Thyroid

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Nuclear medicine techniques to diagnose and treat thyroid diseases have been in routine use for many decades [1, 2]. Most of these methods depend upon the iodine avidity (and related pertechnetate avidity) of thyroid tissues. The radioiodine isotopes (^{123}I and ^{131}I) and ^{99m}Tc (as pertechnetate) are the most commonly used radiopharmaceuticals for thyroid imaging. Both ^{123}I and ^{131}I have been used to determine thyroid iodine uptake as a measure of thyroid function. In patients with thyroid cancer, these radioiodine isotopes can be used to detect sites of remnant thyroid tissue and metastatic disease. In addition to imaging, ^{131}I is used for specific radiotherapy of hyperactive thyroid tissue and thyroid cancer. With the introduction of positron emission tomography, ^{18}F-FDG has acquired a limited role in the evaluation of thyroid cancer. Some centers also use ^{124}I PET to evaluate thyroid cancer.

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Methods

Radiopharmaceuticals

Thyroid follicular cells have mechanisms for both the *trapping* (uptake) and the *organification* of iodine. These mechanisms provide targets for assessing thyroid function, imaging the thyroid gland, and treating hyperthyroidism and thyroid cancer. *Trapping* of iodine depends on the sodium-iodide (NaI) symporter (Fig. 5.1), a sodium-ATPase-linked transmembrane anion transporter [3, 4]. The symporter mediates energy-dependent transport of univalent anions from the extracellular to intracellular space. Although it has greatest avidity for iodide (I^-), the symporter has avidity for other univalent anions, including thiocyanate (SCN^-), perchlorate (ClO_3^-), pertechnetate (TcO_4^-), and nitrate (NO_3^-). Thus, thyroid imaging is performed with radioactive isotopes of

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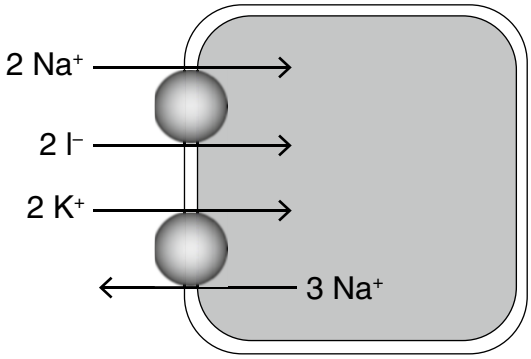

Fig. 5.1 Sodium-iodide symporter. The sodium-iodide symporter is a transmembrane glycopeptide that is the primary cellular mechanism for iodine uptake. In an energy-dependent process, the symporter actively transports two sodium cations for every iodide anion transported into the cell. It is linked to the sodium-potassium ATPase pump, which transports three sodium cations out of the cell for every two potassium cations transported into the cell and provides energy for the active symporter transport. The symporter has avidity for other univalent anions, including pertechnetate (TcO_4^-) [3]

either iodine or technetium, usually in the form of sodium salts of iodide (^{123}I, ^{131}I) or pertechnetate (^{99m}Tc). Thiocyanate or perchlorate uptake can compete with and diminish thyroid uptake of either iodine or pertechnetate.

Organification of iodine occurs in the normal thyroid, but not other tissues of the body. In thyroid follicular cells, iodine is incorporated into thyroglobulin, the tyrosine-rich peptide precursor of active thyroid hormones [5, 6]. Although the iodine symporter is expressed and can trap iodide in a wide range of organs and tissues, in most tissues, trapped iodide is washed out and returned to the extracellular space. Organification limits iodine washout, which amplifies the accumulation of radioiodine within thyroid tissue. Other anions, including pertechnetate, are not organified and are susceptible to washout from all tissues, including the thyroid. These processes of trapping and organification allow the use of iodine radioisotopes (^{123}I, ^{124}I, and ^{131}I) and ^{99m}Tc-pertechnetate to assess thyroid function, image the thyroid gland, and treat thyroid diseases.

For thyroid studies, iodine isotopes are prepared as the sodium salt ([^{131}I]NaI or [^{123}I]NaI) and administered by mouth. Usually, ^{131}I and ^{123}I are administered as a solid capsule, but a liquid formulation is available. The liquid formulation can be particularly useful in pediatrics as it can facilitate titration of a weight-based dose and may be easier for younger patients to swallow. In unusual circumstances, sodium iodide can be custom formulated for intravenous administration. Sodium pertechnetate ([^{99m}Tc]$NaTcO_4$) typically is administered by intravenous injection but also can be administered orally.

Iodine-131

Iodine-131 (physical half-life 8.1 days) has both gamma-emission (predominately 364 keV) and beta-particle emission. As a product of nuclear fission reactors, it has been widely available, and for many decades it served as the routine iodine radiopharmaceutical for both thyroid imaging and therapy. Iodine-131 is an ideal therapeutic radiopharmaceutical for both benign and malignant thyroid diseases as it has a relatively high absorbed radiation dose due to its half-life and beta-particle emission. However, this high radiation dose and the high energy of its gamma-emission make ^{131}I less satisfactory for thyroid imaging or assessing radioiodine uptake.

Iodine-123

Iodine-123 decays (physical half-life of 13.2 h) principally by electron capture and subsequent gamma-emission (159 keV). Unlike ^{131}I, ^{123}I has no beta-emission. The absence of beta-emission and the energy of the gamma-emission make ^{123}I the radiopharmaceutical of choice for thyroid imaging with a gamma-camera. However, ^{123}I decay also produces a low abundance of other higher-energy gamma-emissions (248–784 keV) that occasionally can affect image quality [7].

Iodine-123 is a cyclotron product produced from a ^{124}Xe target. Iodine-123 is produced by two different nuclear reactions with subsequent rapid decay to ^{123}I. The primary nuclear reaction is

$$^{124}\mathrm{Xe}(\mathrm{p},2\mathrm{n})^{123}\mathrm{Cs} >^{123}\mathrm{Xe} >^{123}\mathrm{I}$$

and the secondary nuclear reaction is

$$^{124}\mathrm{Xe}(\mathrm{p,pn})^{123}\mathrm{Xe} > ^{123}\mathrm{I}.$$

Compared to ^{131}I, ^{123}I has more limited commercial availability and is more expensive, but its superior imaging characteristics have made it the preferred choice for diagnostic thyroid imaging [8, 9]. The lower effective radiation dose provided by ^{123}I, compared to ^{131}I, is another reason for its use in pediatric patients.

Iodine-124

Iodine-124 is a positron emitter with a physical half-life of 4.18 days (100.3 h). It also has gamma-emission, which is predominately 603 keV. Like ^{123}I, it is a cyclotron product, which typically is produced by the nuclear reaction ^{124}Te (p,n) ^{124}I. With the widespread availability of PET scanners, some medical centers have investigated the use of ^{124}I-PET for imaging thyroid cancer [10]. Despite the excellent imaging characteristics of PET, the use of ^{124}I as a PET radiopharmaceutical has a number of disadvantages. Due to its limited commercial availability, most users must manufacture ^{124}I in an onsite cyclotron. The emitted positron has a higher energy, and thus higher range than many other PET tracers, which slightly decreases PET resolution. In addition to the predominate 603 keV gamma-emission, ^{124}I also has numerous higher-energy gamma-emissions, including 723 keV and 1,691 keV. Thus, due to its relatively higher radiation dose compared to ^{123}I, ^{124}I is not appropriate for evaluation of benign thyroid disease or for use in children, and it has not entered widespread use.

Technetium-99m Sodium Pertechnetate

Technetium-99m (physical half-life 6.0 h, 140 keV gamma-emission) is readily available in all nuclear medicine departments as a generator product (^{99}Mo > ^{99m}Tc). It also is inexpensive, provides short imaging times, and results in a low radiation dose. For these reasons, ^{99m}Tc-sodium pertechnetate sometimes is preferred for thyroid imaging [11]. After intravenous administration of pertechnetate, there is rapid thyroid uptake of pertechnetate, but, unlike iodine, pertechnetate is not organified within the thyroid cell. In the absence of organification, there is rapid washout, so that thyroid imaging must be performed soon after administration of ^{99m}Tc-pertechnetate. As a result, physiological uptake in other tissues, such as salivary glands, is more prominent on thyroid scans performed with pertechnetate than on scans performed with iodine isotopes.

Thyroid Scintigraphy

Thyroid scintigraphy can be performed with ^{99m}Tc-pertechnetate, ^{123}I, or rarely ^{131}I (Fig. 5.2). The choice of radiopharmaceutical depends upon a number of factors, including tracer availability. Overall image quality will be best with ^{123}I. Concurrent quantitative assessment of uptake requires the use of either ^{131}I or ^{123}I, but ^{131}I should rarely, if ever, be used for thyroid scintigraphy in children. The practice guidelines published by professional societies recommend a range of radiopharmaceutical doses for thyroid scintigraphy [12–14]. At our institution, the administered ^{123}I dose is 0.2 MBq/kg (0.006 mCi/kg) with a minimum dose of 0.925 MBq (0.025 mCi) and maximum dose of 14.8 MBq (0.4 mCi). To ensure rapid and complete absorption of the tracer, patients are asked to fast (except for sips of water) for 2 h before and 1 h after radioiodine administration. For children, an adequate administered dose of ^{99m}Tc-pertechnetate is 1 MBq/kg (0.03 mCi/kg) with a minimum dose of 7.4 MBq (0.2 mCi) and maximum dose of 74 MBq (2 mCi).

Imaging typically is performed 4–6 h after oral administration of ^{123}I or is started 20–30 min after intravenous administration of ^{99m}Tc-pertechnetate. Delayed images are rarely helpful, but if a concurrent thyroid uptake is being performed, then this can be determined 24 h after oral administration of ^{123}I. As a small amount of tracer is excreted with saliva, salivary accumulation in the mouth, pharynx, or even the esophagus occasionally will interfere with imaging. Usually, this can be cleared by having the patient “swish and

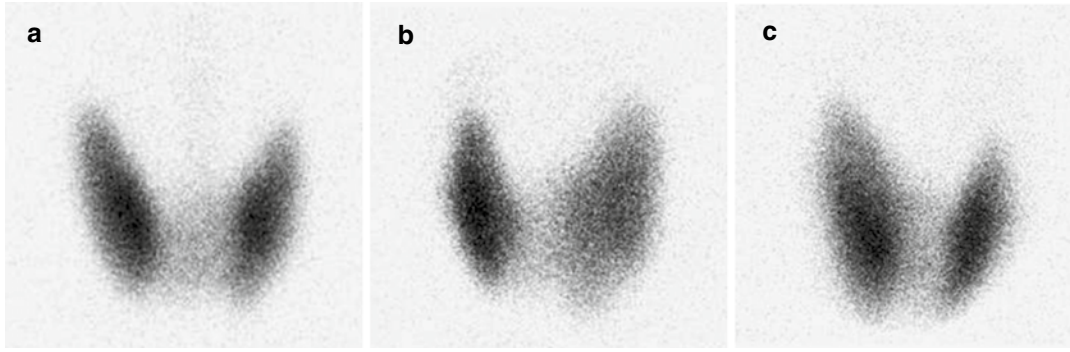

Fig. 5.2 Normal thyroid scan performed with ^{123}I. Images obtained with a pinhole collimator in the anterior (**a**), left oblique (**b**), and right oblique (**c**) projections demonstrate that the normal thyroid gland has homogeneous iodine uptake in both lobes, which should be similar in size and have smooth contours. A small amount of tracer may be seen in the thyroid isthmus, located between the two lobes of the thyroid gland. Normal thyroid uptake of the administered radioiodine dose is approximately 5–15 % at 4 h and 10–35 % at 24 h

swallow" a few sips of water before the start of imaging.

A pinhole collimator with an aperture less than 3 mm produces satisfactory image quality. A pinhole collimator is preferable to a planar collimator, as it will produce images with the fine detail necessary to evaluate thyroid structure. When positioning the pinhole collimator, the thyroid image should fit within the central two-thirds of the field of view to prevent distortion of thyroid anatomy. Images should be acquired in the anterior and two anterior oblique views. An additional "bird's-eye view" acquired with the pinhole collimator approximately 10–20 cm from the neck provides a wider field of view that can demonstrate the location and position of the thyroid gland in relation to other structures in the neck, such as salivary glands. Each image should be acquired for 50,000–100,000 counts with ^{123}I and 100,000–200,000 counts with ^{99m}Tc-pertechnetate.

Images typically are acquired with the neck extended. In some cases, such as localization of an ectopic thyroid gland, it may be helpful to acquire an image in a lateral projection. For example, this may be helpful in discriminating physiological salivary gland uptake from uptake in ectopic thyroid tissue. Anatomical correlation, either with transmission images to outline body margins or with radioactive markers, may be helpful for some studies. Radioactive markers can be placed on a palpable thyroid nodule or on anatomic landmarks, such as the chin and suprasternal notch.

