.[41]

The incidence of hypothyroidism after RAI treatment of nodular disease was believed to be low because of selective uptake of ^{131}I in the dominant nodule(s). However, recent data suggests that up to 60% may develop hypothyroidism at long-term follow-up.[42] This is not surprising because dominant nodules often are associated with autonomous micronodules and small macronodules, which also accumulate RAI but may not be readily visible on the thyroid image.[22]

How much radioiodine is needed to cure Graves' disease? Numerous publications have addressed this issue, and although a detailed discussion of the literature is beyond the scope of this review, a number of observations are worth noting: 1. There is no significant difference in outcome using activities determined empirically or by calculations. 2. In general, high cure rates may be achieved using administered activities of at least 15 mCi (555 MBq), retained activities (in the thyroid) of at least 8 mCi (296 MBq) or 150 to 200 μCi (5.5-7.4 MBq) per gram, or an absorbed thyroid radiation dose of 25,000 rads (250 Gy).[5,30-33] 3. Larger than average doses are needed in conditions increasing radio-resistance, including large goiter, severe hyperthyroidism, and prior PTU therapy.[5,43,44] Larger doses are also preferable in patients with coexisting illnesses that may be aggravated by persistent hyperthyroidism.

How much radioiodine is needed to treat nodular goiter? A solitary toxic nodule may be treated empirically with 15 to 30 mCi (555-1110 MBq) of ^{131}I, or delivered amounts of 200 μCi (7.4 MBq)/g or more. Multinodular goiters require the administration of relatively high activities because the thyroid is large and RAI distribution is heterogeneous.[45,46] For example, a retained dose of 150 μCi (5.55 MBq)/g for a 120g gland with a 30% uptake requires the administration of 60 mCi (2220 MBq) of [131]I. Many goiters weigh more than 150 g and require even higher activities. Despite the use of large doses, however, the reduction in volume of large multinodular goiters may be inadequate. This is a major limitation of RAI treatment. Recent studies with recombinant human TSH-assisted therapy appear encouraging.[47,48] Recombinant TSH increases RAI uptake throughout the thyroid gland and may permit greater volume reduction.

Instructions to Patients Before [131]I Therapy

All patients are routinely tested for pregnancy and nursing mothers are asked to stop breast-feeding.[49] Discussions with the patient should not be limited to concerns about environmental contamination and radiation exposure to others. Clinical information about the nature of the disease, possible outcomes and side effects of RAI treatment (Table 5), and alternative therapies if applicable should be discussed.

Table 5 Side Effects of Radioactive Iodine Treatment

Graves' Disease	Toxic Nodular Disease
Hypothyroidism	Hypothyroidism
Thyroiditis	Thyroiditis
Exacerbation of ophthalmopathy	Upper airway obstruction
Exacerbation of hyperthyroidism	Exacerbation of hyperthyroidism
	Development of Graves' disease

Instructions Pertaining to Clinical Outcome and Side Effects of RAI Treatment

In Graves' disease, patients should be aware that the goal of treatment is to cure hyperthyroidism, preferably within months, and that a cure generally leads to the development of hypothyroidism (see the section "How Much [131]I Is Appropriate for Treatment?"). An older practice of offering patients the option of a "low" or "high" [131]I dose based on concerns about hypothyroidism is not appropriate. Many instructions are specific to each patient. For example, a patient with a large goiter and/or previous treatment with PTU should be informed of the possibility of a second RAI treatment.[5,43,44] Significant Graves' eye disease may occasionally worsen after therapy, and adherence to follow-up appointments with the ophthalmologist should be stressed.[20,25] Patients should also be aware that cigarette smoking has an adverse effect on ophthalmopathy. Because of the potential for increased thyroid hormone release after RAI treatment, patients at risk of thyroid storm, and those with significant cardiovascular disease are urged to stay in touch with the (referring or nuclear medicine) physician.

In toxic nodular disease, patients should be informed of the possibility of hypothyroidism after RAI therapy, with particular emphasis on late hypothyroidism occurring after several years.[42] Patients with large nodular goiters should be aware that radioiodine-induced thyroid swelling occasionally exacerbates airway obstruction. They should also be aware that a residual mass may be left after RAI treatment of a solitary toxic nodule, and that surgery may be an alternative (see "Is RAI Treatment Appropriate?"). Finally, a rare side effect to keep in mind is the development of Graves' disease following RAI treatment of nodular goiter.[50] Release of thyroid antigens with the development of thyroid antibodies is the presumed mechanism.