Thyroid Uptake

Quantitative assessment of radioiodine uptake is useful for assessing thyroid function. When thyroid uptake is determined concurrently with ^{123}I thyroid scintigraphy, then the same dose of ^{123}I is used for both studies, and no additional radioiodine is administered for the uptake determination. When performed without concurrent ^{123}I thyroid scintigraphy, then determination of a radioiodine uptake requires a small dose of either ^{123}I or ^{131}I. Most professional guidelines [13, 15] recommend a pediatric dose of 3.7–7.4 MBq (0.1–0.2 mCi) of ^{123}I or 0.15–0.37 MBq (0.004–0.01 mCi) of ^{131}I for thyroid uptake determination without imaging. Iodine-123 is preferable, as it can provide an approximately 100-fold smaller effective radiation dose than ^{131}I at these recommended administered doses [15]. At our institution, we successfully use weight-based administration of ^{123}I for both thyroid scintigraphy and radioiodine uptake with an administered ^{123}I dose of 0.2 MBq/kg (0.006 mCi/kg) with a minimum dose of 0.925 MBq (0.025 mCi) and maximum dose of 14.8 MBq (0.4 mCi). No more than 0.4 mCi as a maximum dose should be necessary for a thyroid uptake

determination. Some clinicians have advocated ^{99m}Tc-pertechnetate for determination of thyroid uptake. However, the rapid washout of pertechnetate means that uptake must be determined within a few minutes of tracer administration, and this may not be a precise reflection of thyroid activity. Also, quantitation with ^{99m}Tc is more difficult than with radioiodine.

Thyroid radioiodine uptake can be calculated using a probe detector or by quantitative assessment of a planar scintigraphy. A radioiodine uptake calculation may be most informative when performed in conjunction with thyroid scintigraphy. Therefore, in most cases, thyroid scintigraphy, typically with a pinhole collimator, still should be performed even when a probe detector is used to determine thyroid uptake. An accurate uptake measurement requires the use of a standard, typically a second dose of radioiodine with activity similar to the dose administered to the patient. Thyroid uptake can then be determined by calculating the ratio of activity in the thyroid to the activity in the standard. This allows for accurate correction for probe sensitivity and for radioactive decay. It is not ideal practice to rely on a calculated standard activity. Some departments will place the standard dose in a neck phantom to more accurately correct for soft tissue attenuation and geometry. However, these effects are probably small, particularly in children, and not routinely used for pediatric studies.

The standard time for determining thyroid uptake is 24 h after radioiodine administration. Many departments find it useful to perform an uptake measurement at an earlier time, typically 4 or 6 h. If iodine uptake is absent or nearly absent at an early time point, then there may be little reason to have the patient return for another uptake measurement the following day. In other cases, a drop in measured uptake between early and later time points can indicate a state of high-iodine turnover in the thyroid. The typical uptake is 6–18 % at 4–6 h and 10–35 % at 24 h [15]. However, these must not be considered absolute values and must be interpreted within the context of the biochemical thyroid function tests.

Factors Affecting Thyroid Studies

Radioiodine uptake by the thyroid gland can be affected by iodine levels in the thyroid and body. For example, in populations with lower levels of dietary iodine intake, typical thyroid uptake of a radioiodine dose will be higher [16]. Recent iodine intake, whether in diet, dietary supplements, medications, or intravenous iodinated radiographic contrast, will inhibit and lower subsequent radioiodine uptake [15]. This can impair thyroid imaging, reduce the diagnostic value of a radioiodine uptake determination, decrease detection of thyroid cancer metastases, and limit the effectiveness of radioiodine therapy. Therefore, a careful medical and dietary history must be performed with each patient before performing these nuclear medicine procedures.

If feasible, thyroid imaging or uptake determination should be delayed until excess nonradioactive iodine can be cleared (Table 5.1). After administration of iodinated radiographic contrast, thyroid studies should be delayed for at least 1 month [17], although some clinicians may wish to wait up to 3 months before evaluating and treating thyroid cancer. Occasionally, it may be helpful to assess iodine economy by measuring the urinary excretion of iodine. This can be measured most accurately in a 24-h urine collection. Alternatively, iodine excretion can be estimated with the simultaneous measurement of iodine and creatinine in a random urine sample [18]. If urinary iodine excretion exceeds 50 mcg/day, it may be appropriate to delay the thyroid study, if feasible and clinically appropriate [19].

Patients should not be advised to discontinue any prescribed drug without involving the prescribing clinician and the physician managing the patient's thyroid condition. In some clinical situations, the study may need to be performed despite recent iodine intake or drug administration while recognizing that the diagnostic certainty of the study could be limited. The cardiac drug amiodarone deserves special mention. Amiodarone is 37 % iodine by weight, and the drug is cleared very slowly from the body. In some cases, amiodarone may be associated with the onset of thyroid disease. However, in

Table 5.1 Sources of iodine and ideal withholding time period before thyroid imaging

Source	Time period
I. Iodine-rich foods and supplements	
1. Seaweed, kelp, sushi	1 week
II. Medications	
A. Thyroid hormones[a]	
1. Levothyroxine (T4)	6 weeks
2. Triiodothyronine (T3, Cytomel ®)	2 weeks
3. Others (liotrix, Thyrolar ®, Armour Thyroid ®)	6 weeks
B. Antithyroid drugs (methimazole, propylthiouracil)	3 days
C. Iodine supplements[b]	
1. Iodine solutions (SSKI, Lugol's Purepac, Isostat)	1 week
2. Potassium Iodine (KI) tablets	1 week
3. Vitamin or mineral tablets with iodine	1 week
D. Medications that contain iodine	
1. Cough medications (Tussi-Organidin®, Pima syrup®)[c]	6 weeks
2. Skin cleansers and antiseptics (Betadine®)[d]	6 weeks
3. Amiodarone (Coranone®)[e]	1 year
E. Other medications that affect thyroid function	
1. Lithium carbonate[e]	1 year
III. Imaging studies	
A. Tests requiring intravenous iodinated contrast	6 weeks (arteriogram, intravenous pyelogram)
B. Contrast-enhanced CT scan[f]	4–12 weeks
C. Cardiac catheterization	6 weeks

[a]Typically, withdrawal of thyroid hormone is a concern only before performing whole body imaging or radioiodine therapy in a patient with differentiated thyroid cancer.
[b]Whole body iodine content can be confirmed with urinary iodine assay if there is clinical concern about recent iodine supplementation.
[c]Limited availability in the USA.
[d]Primarily a concern in neonates, individuals with impaired skin integrity, and after mucosal application.
[e]Rarely it is clinically appropriate to discontinue these medications, and thyroid function tests and imaging must be interpreted in the context of continued medication administration.
[f]For most thyroid studies, a 1 month period is sufficient. Some clinicians prefer to wait up to 3 months after a contrast-enhanced CT scan before a diagnostic whole body scan or radioiodine therapy in a patient with thyroid cancer

most cases, it is not clinically appropriate to discontinue amiodarone. Although amiodarone is rarely used in children, evaluation and treatment of thyroid disease can be difficult in patients treated with this drug [20].

Drugs that directly affect thyroid function, such as thionamides (e.g., propylthiouracil, methimazole), should be discontinued for a short period of time (typically 3 days) before performing thyroid scintigraphy or a radioiodine uptake study [12, 13, 15]. This is best arranged with collaboration between the referring clinician and the nuclear medicine physician. Lithium carbonate suppresses thyroid function, and in patients treated with lithium-containing drugs, any thyroid tests must be interpreted within the context of lithium therapy. It is not necessary to discontinue other drugs, such as beta-blockers used for symptomatic relief of hyperthyroidism, before performing a thyroid scan or radioiodine uptake determination.

Body Scans Using Radioiodine

Whole body scans are performed for detection of metastatic thyroid cancer [19, 21–23]. They may be performed as a diagnostic scan or may be performed as a post-therapy scan shortly after treatment with ^{131}I. Diagnostic whole body scans are

performed approximately 16–48 h (typically 24 h) after administration of a small diagnostic dose of radioiodine. They may be performed with either ^{131}I or ^{123}I, but ^{123}I has become the preferred agent due to lower radiation dose and improved image quality [9]. For a diagnostic whole body scan in a child, the usual dose of ^{123}I is 3–5 mCi. The sensitivity of a whole body scan for detecting functioning thyroid cancer metastases likely increases with increasing radioiodine dose [19]. Iodine-123 also is preferred because of concerns that diagnostic doses of ^{131}I may "stun" thyroid cancer cells [24]. Stunning potentially may lead to decreased uptake and a diminished therapeutic effect of the subsequent treatment dose of ^{131}I [25]. Iodine-131 is used for a diagnostic whole body scans when ^{123}I is not available or if the whole body scan will be used for formal dosimetry planning before treatment with ^{131}I. To minimize stunning, the administered ^{131}I dose should be limited to less than 3 mCi [26], and the usual diagnostic dose of ^{131}I is 1–2 mCi.

Patient preparation is important to ensure accurate results from a diagnostic whole body radioiodine scan [19]. The scan should be performed only under conditions of TSH stimulation and iodine depletion. Patients should maintain a low-iodine diet for 7–14 days before the diagnostic dose of radioiodine is administered and should be screened for other sources of iodine intake (see "Factors affecting thyroid studies," Table 5.1). Patients with renal failure or on dialysis will need special planning. TSH stimulation could be accomplished with either withdrawal of thyroid hormone replacement therapy or administration of recombinant TSH [23]. However, the use of recombinant TSH in preparation for either whole body scans or radioiodine therapy has not been validated for outcome in children.

Post-therapy whole body scans are performed 3–7 days after administration of ^{131}I therapy. Despite the poorer imaging characteristics of ^{131}I, the post-therapy scan can be highly sensitive for sites of disease not identified with whole body imaging after a diagnostic dose of radioiodine [23, 27, 28]. This increased sensitivity probably reflects both the much higher administered dose of radioiodine and the altered biodistribution of ^{131}I that is seen many days after administration [28]. With increased time after administration, there will be washout of radioiodine from tissues that trap, but do not organify iodine, such as salivary and lacrimal glands and gastric mucosa. With increased soft tissue clearance, there can be improved target-to-background ratio, so that sites of disease that have small size or limited radioiodine avidity may become detectable. After a few days, little radioiodine accumulation is seen in the genitourinary system, but persistent accumulation of radioiodine is seen in bowel. This may be exacerbated by the slowed colonic transit resulting from hypothyroidism due to thyroid hormone withdrawal. Physiological radioiodine uptake in breast and thymus may be more apparent on post-therapy scans. Diffuse liver uptake reflects accumulation and metabolism of thyroglobulin and thyroid hormone. Thus, diffuse liver uptake is an indicator of functional thyroid tissue (either benign or malignant) that can synthesize thyroglobulin, but should not be interpreted to represent diffuse liver involvement with metastatic disease [29].

Whole body scans are acquired with a high-energy collimator in place for ^{131}I and a medium-energy collimator in place for ^{123}I [7]. Whole body imaging is usually performed as a whole body sweep, but in younger children, it may be easier to acquire multiple planar images rather than to attempt a single whole body sweep. Typically, the whole body scan sweep rate is adjusted to take 40 min to image the entire body. If static planar images are to be used, images should be planned to acquire 300,000–500,000 counts. To assist in image comparison and interpretation, all planar images should be acquired for the same period of time. Some institutions routinely image the thyroid bed and neck with a pinhole collimator and may calculate thyroid bed radioiodine uptake as part of pre-therapy diagnostic imaging [22]. If formal dosimetry is planned, then the whole body ^{131}I images should include a standard, typically 0.05–0.1 mCi ^{131}I diluted in water or saline in a small, well-sealed flask. SPECT and SPECT/CT may be useful in some patients for detecting low-avidity lesions and for localizing sites of abnormal radioiodine uptake [30, 31].

Clinical Applications

Congenital Hypothyroidism

Nuclear medicine has little role in the evaluation of hypothyroidism but with one exception, the evaluation of congenital hypothyroidism. Congenital hypothyroidism is not common, with an incidence of approximately 1 in 3,000 live births in North America [32]. However, it is an important public health concern because of the devastating neurocognitive impairment that results from untreated congenital hypothyroidism. Thyroid hormone is critical to normal brain development, and the absence of thyroid hormone during early life results in severe and irreversible neurological damage. Congenital hypothyroidism (endemic cretinism) is the leading cause of preventable mental retardation worldwide. Because of this, all US states and Canadian provinces mandate newborn screening of all infants for congenital hypothyroidism. In much of the world, the primary cause of congenital hypothyroidism is endemic iodine deficiency. In iodine-replete populations, such as in North America, congenital hypothyroidism typically is sporadic but rarely may reflect maternal iodine deficiency.

Treatment with early replacement of thyroid hormone is effective in allowing normal neurological development and has been shown to prevent the neurocognitive damage associated with hypothyroidism. The underlying cause of congenital hypothyroidism does not determine the treatment and rarely influences the neurological outcome of congenital hypothyroidism. Therefore, in these patients, the priority is to provide adequate thyroid hormone replacement before any attempt is made to determine the etiology of the congenital hypothyroidism.

Characterizing the underlying defect in thyroid function may help in predicting the need for lifelong therapy. Most sporadic cases of congenital hypothyroidism are associated with thyroid dysgenesis or thyroid ectopia. Thyroid dysgenesis is twice as common in female as male newborns [33]. Approximately 15 % of cases are familial, typically with autosomal recessive inheritance of a syndrome of thyroid dyshormonogenesis. Other cases may represent transient hypothyroidism due to transplacental passage of maternal blocking antibodies that inhibit the function of the TSH receptor [34]. Rarely, congenital hypothyroidism is the result of a pituitary or hypothalamic abnormality. Rare cases may be caused by thyroid hypoplasia due to congenital TSH deficiency or abnormal binding or signaling of the TSH receptor located on thyroid follicular cells.