Instructions Pertaining to Radiation Exposure

Many patients fear that radioiodine therapy may have the potential to cause thyroid cancer, leukemia, and infertility. They need assurance that such complications have not been found after 50 years of experience with RAI treatment of hyperthyroidism.[32] Patients are routinely advised to limit exposure to family members and close contacts. However, such advice can do more harm than good if it is very stringent, not given in the overall context of ALARA, and not supplemented by a discussion of what RAI treatment can and cannot do, as outlined in earlier sections. Many patients provided with insufficient information simply assume the worst not only for
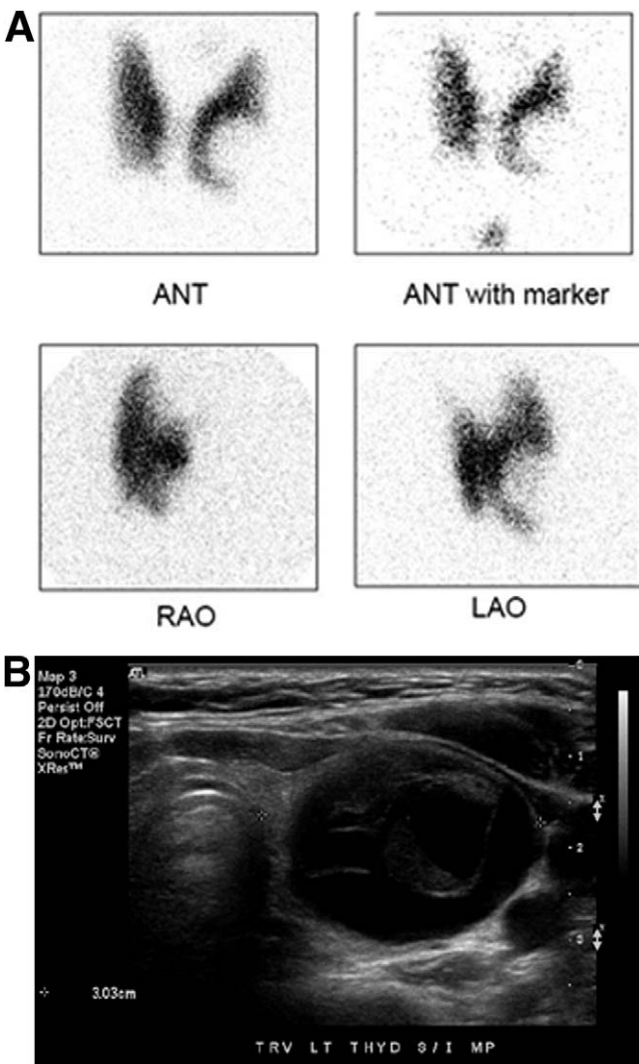
Figure 2 (A) Hypofunctioning ("cold") nodule of the left lobe; (B) corresponding ultrasound image. (Images provided by Simin Dadparvar, MD, and John Hochhold, MD, from the Society of Nuclear Medicine Lifelong Learning & Self-Assessment Program. Reproduced from Sarkar.[52])

themselves but also for their families, and choose to delay RAI therapy, sometimes for years.

Thyroid Nodule

Introduction

The management of thyroid nodules not associated with hyperthyroidism is a highly controversial topic.[51-53] Nodules are routinely evaluated by fine needle aspiration biopsy (FNAB) and cytological examination to evaluate for malignancy. Scintigraphic imaging of nodular function is frequently requested before FNAB. Imaging is based on the premise that functioning ("hot") nodules are unlikely to be malignant, whereas nonfunctioning ("cold") nodules (Fig. 2). may harbor cancer in a small proportion (<10%) of patients.[7]

In the past, only palpable nodules were considered signif-

icant and selected for further diagnostic workup. However, in recent years, the use of high-resolution ultrasound and computed tomography has increasingly led to the discovery of incidental, nonpalpable thyroid nodules. Investigating all "incidentalomas" is clearly not cost-effective, and there is ongoing debate as to their optimal management. At the present time, the most important criterion for FNAB is nodule size.[52,53] Nodules <1.0 to 1.5 cm generally are not subjected to FNAB because cancers of this size, termed "microcarcinomas," are associated with a good prognosis.[54,55] However, small nodules may merit additional evaluation if they are associated with factors that increase the risk of thyroid cancer. The likelihood of thyroid cancer is higher in persons who have had childhood exposure to radioactive iodine after the Chernobyl nuclear reactor accident, or to therapeutic external head and neck radiation.[56] The presence of cervical lymph node metastases, family history of thyroid cancer, and focal thyroid uptake of ^{18}F-fluorodeoxyglucose (FDG) (see later) also are associated with increased cancer risk. Various ultrasound and color flow Doppler characteristics of malignant nodules are being studied to help select smaller nodules for FNAB.[57,58]

Focal thyroid uptake of FDG occasionally is an incidental finding during positron emission tomography (PET) for nonthyroid conditions. Although FDG uptake may occur in benign nodules and focal thyroiditis, it may be related to thyroid cancer in a significant number of patients. Incidental focal thyroid uptake of FDG, therefore, may be another indication for FNAB.[59] Is there a role for PET in evaluating thyroid nodules? Although not cost-effective for routine use before FNAB, PET could be of value in selected patients. A sizeable number of patients undergoing FNAB have nondiagnostic cytology. These patients may be subjected to a 2-stage surgery—partial thyroid resection for a histological diagnosis, and completion thyroidectomy if cancer is found. FDG-PET of patients with nondiagnostic FNAB may help to decrease the number of unnecessary thyroid surgeries.[60]

What is the role of the nuclear medicine practitioner in evaluating thyroid nodules? First, he or she should determine whether scintigraphic imaging is indicated or likely to be productive. Second, the history should be checked for exposure to iodinated products or thyroid hormone, which decrease thyroid uptake of radioiodine and technetium pertechnetate. Third, the nodule should be palpated and imaged using appropriate techniques.

Is Scintigraphy Indicated?

The size of the thyroid nodule is a key factor when considering scintigraphic evaluation. As noted previously, nodules <1.0 to 1.5 cm generally may not be worth pursuing aggressively.[51-55] Nodules of this size are also less likely to be visualized at scintigraphy. Most palpable nodules are large enough to be imaged. Many nodules found incidentally at ultrasound examination are ≥1.5 to 2.0 cm and could benefit from scintigraphy.

Was Patient Recently Exposed to Stable Iodine or Thyroid Hormone?

Exposure to exogenous iodine or thyroid hormone is a common cause of decreased thyroid uptake. Iodinated radiographic contrast used with computed tomography is a frequent cause of a lower thyroid uptake. For the evaluation of nodular function, a 2-week waiting period generally is adequate, especially if 5 to 10 mCi (185-370 MBq) of ^{99m}Tc-pertechnetate is used.[7,52]

Thyroid hormone treatment should be discontinued for 4 weeks or longer before thyroid scintigraphy. However, the physiological impact of hormone withdrawal can be significant and may well be unnecessary in some circumstances. Many individuals are chronically treated with thyroid hormone supplements to reduce goiter volume, which easily can be monitored by periodic ultrasound examinations.

Is The Nodule Palpable?

Palpating the thyroid gland and locating the thyroid nodule(s) is the next step. Thyroid palpation is an area of widely varying expertise, and little has been done to standardize the technique. Although experience in palpating thyroids is the key, even the best practitioners may miss relatively large nodules because of such factors as obesity, spinal deformity, and a low-lying (partly substernal) thyroid gland.

Is The Scintigraphic Technique Optimal?

The scintigraphic technique is perhaps more important today because of the increasing number of patients referred for relatively small and frequently nonpalpable thyroid incidentalomas. Small "hot" nodules are readily visualized, but small "cold" nodules, which comprise the majority of thyroid nodules, require optimal imaging methodology. The availability of a pinhole collimator is a plus. Anterior images are supplemented by oblique or lateral images if needed. Because of an inherently lower sensitivity, pinhole imaging requires the administration of sufficient amounts of radiotracer. Count rates with the standard 200 to 400 μCi (7.4-14.8 MBq) of ^{123}I may be inadequate if the thyroid uptake is low. If needed, imaging may be repeated with 5 to 10 mCi of ^{99m}Tc-pertechnetate. Thyroid glands that are predominantly mediastinal ideally should be imaged using approximately 600 μCi (22.2 MBq) of ^{123}I.

Finally, the location of the palpable nodule should be marked as accurately as possible on the thyroid image. Errors in localization may lead to mischaracterization of nodular function, particularly if radiotracer distribution in the thyroid is heterogeneous. A "hot" marker, usually consisting of a "Q-tip" with ^{99m}Tc-pertechnetate, may be used for this purpose.