The appropriate role for imaging in the management of congenital hypothyroidism is unclear [32, 35]. Some clinicians will treat congenital hypothyroidism presumptively with thyroid hormone replacement therapy for the first 3 years of life, the critical period of neurological development. Once the child reaches age three, thyroid hormone is discontinued or decreased in dose, and an elevation in TSH level interpreted as a sign of persistent congenital hypothyroidism. In some cases, measurement of a serum thyroglobulin level can be helpful in determining the presence of functional thyroid tissue. Some clinicians find it useful to demonstrate the location and function of thyroid tissue. Identification of thyroid absence or ectopia (a majority of cases in North America) will indicate a need for lifelong thyroid hormone replacement [36].

A thyroid scan with either ^{123}I (Fig. 5.3) or ^{99m}Tc-pertechnetate (Fig. 5.4) can be useful both to demonstrate the presence and location of any functional thyroid tissue, as well as providing an indication of thyroid function. For example, rapid washout of ^{123}I between 4 and 24-h images suggests an error in iodine organification. Thus, ^{123}I may be the preferable radiopharmaceutical for assessing congenital hypothyroidism. However, thyroid hormone replacement therapy should not be discontinued with the purpose of assessing thyroid function in an infant [32, 35]. Thyroid ultrasound can be helpful in confirming that the thyroid has normal morphology and location, but ultrasound is less sensitive for localizing ectopic thyroid tissue and does not provide information about

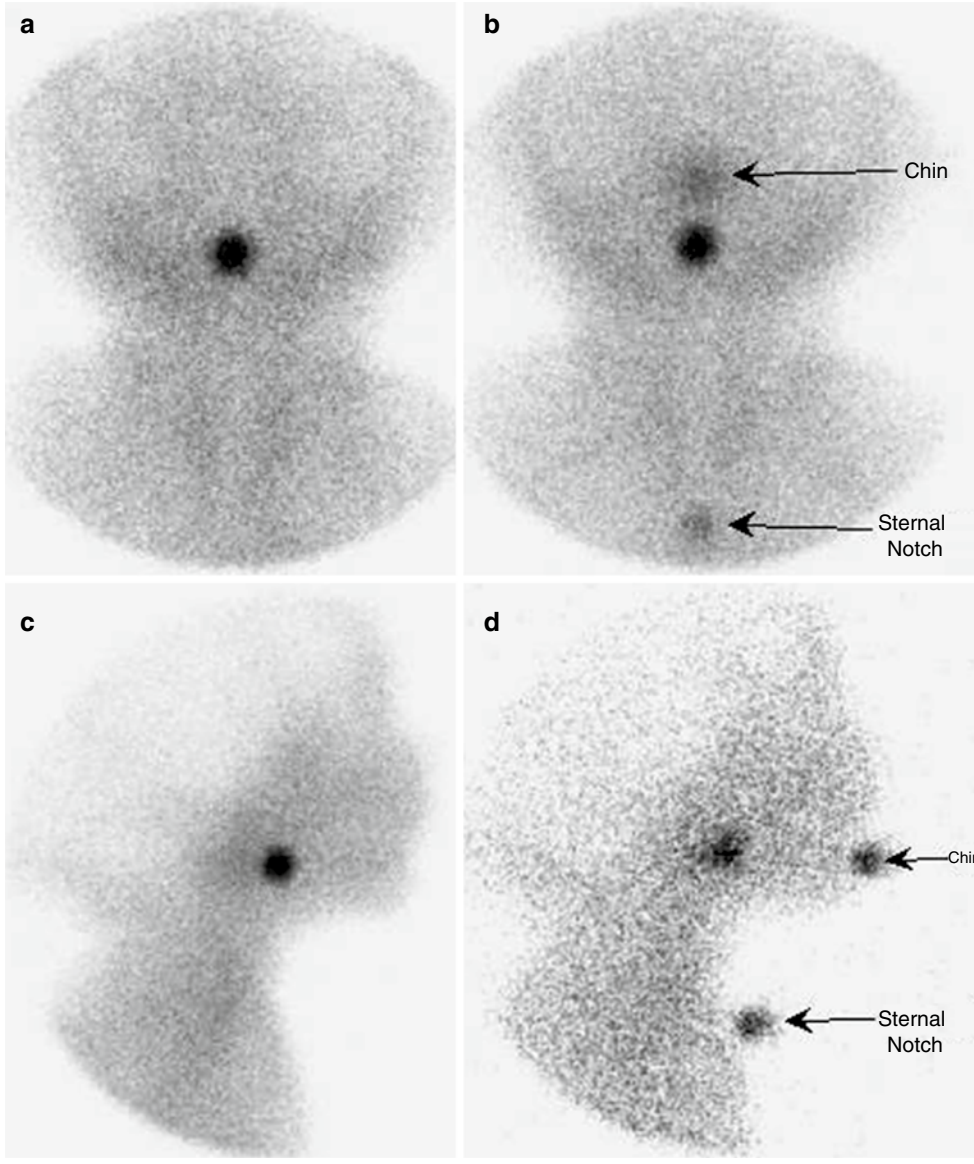

Fig. 5.3 Lingual thyroid gland detected with an ^{123}I scan. (**a**) In a patient with congenital hypothyroidism, a planar ^{123}I scan of the head and neck in the anterior projection demonstrates no thyroidal uptake in the expected location of the thyroid gland. A focus of intense radioiodine is located in the midline and superior to the neck. (**b**) External markers on the chin and at the upper sternal notch can be helpful for localization. (**c**) A planar image in a lateral projection demonstrates focal uptake in the region of the oropharynx. (**d**) External markers help confirm the likely location of the ectopic thyroid tissue to the base of the tongue

function. Infants with absent uptake on a thyroid scan should be evaluated by thyroid ultrasound. Other imaging tests, such as CT and MRI rarely, if ever, have a role in the evaluation of congenital hypothyroidism.

A young patient with no prior history of hypothyroidism may present with an ectopic thyroid gland. Ectopic thyroid tissue can be found anywhere along the usual embryological migration pathway from the foramen cecum at the base

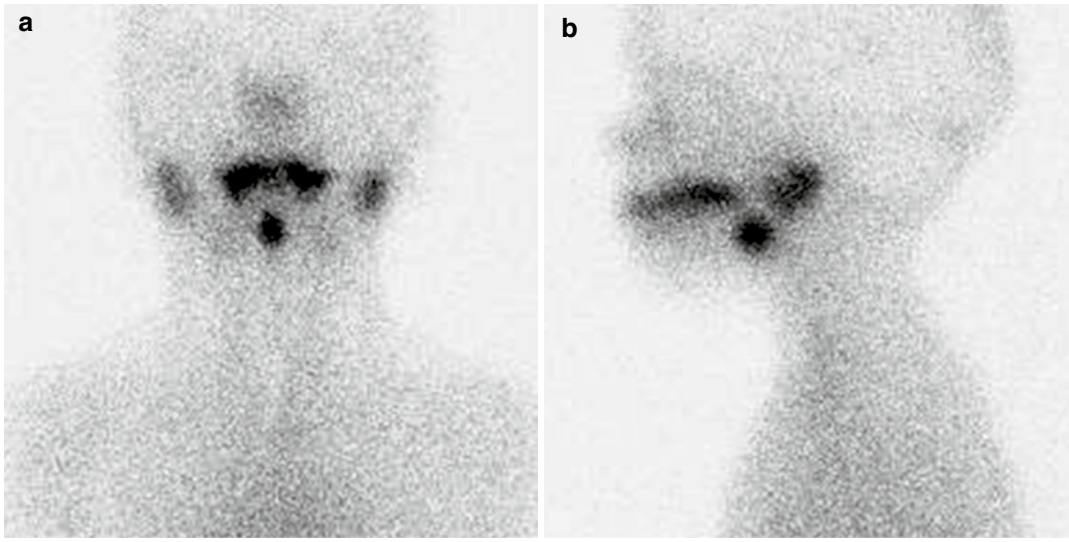

Fig. 5.4 Lingual thyroid gland detected with thyroid scan performed with [^{99m}Tc] sodium pertechnetate. (**a**) In a 3-year-old boy with congenital hypothyroidism, a planar scan performed with [^{99m}Tc] sodium pertechnetate. A planar image acquired in the anterior projection demonstrates no thyroidal uptake in the expected location of the thyroid gland. Extensive and expected uptake is seen in salivary glands and in secretions in the oral and nasal cavities. Above the neck, a midline focus of uptake is at a typical location for a lingual thyroid gland. (**b**) A planar image acquired in a lateral projection confirms the location of an ectopic lingual thyroid gland

of the tongue to the mediastinum, but development of clinically identifiable thyroid tissue is rare. Occasionally, ectopic thyroid tissue rarely is discovered elsewhere in the neck. Rarely, multiple sites of ectopic thyroid tissue can be identified [37]. At least two-thirds of patients with a clinically apparent ectopic thyroid mass have no thyroid gland in the expected location in the thyroid bed. The most common presenting symptom is new awareness of a mass in the anterior neck or at the base of the tongue. Other presenting symptoms can include dysphagia, dysphonia, or hemorrhage from a lingual thyroid gland. Almost always, the growing thyroid tissue represents histologically benign thyroid tissue, but thyroid carcinoma has been reported in ectopic thyroid tissue.

Unusual sites of ectopic thyroid tissue in the ovary (struma ovarii) and elsewhere in the abdomen and pelvis likely reflect ectopic development of thyroid tissue and not abnormal migration from the foramen cecum [37]. These sites of abnormal thyroid tissue have a higher incidence of hyperfunction and malignancy. In cases of suspected ectopic thyroid, thyroid scintigraphy can be helpful confirming that the mass represents functional thyroid tissue and at the same time can help determine if a normal thyroid gland is present [38].

Evaluation of Hyperthyroidism

Thyroid hormone contributes to the regulation of metabolic activity throughout the body. Excess levels of thyroid hormone produce symptoms of hypermetabolism, such as heat intolerance and weight loss, and symptoms of adrenergic excess, such as tremor, hyperactivity, tachycardia, palpitations, increased frequency of bowel movements, and sleep disturbance. In children, other symptoms can include behavioral disturbance, impaired school performance, and growth disturbance [39–41]. The term thyrotoxicosis refers to the clinical syndrome resulting from excess circulating levels of thyroid hormone.

Thyroid hormone excess can result from a variety of disorders (Table 5.2). With the exception of rare cases of secondary hyperthyroidism,

Table 5.2 Thyrotoxicosis in children

Cause	Typical thyroid radioiodine uptake
Graves' disease	Autonomous (usually elevated)
Toxic ("hot") nodule	Autonomous uptake in the nodule (with suppression of normal thyroid tissue)
Toxic multinodular goiter	Autonomous uptake in overactive nodules (with suppression of normal thyroid tissue)
Subacute thyroiditis	Decreased
Chronic thyroiditis ("hashitoxicosis")	Decreased
Factitious thyrotoxicosis (excess thyroxine intake)	Suppressed
Secondary thyrotoxicosis (elevated TSG, hCG)	Elevated
Ectopic thyroid tissue	Suppressed

elevated levels of thyroid hormone suppress secretion of thyroid-stimulating hormone (TSH) through the process of negative feedback on the hypothalamic-pituitary-thyroid axis. Strictly speaking, the term hyperthyroidism refers only to the overproduction of thyroid hormone by thyroid tissue, but any inappropriate elevation of circulating thyroid hormone sometimes is referred to as hyperthyroidism. The diagnoses of thyrotoxicosis and hyperthyroidism are based on clinical findings and blood tests (plasma T4, T3, and TSH). Determination of radioiodine uptake and thyroid scintigraphy can further characterize the underlying cause of the thyrotoxicosis, which is useful in guiding appropriate therapy.

Thyrotoxicosis can result from hyperthyroidism due to overproduction of thyroid hormone by a toxic goiter (Graves' disease), a toxic thyroid nodule, or a toxic multinodular goiter. These conditions are characterized by increased thyroid uptake of iodine in the overactive thyroid tissue. Graves' disease represents autonomous thyroid hyperfunction due to circulating stimulating antibodies directed against the TSH receptor on the cell surface of thyroid follicular cells. The resulting hyperthyroidism produces hyperthyroxinemia with subsequent suppression of TSH levels. Most cases of Graves' disease are characterized by elevated circulating levels of both levothyroxine (T4) and triiodothyronine (T3). However, occasional patients with Graves' disease may have elevated T3 levels without T4 elevation [39], which sometimes is referred to as "T3 toxicosis."

In patients with Graves' disease, autonomous thyroid function almost always is associated with increased radioiodine uptake. While assessing thyroid radioiodine uptake, most institutions will perform thyroid scintigraphy to assess the functional structure of the thyroid gland (Figs. 5.5 and 5.6). Occasional mild cases of Graves' disease may be associated with "normal" radioiodine uptake (Fig. 5.7). However, in the absence of circulating TSH, a normal radioiodine uptake is inappropriately normal and still consistent with Graves' disease. Other causes of a normal radioiodine uptake in Graves' disease include recent iodine intake (Table 5.1) or administration of radiographic contrast. Thyrotropin receptor antibodies (TRAb) or thyroid-stimulating antibodies (TSAb) may be assayed in patients with suspected Graves' disease, but these assays may have a false-negative rate of 10–20 %. These antibody assays are rarely necessary as the combination of thyrotoxicosis and an elevated (or inappropriately normal) radioiodine uptake is virtually diagnostic of Graves' disease [42]. While assessing thyroid radioiodine uptake, most institutions will perform thyroid scintigraphy to exclude either an autonomous or a hypofunctioning thyroid nodule (Fig. 5.8). Although cold nodules are an infrequent finding in the setting of Graves' disease, some reports have suggested that they may have an increased likelihood of malignancy or aggressive clinical features [39].