The common causes of error in the marking of nodules are worth remembering. (1) The marker may have too much activity. (2) The thyroid may be difficult to palpate during supine imaging because of an inconvenient location of the imaging table, or because the neck is underextended or overextended. A "thyroid chair" with a head-holder may be an
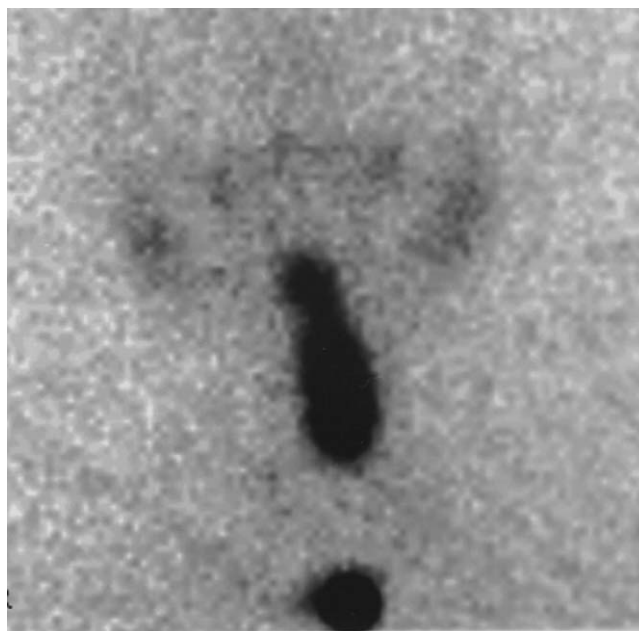

Figure 3 Partially descended thyroid gland in upper cervical region (suprasternal notch is marked at bottom of image). Note characteristic absence of lateral lobes. (Adapted from Sarkar,[22] with permission from Springer Science and Business Media.)

advantage in this regard. (3) Anatomic factors, such as kyphosis, retrosternal extension of the thyroid, and obesity, may pose additional difficulties.

Congenital Abnormalities

Neonatal Hypothyroidism

Newborns are routinely screened for hypothyroidism, generally with measurements of serum T4 with or without TSH.[61] Hypothyroidism requires prompt treatment since adequate thyroid hormone levels are needed in the newborn for normal intellectual-psychological development, and there is no longer a protective effect of maternal hormone. Because of the need for immediate treatment, most newborns with hypothyroidism are not referred to nuclear medicine. However, nuclear imaging can be useful, and it is feasible even after initiation of thyroid hormone treatment because TSH levels are not lowered immediately.[62] Imaging with ^{99m}Tc-pertchnetate may be convenient, but ^{123}I may also be used. If the cause of hypothyroidism is unclear at birth, a complete investigation is usually done after stopping the thyroid hormone supplement when the infant is older.

Hypothyroidism in the newborn may be temporary or permanent. Temporary hypothyroidism may be caused by treatment of the pregnant mother with excessive amounts of PTU or methimazole[63]; maternal autoimmune thyroid disease and the transplacental passage of TSH-receptor blocking antibodies[64]; exposure of the newborn to large amounts of iodine in antiseptic solutions, which initiates the Wolff-Chaikoff effect,[15] and decreases thyroid hormone synthesis; mild dyshormonogenesis; and maternal hyperthyroidism, which increases circulating fetal hormone levels and suppresses the

hypothalamus-pituitary-thyroid axis.[65] Permanent hypothyroidism may be associated with agenesis, severe dyshormonogenesis, and a lingual thyroid gland.[61,62]

Some causes of neonatal hypothyroidism may be anticipated from the maternal thyroid status and clinical history, and confirmed by imaging. In hypothyroidism due to TSH-receptor blocking antibodies, a thyroid gland is identified by ultrasound examination, but is not visible by scintigraphy. Severe dyshormonogenesis is associated with a similar finding. In thyroid agenesis, thyroid tissue is not identified by either ultrasound or scintigraphy.

Older children often are referred to nuclear medicine for the evaluation of an ectopic thyroid gland or a defect in organic iodination. An ectopic gland is usually sublingual or partially descended and characteristically lacks the lateral lobes (Fig. 3). Anterior and lateral images are routinely obtained, with appropriate markers to identify the location of the gland.

The Perchlorate discharge test is used to evaluate for an organification defect. Such defects result in increased amounts of unbound iodine in the thyroid gland, which can be discharged by potassium perchlorate. The test involves baseline and postperchlorate measurements of thyroid uptake of ^{131}I. A decrease in uptake after perchlorate administration confirms an organification defect. The diagnostic sensitivity may be increased by the addition of stable iodine.[66]

Neonatal Hyperthyroidism

Transient hyperthyroidism in the newborn is caused by the passage of maternal TSH-receptor stimulating antibodies into the fetal circulation.[63] It may occur if Graves' disease in the mother is inadequately treated with PTU/methimazole, which lower these antibodies. Because the condition usually is anticipated and diagnosed clinically, there is little need for assistance from nuclear medicine.

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