Autonomous thyroid nodules [39–41], whether solitary or within a multinodular goiter, produce elevated thyroid hormone levels that will suppress TSH levels. With the absence of TSH stimulation, the function of the remaining nonautonomous thyroid tissue is suppressed, and it will demonstrate decreased radioiodine uptake on thyroid scintigraphy. The resulting pattern of autonomous radioiodine uptake in the

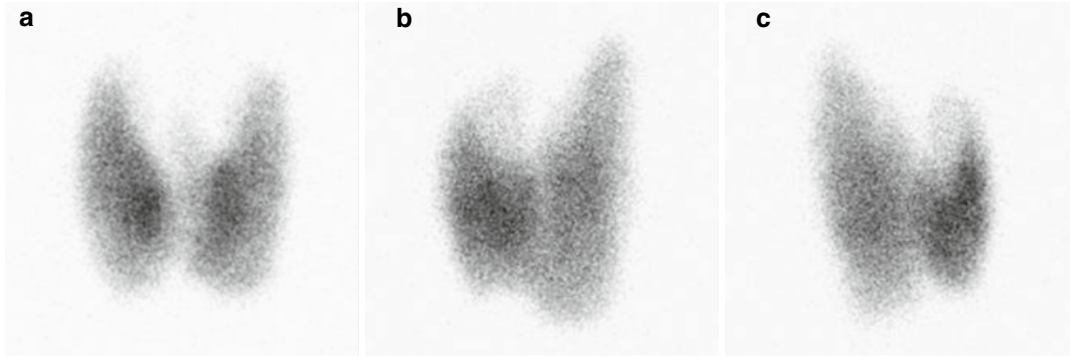

Fig. 5.5 Thyroid scintigraphy in Graves' disease. In a 15-year-old female with Graves' disease of 2 years duration, thyroid scintigraphy was performed with ^{123}I. Pinhole images acquired in the anterior (**a**), left anterior oblique (**b**), and right anterior oblique (**c**) projections demonstrate a symmetrically enlarged thyroid gland with diffuse or mildly heterogenous iodide uptake. The thyroid isthmus and a small pyramidal lobe can be identified. Radioiodine uptake was 85 % at 4 h and 83 % at 24 h. The patient was treated successfully with 15 mCi ^{131}I

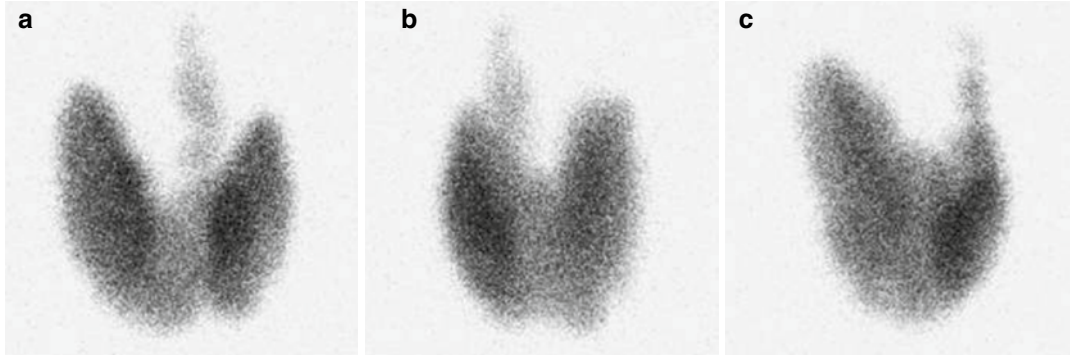

Fig. 5.6 Thyroid scintigraphy in Graves' disease. A 15-year-old male developed palpitations and heat intolerance and was diagnosed with hyperthyroidism (TSH <0.001 mU/l, free T4 >7.5 ng/dl). Iodine-123 scintigraphy was performed with pinhole images of the thyroid gland acquired in the anterior (**a**), left anterior oblique (**b**), and right anterior oblique (**c**) projections. There is diffuse or mildly heterogenous uptake in both enlarged thyroid lobes and in a long pyramidal lobe that extends along the anterior neck. Radioiodine uptake was 79 % at 4 h and 82 % at 24 h. He was treated successfully with 18 mCi ^{131}I

nodule with suppression of uptake in the remaining thyroid tissue is that of a "hot nodule" (Fig. 5.9). Other thyroid nodules may have mild autonomous overactivity, but, without suppression of TSH levels, the radioiodine uptake in the nodule will be similar to the surrounding thyroid tissue; these are "warm" thyroid nodules (Fig. 5.10)

Other causes of thyrotoxicosis [39–41] typically are associated with decreased iodine uptake throughout the thyroid gland. The combination of thyrotoxicosis with suppressed thyroid

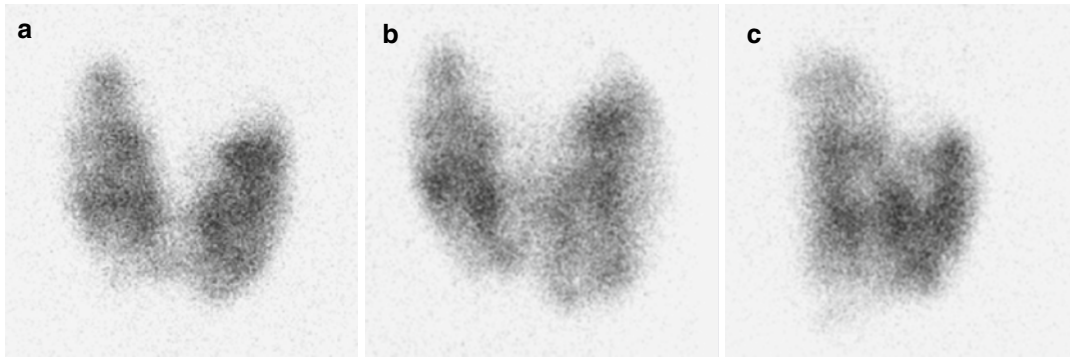

Fig. 5.7 Thyroid scintigraphy in Graves' disease with inhibited radioiodine uptake. An 11-year-old girl with Graves disease previously had been treated with oral antithyroid medications and then had been in remission without therapy for 2 years. After recurrence of Graves' disease (TSH 0.009 mU/l, free T4 1.95 ng/dl), thyroid scintigraphy was performed with ^{123}I. Pinhole images acquired in the anterior (**a**), left anterior oblique (**b**), and right anterior oblique (**c**) projections demonstrate patchy uptake throughout an enlarged thyroid gland. Radioiodine uptake was only 14 % at 4 h and 24 % at 24 h. The uptake was inappropriately normal in the absence of circulating TSH. The differential includes thyroid hormone ingestion, recurrent Graves' disease complicated by self-treatment with antithyroid medication, iodine ingestion, and mild Graves' disease. Further investigation revealed that the patient was taking an unreported dietary supplement that contained an unexpectedly high level of iodine. Three months after discontinuation of the supplement, radioiodine uptake increased to 53 % at 4 h and 61 % at 24 h, the patient was treated with 20 mCi ^{131}I

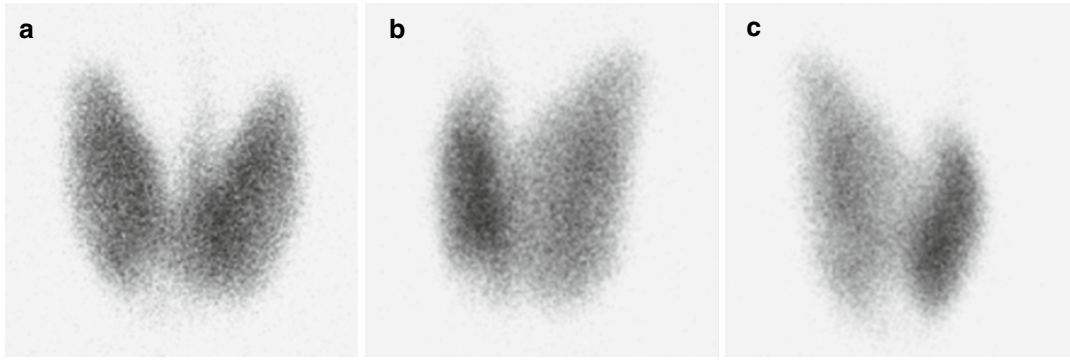

Fig. 5.8 Thyroid scintigraphy of papillary thyroid cancer in a patient with Graves' disease. An 12-year-old girl with a sore throat was found to have an enlarged thyroid gland and thyrotoxicosis (TSH <0.001 mU/l, free T4 2.8 ng/dl). Physical examination by an endocrinologist revealed an enlarged thyroid with a palpable nodule in the lower pole of the right lobe. Iodine-123 scintigraphy with pinhole images of the thyroid gland acquired in the anterior (**a**), left anterior oblique (**b**), and right anterior oblique (**c**) projections showed a bilaterally enlarged and symmetrical thyroid gland, with slightly patchy tracer uptake and prominent uptake in a pyramidal lobe. There is minimal uptake in the palpable nodule at the lower pole of the right lobe of the gland. The nodule was evaluated by fine-needle aspiration under ultrasound guidance, and cytology was suspicious for papillary carcinoma. After treatment with methimazole and SSKI, a total surgical thyroidectomy was performed, and pathology showed a 1.2 cm papillary thyroid carcinoma

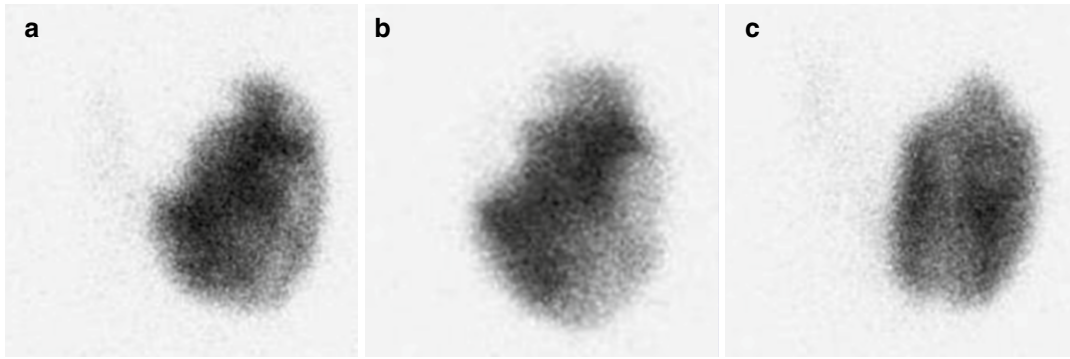

Fig. 5.9 Thyroid scintigraphy of an autonomous ("hot") thyroid nodule. A 13-year-old girl with an enlarged left thyroid lobe was found to have hyperthyroidism (TSH <0.005 mU/l, free T4 1.7 ng/dl). Iodine-123 scintigraphy was performed with pinhole images of the thyroid gland acquired in the anterior (**a**), left anterior oblique (**b**) and right anterior oblique (**c**) projections. There is mildly heterogenous and intense uptake in a large nodule in the left lobe of the thyroid gland. There is minimal uptake in the normal thyroid gland. Radioiodine uptake was 30 % at 4 h and 51 % at 24 h. Surgical thyroidectomy was performed and pathology showed benign nodular hyperplasia

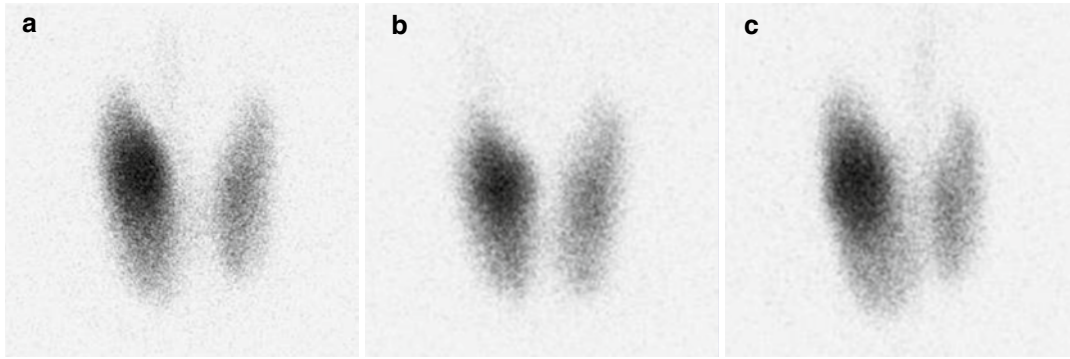

Fig. 5.10 Thyroid scintigraphy of a "warm" thyroid nodule. In a 14-year-old girl with a palpable thyroid nodule and subclinical hyperthyroidism with free T4 1.24 ng/dl (reference 0.8–1.9 ng/dl) and TSH 0.3 mU/l (reference 0.7–5.0 mU/l), ultrasound demonstrated a 3 cm nodule in the upper pole of the right lobe of the thyroid gland. Iodine-123 scintigraphy was performed with pinhole images of the thyroid gland acquired in the anterior (**a**), left anterior oblique (**b**), and right anterior oblique (**c**) projections. There is increased uptake within the nodule in the upper region of the right lobe of the thyroid, but there is no suppression of the rest of the normal appearing thyroid gland. Fine-needle aspiration revealed benign cytology, and the patient and her family have opted for close clinical follow-up

uptake most commonly represents either a subacute or chronic thyroiditis (Fig. 5.11). *Subacute* thyroiditis represents an autoimmune-mediated inflammation, and possible destruction, of the thyroid gland. There are various subgroupings and categorizations of subacute thyroiditis, such as painless or painful and lymphocytic or granulomatous, but all appear similar on thyroid scintigraphy. Postpartum thyroiditis is a common cause of painless thyroiditis. *Chronic* thyroiditis, also called Hashimoto's thyroiditis, is characterized by autoimmune inflammation and destruction of the thyroid gland that usually results in hypothyroidism, but a subset of patients

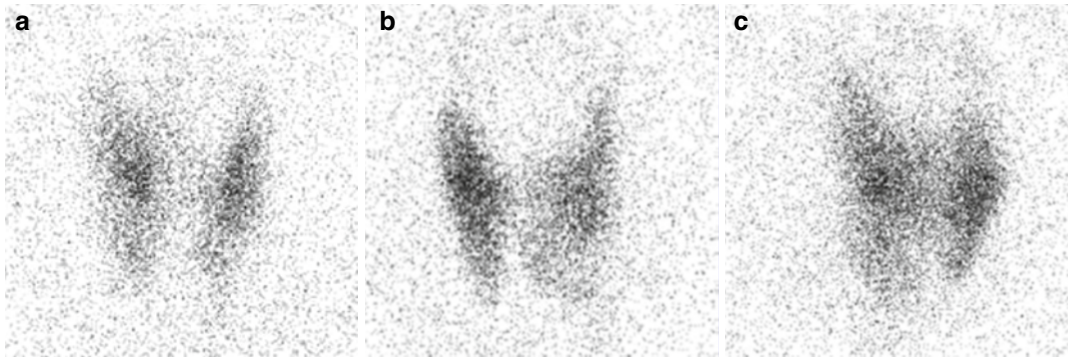

Fig. 5.11 Thyroid scintigraphy of subacute thyroiditis. A 14-year-old girl with sweating and hot flashes was found to have a suppressed TSH (0.2 mU/l) and elevated total T4 level (14.7 mcg/dl). There was no thyroid tenderness. After administration of ^{123}I, radioiodine uptake was 5 % at 4 h and 3 % at 24 h. Scintigraphy performed with pinhole images of the thyroid gland acquired in the anterior (**a**), left anterior oblique (**b**), and right anterior oblique (**c**) projections showed minimal uptake in a symmetrical thyroid gland. Symptoms of sweating and hot flashes responded to symptomatic therapy, and the patient eventually developed chronic hypothyroidism

developed transient thyrotoxicosis (sometimes called "hashitoxicosis") characterized by decreased radioiodine uptake. *Acute* thyroiditis, by comparison, refers to a suppurative infection of the thyroid, an extremely rare condition that is associated with a heterogeneous pattern of radioiodine uptake.

Suppressed radioiodine uptake has a broad differential beyond thyroiditis (Table 5.3). Other causes of thyrotoxicosis with suppressed radioiodine uptake include excess intake of thyroid hormone (*thyrotoxicosis factitia*) and ectopic thyroid tissue. Factitious thyrotoxicosis has been reported with inappropriate intake of thyroid hormone in misguided attempts at weight loss or energy stimulation, unintentional intake in non-traditional diet supplements containing thyroid hormone or the result of contamination of meat products with bovine or porcine thyroid tissue ("hamburger thyrotoxicosis"), and, in children, surreptitious ingestion of thyroid medications prescribed for family members. Ectopic thyroid tissue, such as *struma ovarii* or functional metastatic thyroid cancer, is rare but can demonstrate TSH-independent autonomy with suppression of a normal thyroid gland. Decreased or absent radioiodine uptake is seen with hypothyroidism and in patients with thyroid tissue absent due to surgery or radioiodine ablation. Antithyroid medications will decrease radioiodine uptake, so that these medications must be discontinued (typically for 3 days) before thyroid scintigraphy or determination of radioiodine uptake. Prior to performing thyroid scintigraphy, it is important to obtain a thorough dietary and medical history and to delay the study if appropriate (Table 5.1).

Table 5.3 Causes of decreased thyroid radioiodine uptake

Thyrotoxicosis
Subacute thyroiditis (lymphocytic)
Subacute thyroiditis (granulomatous)
Subacute phase of chronic thyroiditis
Factitious thyrotoxicosis
Ectopic thyrotoxicosis
Increased iodine intake/administration
Iodine-rich diet
Iodine-containing medications/supplements
Intravenous iodinated radiological contrast
Hypothyroidism
Autoimmune hypothyroidism
Athyreosis/ectopic thyroid gland
Prior thyroidectomy
Prior thyroid ablation
Antithyroid medications

Treatment of Hyperthyroidism

Treatment of thyrotoxicosis depends upon the underlying mechanism of thyroid hormone excess. No definitive therapy is available for thyroiditis, and possible medical therapy includes symptomatic therapy, such as beta-blockers, to decreased cardiac awareness and palpitations. On the other hand, the options for treatment of hyperthyroidism [39–42] include medical therapy, radioiodine therapy [43], and surgery [44]. The treatment plan must be developed in consultation with the patient and family, and usually is made in collaboration with the referring physician.

For most patients with hyperthyroidism due to Graves' disease or an autonomous thyroid nodule, medical therapy is the preferred first choice for therapy. The thionamides (propylthiouracil, methimazole) have an antithyroid effect and can be highly effective for the treatment of hyperthyroidism. In children with Graves' disease, up to one-third of patients may obtain disease remission within 2 years of starting antithyroid medications. Other patients can use these medications for long-term control of the hyperthyroidism, and some may achieve long-term remission. However, up to a third of children that go into remission may relapse [45]. Due to recent reports of hepatotoxicity associated with the use of propylthiouracil (PTU) in pediatric patients, methimazole has become the antithyroid medication of choice for children. PTU should not be the first drug of choice, and long-term PTU therapy should never be used in children [46]. However, PTU may have a very limited short-term role during the first trimester of pregnancy and in the treatment of thyroid storm [47]. Other supportive therapies, such as beta-blockers to lessen cardiac symptoms, also may be helpful early in treatment [40, 47].

Many patients experience good clinical results with medical treatment of hyperthyroidism. However, patients can have difficulty with the strict regimen of taking medication two to four times a day, and poor compliance can result in suboptimal control or treatment failure. Up to one-quarter of patients may develop minor side effects, such as pruritus, hives, myalgias, arthralgias, mild increases in liver enzymes, or mild decreases in white blood cell count [40]. Severe or life-threatening side effects of antithyroid medications are rare (probably less than 5 %) but include severe hepatotoxicity and bone marrow suppression [48, 49]. Unlike the hepatocellular injury and liver failure associated with PTU, cholestasis is more likely to be associated with methimazole [50]. Patients who do not achieve adequate long-term disease control or have medication side effects usually seek definitive therapy. Definitive therapy, with either surgery or radioiodine therapy, likely will result in permanent hypothyroidism requiring lifelong thyroid hormone replacement therapy.

Although surgical thyroidectomy was the first definitive therapy developed for hyperthyroidism, it is now rarely the first treatment of choice. Possible risks of thyroidectomy include anesthesia complications, damage to the recurrent laryngeal nerve, hypoparathyroidism due to inadvertent injury or removal of the parathyroid glands, and bleeding necessitating reoperation. These risks should be extremely low with an experienced thyroid surgeon. Surgical thyroidectomy may be the choice for definitive therapy in selected circumstances, including failed radioiodine therapy, pregnancy with intolerance or allergy to antithyroid medications, or for women planning a pregnancy in less than 4–6 months. Surgical therapy also will be the first choice for treatment of Graves' disease when concurrent thyroid malignancy is documented by cytopathology or suspected in a concurrent nonfunctioning thyroid nodule (Fig. 5.8) [47]. Surgical therapy may be an appropriate first choice for treatment of an autonomous ("hot") thyroid nodule (Fig. 5.9), particularly if the nodule is large enough to cause compressive symptoms, if there are concomitant nonfunctioning thyroid nodules, or for cosmetic reasons.

Radioiodine Therapy for Hyperthyroidism

Radioiodine therapy has been used for over 65 years for the treatment of hyperthyroidism [1, 2, 51, 52]. Iodine-131, administered as [^{131}I]

sodium iodide, is effective for treatment of both Graves' disease and toxic thyroid nodules [53]. After administration of adequate ^{131}I radioiodine therapy, approximately three-quarters of patients with Graves' disease will be euthyroid within 2 months, and over 90 % eventually will achieve hypothyroidism. Although some attempts have been made to carefully titrate the radioiodine dose in an effort to achieve post-therapy euthyroidism, this approach had an increased risk of disease recurrence, and the current consensus is to aim for thyroid ablation as definitive therapy of Graves' disease.

Although rare in young children (less than 5 years of age), Graves' disease can occur in this age group. Some clinicians advocate against radioiodine therapy in these very young children due to concerns about radiation risk, but the complication rate of surgical thyroidectomy also is greater in children than adults. Young children provide a challenge for radiation safety, as they require closer involvement with caretakers and may not yet be toilet trained. Therefore, it is preferable that the few young children requiring treatment for Graves' disease be treated with antithyroid medications until old enough for definitive therapy. However, when indicated, radioiodine therapy can be used in young children [42, 47].

For treatment of hyperactive thyroid nodules, radioiodine therapy may be the preferred therapy for a small nodule or in a patient with a higher surgical risk [53, 54]. Ablation of hyperactive thyroid tissue allows TSH levels return to normal with subsequent return of normal thyroid function [55]. The response to radioiodine therapy is more rapid with a single toxic nodule. Three-quarters of patients will reach euthyroidism within 3 months after treatment for a single nodule and within 6 months after treatment for a toxic multinodular goiter. A small number of patients will develop hypothyroidism within the first year, but nearly two-thirds of patients treated as children may develop hypothyroidism by two decades [56, 57]. Some clinicians prefer to not use radioiodine for treatment of thyroid nodules due to concerns about the theoretical risks of radiation exposure to the rim of normal thyroid tissue adjacent to the treated nodule.

Many approaches have been advocated for choosing the appropriate administered dose of ^{131}I for the treatment of hyperthyroidism [53, 58–60]. Some practitioners have administered the same empiric dose of ^{131}I, typically ranging between 5 and 29 mCi, to every patient. Another approach has been to correct an empiric dose for the measured uptake of radioiodine as determined by a prior radioiodine uptake measurement. For example, the intended goal may be to achieve delivery of 8 or 12 mCi of ^{131}I to the thyroid gland. However, both of these approaches seem less appropriate for pediatric patients, and ideally, the administered dose of ^{131}I is adjusted for both thyroid size and radioiodine uptake. The effectiveness of radioiodine therapy depends upon an adequate radiation dose to the thyroid gland. Usually, this can be achieved with an administered dose of 0.08–0.22 mCi per gram of thyroid, corrected for thyroid uptake [51, 53].

$$\text{I-131 Dose}\left(\text{mCi}\right) = \frac{\left(0.08 - 0.22\,\text{mCi/g}\right) \times \text{estimated thyroid weight}\left(\text{g}\right)}{\text{iodine uptake at 24 h}}$$

Thyroid radioiodine uptake (ranging between 0.00 and 1.00) is determined 24 h after oral administration of a small dose of ^{123}I (see section "Thyroid Uptake"). Estimated thyroid size is determined by physical examination of the neck by an experienced clinician. Imaging studies, such as ultrasound or CT, are not reliable methods for estimating thyroid gland size. A dose at the higher range (0.2 mCi/g) is used for younger patients (i.e., most pediatric patients), if the gland is relatively large, or when there has been prior failure of radioiodine therapy. The higher dose also is used when the thyroid has a high iodine turnover, demonstrated by 24 h radioiodine uptake less than the 4-h radioiodine uptake. In

children, the administered dose of ^{131}I should not be decreased solely based on age, as this risks undertreatment and the need for additional doses of radioiodine therapy [47, 53].

Most guidelines recommend a low-iodine diet for at least 2 weeks before administration of radioiodine. This should include maintaining a low-salt diet, as salt may be supplemented with iodine. Although there is little evidence that a strict low-iodine diet improves outcome, substantial prior iodine intake will decrease radioiodine uptake, even in a thyroid gland with Graves' disease. As this can decrease uptake of the therapeutic dose and could require administration of a larger dose of ^{131}I to achieve adequate thyroid uptake of the therapeutic dose, it is most important to avoid sources of large doses of iodine, such as iodine-containing medications and iodinated radiological contrast. Unless contraindicated, most patients will have received treatment with antithyroid medications prior to radioiodine therapy. These medications should be discontinued 3–5 days before administration of radioiodine [47, 53]. Typically, patients will discontinue antithyroid medications at least 3 days before the pretreatment thyroid scintigraphy and uptake. In some patients, antithyroid medications will be restarted 3–7 days after radioiodine administration.

Radioiodine therapy has a number of side effects and risks [53] that should be discussed with the patient and family before making a decision to use radioiodine therapy. Transient worsening of hyperthyroidism may occur due to withdrawal of antithyroid medications or due to a potential unregulated release of thyroxine during the inflammatory response to ^{131}I. Persistent or recurrent hyperthyroidism occurs in less than 10 % of patients. Patients must understand that the goal of ^{131}I therapy is permanent hypothyroidism, which will require lifelong thyroid hormone replacement therapy. Another potential short-term complication is thyroid or salivary gland pain, which usually responds to over-the-counter anti-inflammatory agents. Long-term salivary damage is possible but very unlikely at the radioiodine doses used to treat Graves' disease. Many authorities recommend sour candies or tart juice to increase salivary flow with the goal of decreasing ^{131}I residence time in the salivary glands. Typically, this is started soon after administration of the radioiodine dose, but some studies suggest that the start of these agents be delayed for 24 h after ^{131}I administration. Antiemetics may be useful in children. As the mass of administered iodine is less than 1 microgram, allergy to iodine is not a contraindication to radioiodine therapy. There has been concern that radioiodine therapy may lead to a worsening of thyroid ophthalmopathy. More recent findings suggest that the incidence of new eye disease or worsening of know eye disease is no greater with radioiodine than other forms of therapy and that early post-therapy thyroid hormone replacement is important in limiting Graves' ophthalmopathy [61]. As a general rule, definitive therapy of Graves' disease should not be delayed due to concerns about thyroid ophthalmopathy. However, it is important that patients with eye findings receive appropriate ophthalmological care.

The potential risk of carcinogenesis after radioiodine therapy should be discussed with a patient and family. Long-term studies of large medical registries, mostly in the USA and Scandinavia, have produced conflicting results about the risk of cancer after ^{131}I therapy [62–66]. Although an increase in overall risk of cancer has not been clearly demonstrated, there may be a small increase in the risk of solid tumors in tissues that may have the greatest iodine accumulation, such as stomach, kidney, and breast. A possible increased risk of thyroid cancer reported by some early studies probably reflects the use of relatively low doses of ^{131}I resulting in incomplete thyroid ablation [47]. Prior concerns regarding leukemia risk after radioiodine therapy for hyperthyroidism have not been confirmed with any of these more recent studies. In patients receiving radioiodine for treatment of an autonomous thyroid nodule, there is concern about the theoretical risk of radiation exposure to the rim of normal thyroid adjacent to the nodule. Because of this, it may be appropriate to delay radioiodine therapy of a thyroid nodule, possibly until the patient reaches adulthood.

Pregnancy is an absolute contraindication to radioiodine therapy, and pregnancy must

be excluded before a therapeutic dose of ^{131}I is administered to a female patient. Most hospitals have clear policies regarding the timing of pregnancy testing in female children before radioiodine therapy. Gonadal radiation dose is enhanced with accumulation of ^{131}I in the bladder, so patients should be encouraged to drink copiously during the first few days after radioiodine administration. There is no evidence of teratogenesis or other adverse outcomes in future offspring conceived after administration of radioiodine therapy. Many guidelines recommend that pregnancy be delayed for a period of time, typically 3–6 months, after therapy with ^{131}I [53]. Similarly, breastfeeding must be discontinued prior to radioiodine therapy. There is no contraindication to breastfeeding children that are born of subsequent pregnancies.

Radioiodine is not indicated for some forms of thyrotoxicosis. Radioiodine is not effective in the treatment of any form of thyroiditis. The minimal iodine uptake associated with thyroiditis means that little of the administered radioiodine would be taken up in the thyroid gland. More importantly, subacute thyroiditis and chronic thyroiditis are self-limited processes of thyroid inflammation, and treatment with ^{131}I will have little effect on the course of the disease.

Radioiodine therapy should never be used for acute treatment of thyroid storm. The beneficial effects of radioiodine therapy occur over months, which is not rapid enough to serve as a useful treatment of thyroid storm. The inflammatory response to radioiodine may cause release of additional thyroid hormone, which potentially could worsen the thyrotoxicosis. Many patients with thyroid storm will have received large doses of nonradioactive iodine in an attempt to transiently decrease thyroid hormone secretion (the Wolf-Chaikoff effect), which will limit thyroid uptake of administered radioiodine. Finally, administration of a therapeutic dose of radioiodine will necessitate radiation safety precautions, which may interfere with the intensive medical and nursing care needed by a patient with thyroid storm. Thus, requests for radioiodine therapy should be strongly resisted, and ^{131}I should never used for the acute treatment of thyroid storm.

Thyroid Nodules

Thyroid nodules, and their appropriate evaluation, are important because of the concern that they may represent thyroid cancer. Thyroid nodules are a frequent finding on physical examination. Incidental thyroid nodules can be identified on any study that includes the thyroid gland in the field of view, including neck ultrasound and chest CT. Up to one-third of all women in North America may have an identifiable thyroid nodule at some time in their lives. However, thyroid cancer is rare, with approximately 40,000 new cases per year diagnosed in the USA [67]. A thyroid nodule is more likely to represent thyroid cancer in the elderly and in children. Other risk factors that increase the likelihood of thyroid cancer include a hard, fixed nodule, lymphadenopathy, hoarseness, and dysphagia, but even most of these thyroid nodules will not be cancerous. Prior neck irradiation is a risk factor for thyroid cancer, but even with prior radiation therapy, there is only a 50 % likelihood that a thyroid nodule represents cancer. Therefore, the challenge is the effective and efficient evaluation of a large number of thyroid nodules to identify the small fraction that do represent thyroid cancer. Incidental thyroid nodules may be identified on FDG-PET [68, 69]. Little data is available for children, but for all ages, focal FDG uptake in the thyroid gland is quite likely to represent thyroid cancer and deserves further evaluation.

Thyroid scintigraphy has little role in the evaluation of most thyroid nodules [21, 70]. In the past, characterizing thyroid nodule activity by scintigraphy was an important part of determining the risk that the nodule represented thyroid cancer. An autonomous ("hot") nodule (Fig. 5.9) almost never represents thyroid cancer, while cancer cannot be excluded in a thyroid nodule with any other pattern ("not hot") of uptake. Thus, thyroid nodules with uptake that is less than ("cold", Fig. 5.12) or similar to ("warm," Fig. 5.10) normal thyroid tissue must undergo further evaluation to exclude cancer. Rarely, a hypofunctioning thyroid nodule may represent a parathyroid adenoma or metastases of a nonthyroidal cancer. Therefore, thyroid scintigraphy

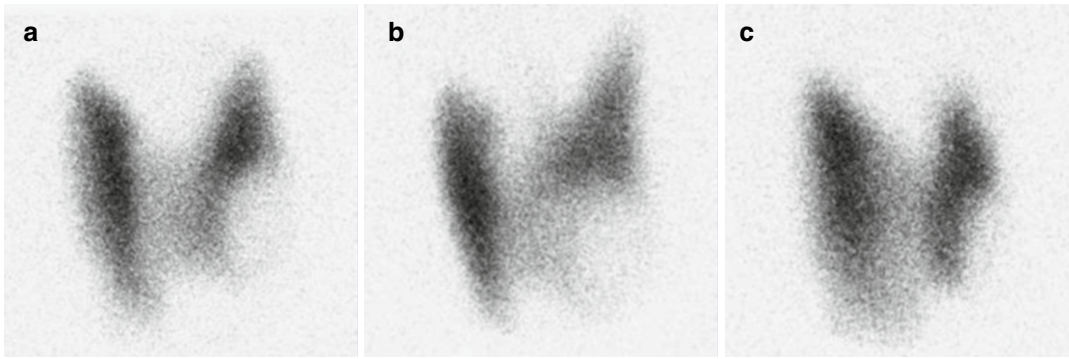

Fig. 5.12 Thyroid scintigraphy of a "cold" thyroid nodule. A 15-year-old female was found to have a thyroid nodule during a preoperative evaluation, and ultrasound confirmed a 2 cm nodule with mixed solid and cystic components in the lower pole of the left lobe of the thyroid gland. Thyroid function tests showed a TSH level of 0.95 mU/l (reference 0.7–5.0 mU/l). Iodine-123 scintigraphy was performed with pinhole images of the thyroid gland acquired in the anterior (**a**), left anterior oblique (**b**), and right anterior oblique (**c**) projection. The thyroid gland has a normal size and shape, with an ovoid region of photopenia corresponding to the palpable thyroid nodule in the lower pole of the left lobe. Radioiodine uptake was 11 % at 4 h and 28 % at 24 h. A surgical hemithyroidectomy was performed and the nodule had benign pathology

will be useful for excluding cancer in only the small fraction (<10 %) of thyroid nodules that have autonomous function. With hot nodules, the autonomous secretion of thyroid hormone from the nodule suppresses normal thyroid function by suppressing TSH secretion. Therefore, thyroid scintigraphy can be useful for thyroid nodule evaluation only in those patients with a suppressed TSH level. In all other cases, thyroid scintigraphy usually should not be performed, and a thyroid nodule should be evaluated by fine-needle aspiration, typically under ultrasound guidance. In the absence of a suppressed TSH level, thyroid scintigraphy should be considered only in unusual circumstances, such as a patient with a medical contraindication to fine-needle aspiration.

Thyroid Cancer

Nearly all thyroid cancer is categorized as differentiated thyroid cancer. Anaplastic thyroid cancer is exceedingly rare in children, but other uncommon forms of thyroid cancer, such as medullary thyroid cancer, can occur in children and young adults. The two major histological types of differentiated thyroid cancer are papillary thyroid cancer and follicular thyroid cancer. Most differentiated thyroid cancer is iodine avid and so can be imaged with radioiodine imaging and treated with ^{131}I.

Thyroid cancer is the most common endocrine malignancy in children and young adults. It represents over 3 % of all cancers diagnosed before the age of 20 years [67]. It is more common in teenagers than younger children, and it is five times more common in females than males. As in adults, the incidence of pediatric thyroid cancer has increased over the past few decades. Compared to adults, children with thyroid cancer are more likely to have widespread disease [71]. Although less common in children under the age of 10 years, thyroid cancer appears to be particularly aggressive in younger children, with higher rates of recurrence and mortality. Children are more likely than adults to have multifocal disease (up to 40 %) and disease spread to lymph nodes (greater than 50 %). Up to 30 % of all children with differentiated thyroid cancer will have distant metastatic disease, with half having metastases at the time of diagnosis. The most common site for distant metastases is the lungs. More than half the cases of lung metastases will

be micrometastases that are not evident of chest CT, but are detectable by radioiodine whole body scans [72]. Up to a third of thyroid cancer patients develop recurrent disease, and two-thirds of those will recur in the thyroid bed or cervical lymph nodes. However, one-third will recur with distant metastases, which is a risk factor for decreased survival [73].

Therapy of Thyroid Cancer

The primary treatment for thyroid cancer is surgical resection. Ideally, a near-total thyroidectomy will be performed. Compared to unilateral hemithyroidectomy, a bilateral thyroidectomy is associated with a lower rate of disease recurrence and an improved tumor-free survival rate [74, 75]. In some centers, patients with a lower risk of cancer may have surgical resection of the primary nodule and a hemithyroidectomy, with a completion thyroidectomy performed only if histology demonstrates cancer. Adjuvant chemotherapy or external beam radiation has little benefit for the treatment of differentiated thyroid cancer. Effective post-thyroidectomy treatments include TSH suppression with levothyroxine, surgical re-exploration of the neck, and ^{131}I therapy. Iodine-131 therapy increases recurrence-free survival and may increase overall survival. Iodine-131 is used for three indications: ablation of a thyroid remnant, treatment of residual disease, and treatment of metastatic disease.

Radioiodine ablation of postsurgical remnant thyroid tissue decreases recurrence of differentiated thyroid cancer [71, 76, 77], probably by treating microscopic sites of disease. Remnant ablation also facilitates post-therapy scanning for detecting disease and permits serum thyroglobulin to be used as a noninvasive marker to assess for disease recurrence [26]. Most guidelines recommend radioiodine remnant ablation in all except the very lowest-risk patients. These very low-risk patients are those who had a complete thyroidectomy with favorable histology, a single small (e.g., less than 1 cm) tumor, no local invasion, and no lymph node involvement. The typical adult ^{131}I dose for remnant ablation is 30–100 mCi, which can be scaled by patient size for younger patients [78]. However, treatment with less than 30 mCi is associated with a high failure rate, which results in the patient requiring a second dose of ^{131}I for remnant ablation [73]. In patients with known locoregional disease, remnant ablation can be combined with the first radioiodine therapy administered with therapeutic intent.

For treatment of residual neck disease or metastatic disease, the administered dose of ^{131}I is a clinical and dosimetric decision. The administered dose may depend on histology, extent of disease, location of metastases (lymph nodes, lung, or bone), and any prior therapy. There are multiple empiric approaches for determining the dose of ^{131}I [79], but most approaches typically use an adult dose of between 100 and 300 mCi per administration, which can be scaled based on patient size [78]. There is a wide variation in the frequency of ^{131}I treatment, but, for most patients, repeated radioiodine therapy is performed as long as iodine-avid disease is present. For physicians with limited experience in treating thyroid cancer, particularly in children, the most appropriate approach may be to provide treatment in collaboration with a more experienced physician or by referral to an institution with expertise in pediatric thyroid cancer.

An elevated circulating TSH level (typically greater than 30 mIU/ml) is needed to ensure adequate uptake of a therapeutic ^{131}I dose. This can be accomplished by withdrawing thyroid hormone replacement therapy for approximately 2–6 weeks prior to the anticipated treatment date. Although some adults may require up to 6 weeks to reach an adequate TSH level, young children may require as little as 1–2 weeks. Typically, thyroid hormone withdrawal is managed by the referring or treating physician. Patients and families should be advised that the patient will develop some symptoms of hypothyroidism during this time. If thyroid hormone will be withdrawn for a long period of time, some clinicians will treat with triiodothyronine (T3) for the first few weeks of thyroid hormone withdrawal [23]. As T3 has a shorter half-life than T4, it can be withdrawn 2 weeks before the planned therapy.

However, this rarely needs to be done in children. Adequate elevation of the circulating TSH level to greater than 30 mIU/l can be confirmed with a TSH blood level measured a day or two before pre-therapy imaging or administration of radioiodine. When recombinant TSH was available, some clinicians used it for preparation for radioiodine therapy in children, although the efficacy of this approach was never fully validated in this age group [19, 80].

Achieving a low-iodine state is important for ensuring that there is optimal uptake of radioiodine by thyroid cancer cells. Therefore, patients should avoid iodine intake (Table 5.1) and be placed on a low-iodine diet for 7–14 days before imaging or therapy. If there is any doubt about the success of iodine restriction, iodine economy can be assessed by measuring urinary excretion of iodine. This can be most accurately measured in a 24-h collection. Alternatively, iodine excretion can be estimated with the simultaneous measurement of iodine and creatinine in a random urine sample [18]. If urinary iodine excretion exceeds 50 mcg/day, then the patient probably has not reached an optimal low-iodine state [19].

Pregnancy is an absolute contraindication to radioiodine therapy, and a quantitative serum hCG level should be measured within 24–48 h before administration of radioiodine to any female patient at risk for pregnancy. Most institutions have established policies for determining which female patients must have a pregnancy test prior to radioiodine administration. For example, the policy may require pregnancy testing in all female patients determined to be post-menarchal by history or in all female patients older than age 10 years. Breastfeeding must be discontinued, preferably with adequate lead-time to allow involution of breast tissue, which will limit radioiodine uptake by the breasts. Breastfeeding cannot be resumed for the same child but can be done after any subsequent deliveries [19].

Many of the potential complications and long-term risks of radioiodine therapy for thyroid cancer are similar to those for treatment of hyperthyroidism. Patients should understand the lifelong need to take thyroid hormone replacement, usually at doses that will suppress TSH. Antiemetics can be useful, particularly with higher doses of radioiodine, which may be associated with nausea and vomiting [19]. Determinant (dose-dependent) risks of higher dose ^{131}I therapy include sialadenitis, xerophthalmia, and bone marrow suppression. Occasionally, there may be increased local radiation dose near sites of metastatic uptake, for example, brain and lungs, or near sites of a thyroid remnant or locoregional disease in the neck, and this may cause local tissue swelling [81]. The critical organs for radiation dose are bone marrow and sites of metastatic disease. The aim is to provide the largest effective radiation dose to sites of disease while avoiding bone marrow suppression or pulmonary fibrosis. Formal dosimetry may be useful in some cases, particularly in patients with extensive lung metastases [82, 83]. Although formal dosimetry typically has been performed with ^{131}I whole body scans, PET or PET/CT with ^{124}I may become an alternative for pre-therapy planning [10, 84].

In females, high-dose radioiodine therapy may be associated with earlier menopause [85]. In males, repeated administration of radioiodine may be associated with impaired spermatogenesis [86], leading some clinicians to suggest sperm banking if the cumulative dose of ^{131}I is likely to exceed 14 GBq (378 mCi) [71, 87]. There is no evidence of increased malformations or malignancy in offspring of males or females treated with radioiodine [71, 81]. Many guidelines recommend that pregnancy be delayed for at least 6 months after radioiodine therapy, but there is little data to support concerns that residual ^{131}I could harm a fetus conceived after radioiodine administration. However, due to normal alterations in thyroid hormone replacement needs during pregnancy [88], it may be prudent to delay pregnancy until the thyroid hormone replacement dose has been stabilized [81].

In patients treated with radioiodine for thyroid cancer, the risk of second primary malignancy is a concern. However, this is complicated by an increased risk of malignancy in patients with thyroid cancer, independent of therapy, and ascertainment bias [71, 89]. The few long-term

studies that specifically address the risk to individuals treated as children have not documented an increased risk [90]. In larger studies, including patients of all ages, radiation-related leukemia is rare but has been reported after high-dose (typically greater than a cumulative dose of 500 mCi) radioiodine therapy in a small number of cases [81]. Overall, there may be a slightly increased risk of tumors of the salivary glands, gastrointestinal tract, and soft tissue in adults receiving radioiodine for treatment of thyroid cancer [71, 81, 89].

Whole Body Scans in the Management of Thyroid Cancer

The utility of a diagnostic whole body scan (Fig. 5.13) in the management of thyroid cancer remains controversial [19, 21, 22]. A diagnostic whole body scan may be most useful in two circumstances (1) before planned therapy, when the amount of remnant thyroid tissue cannot be determined by the surgical report or ultrasound or (2) for surveillance, when the results will clearly affect the decision to administer radioiodine or the dose of radioiodine. Diagnostic

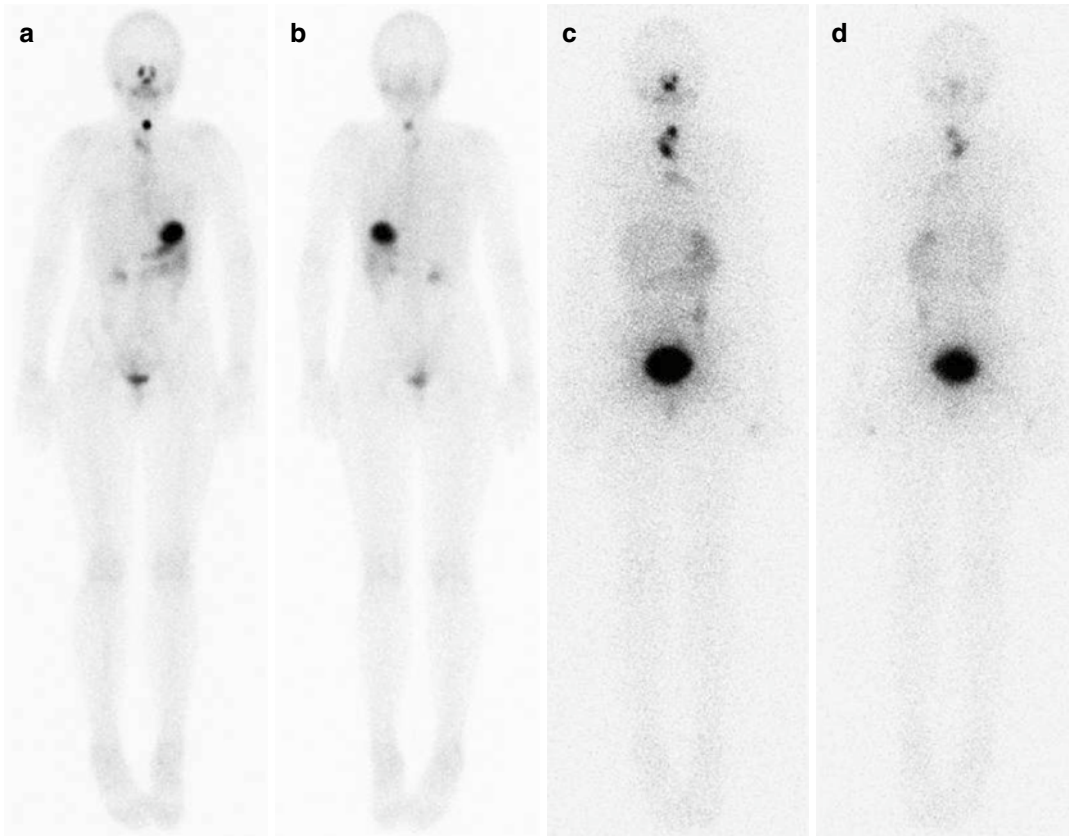

Fig. 5.13 Diagnostic and post-therapy whole body scintigraphy for thyroid cancer. A 14-year-old female with papillary thyroid cancer underwent near-total surgical thyroidectomy. Three months later, diagnostic whole body scintigraphy was performed with ^{123}I. Images acquired in the anterior (**a**) and posterior (**b**) projections demonstrate a poorly defined region of uptake in the lower right thyroid bed and an intense focus of uptake in the upper midline of the neck. Localization was confirmed with a marker at the suprasternal notch. Normal physiological accumulation of ^{123}I is seen in the lacrimal glands and nasal secretions, salivary glands and mouth, stomach, bowel, and bladder. Five days after treatment with 64 mCi ^{131}I, a post-therapy whole body scan was performed. Images acquired in the anterior (**c**) and posterior (**d**) projections demonstrate intense uptake in the remnant thyroid tissue in the neck. Physiological accumulation of ^{131}I is seen in lacrimal glands and nasal secretions, salivary glands and mouth, thymus, liver, and bowel. Intense uptake in the pelvis is in the sigmoid colon and rectum

whole body scans are not recommended for routine use in all patients by current guidelines of the American Thyroid Association [21]. However, advocates argue that pre-therapy whole body scans have the potential to provide unexpected information that may change care for many patients [22]. Primarily, this has included patients in whom identification of unexpected distant metastases leads to a decision to appropriately increase the ^{131}I dose. Pre-therapy diagnostic scans also may benefit patients found to have large thyroid remnants or unanticipated cervical lymph node metastases, as they may be advised to undergo repeat surgery before radioiodine therapy. Rarely, diagnostic scans can identify unexpected metastatic disease in the brain or spinal cord, which may require pretreatment with corticosteroids to limit post-therapy swelling [19].

Post-therapy scans will demonstrate uptake of radioiodine at sites of iodine-avid disease [21, 23, 26–28]. Approximately 10 % of patients will have iodine-avid disease identified on post-therapy whole body scan that was not apparent on the pre-therapy whole body scan [23, 26]. The post-therapy scan may be most useful in patients with elevated thyroglobulin levels and a negative diagnostic whole body scan [27]. Up to half of these individuals may be shown to have iodine-avid metastases to lung (Fig. 5.14) or bone [26, 28]. Therefore, a post-therapy whole body scan is recommended by the clinical guidelines of the American Thyroid Association [21] and American Association of Clinical Endocrinology [26].

Evaluation and Follow-Up of Patients with Thyroid Cancer

The risk of recurrence of thyroid cancer has been reported to be between 15 % [91] and 30 % [92], with the wide range likely reflecting differences in the aggressiveness of primary therapy. Age also is a risk factor for recurrence, with younger age associated with a higher risk of recurrence [73]. A third of all patients with recurrent thyroid cancer will have distant metastatic disease. Therefore, the evaluation and surveillance of patients with thyroid cancer depends on being able to detect recurrence and to localize sites of distant disease. The appropriate strategy for following patients with thyroid cancer can vary among institutions and treating physicians and is best guided by clinical guidelines developed by professional organizations, including the Society of Nuclear Medicine and Molecular Imaging [19], the American Thyroid Association [21], and the American Association of Clinical Endocrinologists and American College of Endocrinology [26]. Although there may be some variations among these guidelines, they represent the consensus opinions of clinical experts guided by the current medical literature. These guidelines recommend post-therapy surveillance with some combination of serum thyroglobulin and whole body radioiodine imaging (Figs. 5.13, 5.14, and 5.15), with the addition of neck ultrasound and chest CT when needed. The appropriate approach to long-term surveillance depends upon the risk of having persistent or recurrent disease [21].

Thyroglobulin is produced only by thyroid tissue, so serum thyroglobulin serves as a sensitive indicator of the presence of thyroid tissue. Therefore, after radioiodine ablation of normal thyroid tissue, serum thyroglobulin level can be used as a tool to follow thyroid cancer. In a patient with prior thyroid remnant ablation, serum thyroglobulin should be undetectable (<2 ng/ml) after TSH stimulation, and a rising serum thyroglobulin level is a sign of persistent or recurrent thyroid cancer [21, 93, 94]. The appropriate approach to evaluating a patient with a rising thyroglobulin level depends on the prior history of the patient but could include neck ultrasound, chest radiograph/CT, or whole body radioiodine scintigraphy.

Management of Non-iodine-avid Thyroid Cancer

Some patients with a rising serum thyroglobulin will have no iodine-avid disease identified with whole body radioiodine scanning. This so-called Thyroglobulin Elevation, Non-Iodine-avid Syndrome (TENIS) [94] is a management challenge. One approach is therapeutic administration of a relatively large dose of ^{131}I with the goal of treating disease that was not apparent on whole

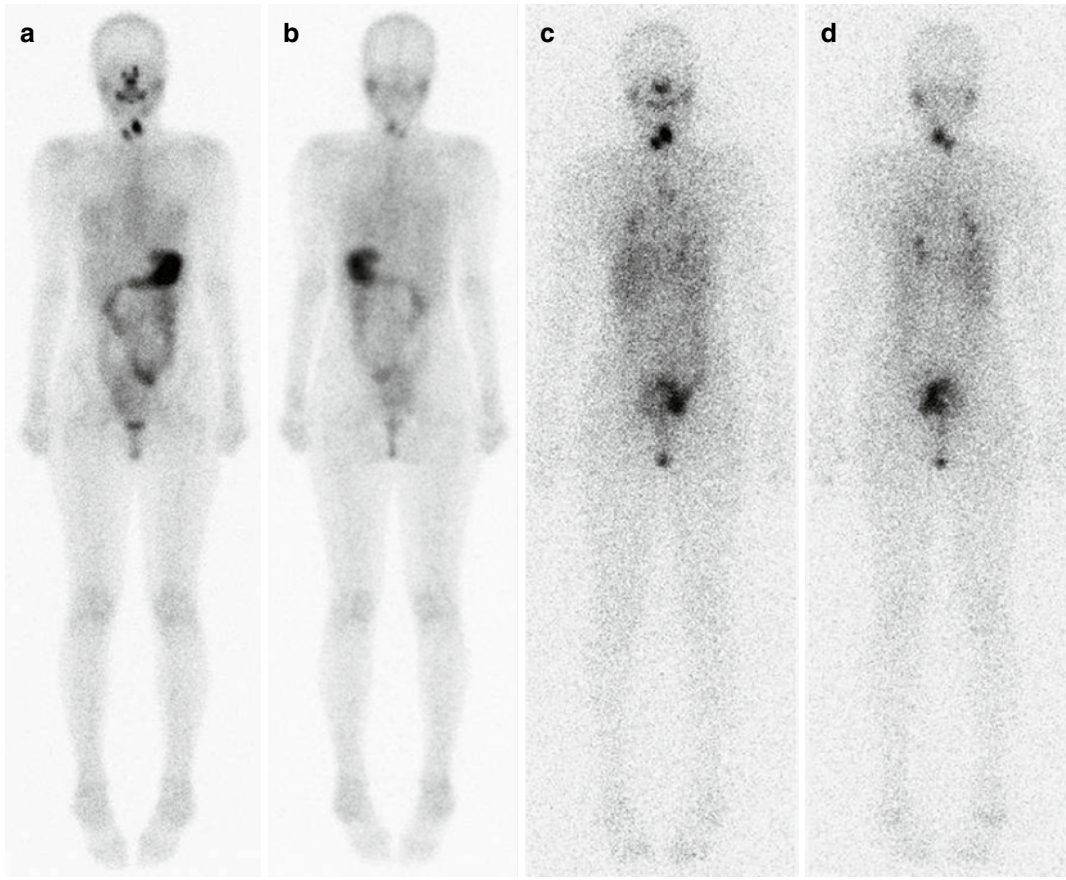

Fig. 5.14 Diagnostic and post-therapy whole body scintigraphy for metastatic thyroid cancer. A 15-year-old girl with papillary thyroid cancer underwent near-total surgical thyroidectomy, which showed disease involvement in multiple cervical lymph nodes. Six weeks later, diagnostic whole body scintigraphy was performed with ^{123}I. Images acquired in the anterior (**a**) and posterior (**b**) projections show physiological tracer accumulation is seen in the lacrimal glands and nasal secretions, salivary glands and oral secretions, breasts, stomach, bowel, and bladder. Focal uptake on each side of the thyroid bed could represent remnant thyroid tissue or metastatic disease in cervical lymph nodes, but ultrasound identified no abnormal cervical lymph nodes, and the patient was treated with 100 mCi ^{131}I. Six days later, a post-therapy whole body scan in anterior (**c**) and posterior (**d**) projections shows expected uptake in the neck. Multiple foci of uptake in the chest are consistent with multiple lung metastases. Physiological accumulation of ^{131}I is seen in nasal secretions, salivary glands and oral secretions, liver, and bowel. These findings demonstrate visualization of metastatic sites of iodine-avid disease on the post-therapy whole body scan that could not be detected on the pre-therapy diagnostic whole body scan

body scan due to either small size or diminished (but not absent) iodine avidity. The post-therapy whole body scan may detect sites of disease not detected on the pre-therapy diagnostic scan [23, 27, 28]. Imaging with neck ultrasound and chest CT may identify sites of non-iodine-avid disease, and surgical resection may be a good option for non-iodine-avid disease in cervical lymph nodes. More recently, FDG-PET has been used to evaluate patients with TENIS. FDG-PET also may be helpful when anatomic imaging, such as chest CT, indicates progressive disease, despite diminished uptake on whole body radioiodine scan (Figs. 5.15 and 5.16). In general, as iodine avidity decreases, FDG avidity increases, probably reflecting de-differentiation of tumor cells and loss of sodium-iodide symporter expression. Patients with FDG-avid thyroid cancer have decreased

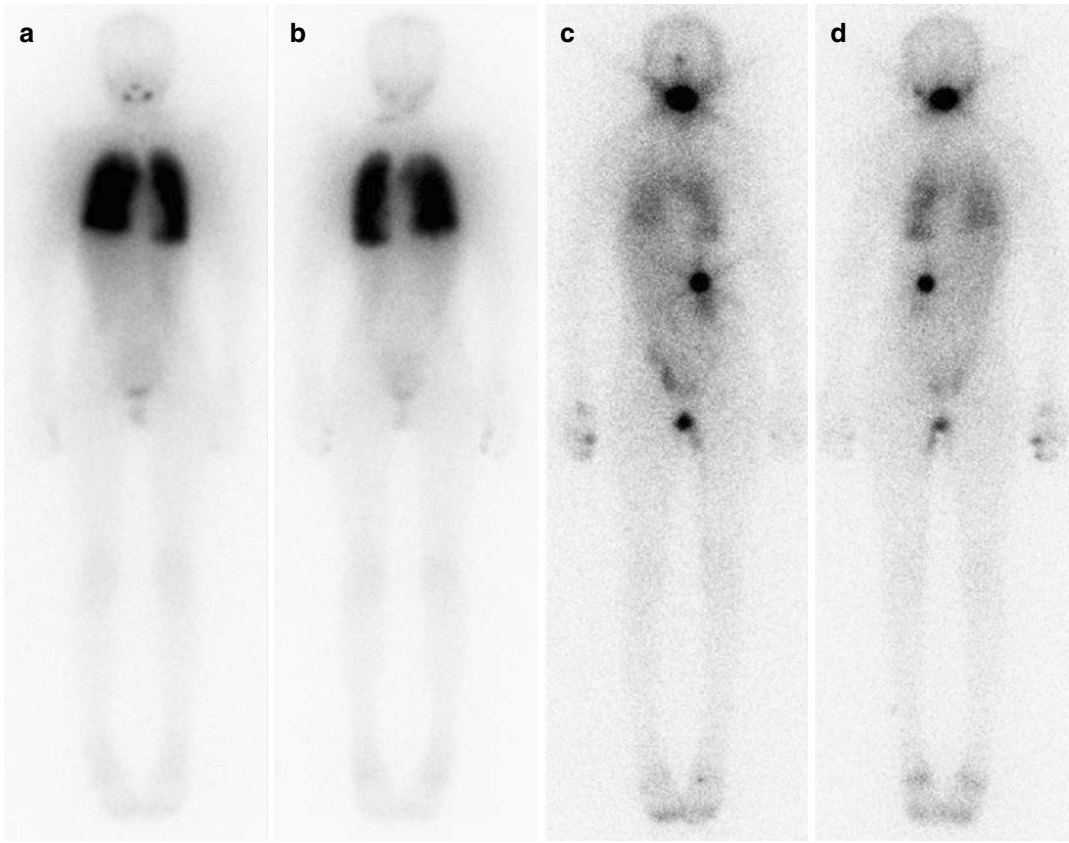

Fig. 5.15 Post-therapy whole body scintigraphy demonstrating loss of iodine avidity in metastatic thyroid cancer. A 12-year-old girl with metastatic thyroid cancer previously had been treated with 50 mCi ^{131}I and then was referred for further management and therapy. A post-therapy whole body scan performed in anterior (**a**) and posterior (**b**) projections 6 days after administration of 203 mCi ^{131}I shows intense uptake throughout both lungs, consistent with extensive metastatic disease seen on chest CT. Little uptake is identified elsewhere in the body. Because of persistent elevation in serum thyroglobulin and progression of lung disease demonstrated on chest CT 11 months later, whole body dosimetry was performed and the patient was again treated with radioiodine. Seven days after oral administration of 327 mCi, a post-therapy whole body scan was performed in anterior (**c**) and posterior (**d**) projections. Physiological accumulation of radioiodine is seen in the nasal secretions, mouth, liver, and bowel. A percutaneous gastrostomy had been placed due to frequent vomiting, and intense radioiodine accumulation is present in the mouth and on the gastrostomy. Uptake in the lungs is more heterogeneous and less intense than on the prior post-therapy scan, despite progression of disease identified by chest CT. These findings suggested that, since the previous radioiodine therapy, papillary thyroid carcinoma metastatic to the lungs had lost iodine avidity

survival compared to patients with iodine-avid disease [95]. This reflects the loss of effective therapy with radioiodine, but also likely reflects the poorer prognosis of de-differentiated disease.

Incidental Findings on FDG-PET

Large screening studies in apparently healthy adults have reported a prevalence of incidental thyroid uptake of up to 3 % [68, 69]. About half of these (1.5 %) will have focal uptake, of which 15–50 % will be found to represent thyroid cancer. Rarely, focal thyroid uptake may represent metastatic disease [96]. Diffuse ^{18}F-FDG uptake typically represents autoimmune thyroiditis, and uptake may not be affected by thyroid hormone replacement therapy [97]. Postradiation thyroiditis may be common among the patients undergoing imaging with FDG-PET.

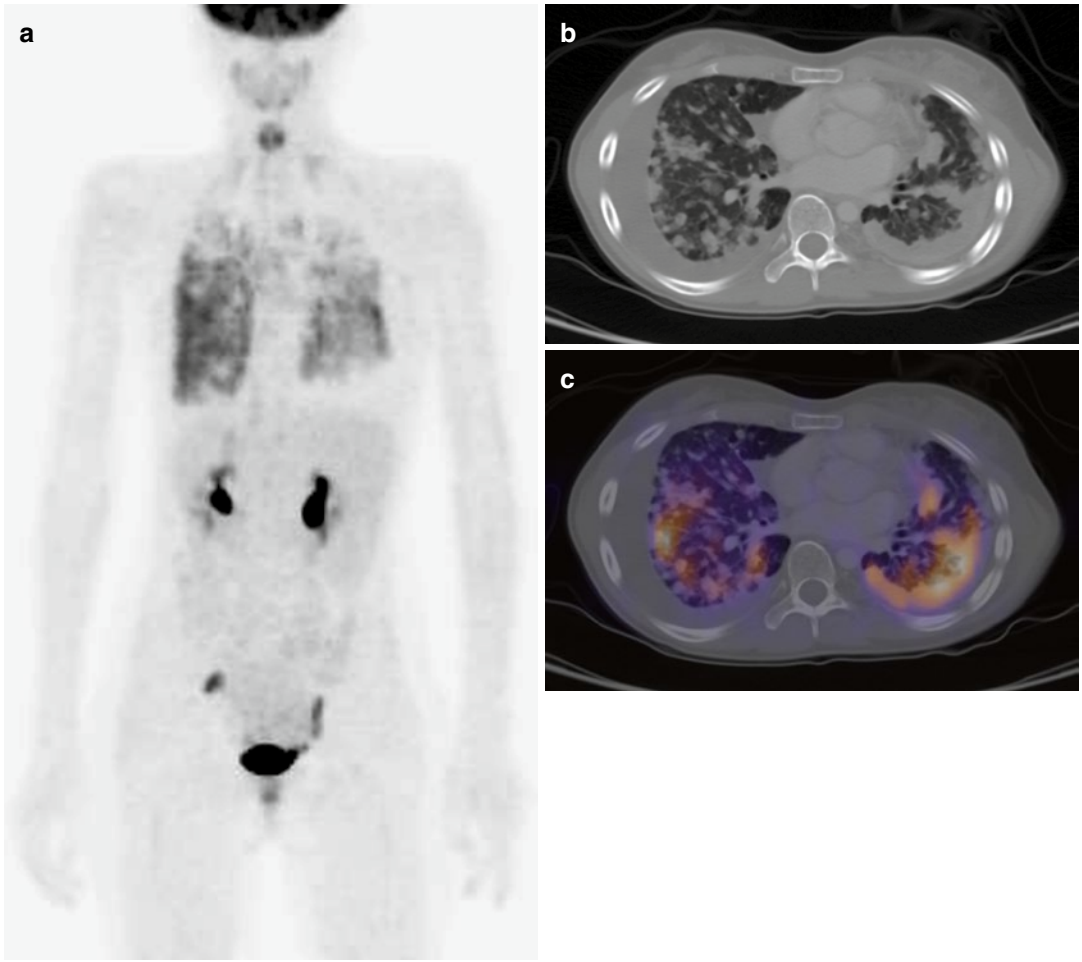

Fig. 5.16 ^{18}F-FDG PET of metastatic thyroid cancer. In a 13-year-old girl with metastatic thyroid cancer (see Fig. 5.15), decreasing radioiodine uptake in lung metastases despite progression of disease suggested that the metastases were losing iodine avidity. An ^{18}F-FDG PET was performed. A maximum intensity projection of the PET (**a**) demonstrated abnormal moderate heterogeneous uptake in both lungs. This corresponds to widespread metastatic disease identified by CT scan (**b**) in both lungs. Co-registration of PET and CT images (c) confirms abnormal uptake in widespread metastases. Note absent FDG uptake in bilateral pleural effusions. These findings in Figs. 5.15 and 5.16 demonstrate FDG avidity in metastatic thyroid carcinoma that had developed decreasing iodine avidity

Less commonly, diffuse ^{18}F-FDG uptake may reflect Graves' disease or malignancy [98]. Therefore, thyroid uptake of FDG frequently represents significant thyroid disease, and referring clinicians should be made aware of this potentially important finding. Although it may not the first clinical priority in all patients imaged with FDG-PET, the patient may benefit from further diagnostic evaluation and therapy [99].

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