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Differentiated Pediatric Thyroid Cancer: Correlates With Adult Disease, Controversies in Treatment

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The biologic behavior of differentiated thyroid cancer can differ between adults and children, especially in those children younger than 10 years of age. Unlike adults, young children typically present with advanced disease at diagnosis. Despite this, children respond rapidly to therapy and have an excellent prognosis that is significantly better than that of their adult counterparts with advanced disease. In contradistinction to adults, children with thyroid cancer also have higher local and distant disease recurrences with progression-free survival of only 70% at 5 years, mandating life-long surveillance. Although thyroid cancer is the most common carcinoma in children, overall incidence is low, a factor that has prevented performance of a controlled, randomized, prospective study to determine the most efficacious treatment regimen in this age group. So, although extensively investigated, treatment of pediatric patients with differentiated thyroid cancer remains controversial. This article reviews the current controversies in the treatment of pediatric differentiated thyroid cancer, focusing on issues of optimal initial and subsequent therapy as well as that of long-term follow-up. Our approach to treatment is presented. In so doing, similarities and differences between adults and children with differentiated thyroid cancer as regards unique considerations in epidemiology, diagnosis, staging, treatment, therapy-related late effects, and disease surveillance are presented. The expanding use of and appropriate roles for thyrogen and fluorine-18-fluorodeoxyglucose positron emission tomography in disease evaluation and surveillance will be addressed.
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Thyroid cancer is the most common endocrine malignancy, comprising 1% to 2% of all malignancies and 5% to 6% of the head and neck malignancies.[1] There are wide interethnic and geographic variations in the incidence of thyroid cancer. There are approximately 100 cases of thyroid cancer per million adults, which translates into 14,000 to 17,000 new cases per year in the United States. There is a 1% associated cancer mortality resulting in 1,200 thyroid cancer deaths per year.[2] Although the majority of patients with thyroid cancer are adults, a substantial number of patients are children, making it a not uncommon childhood malignancy.[3]

There are 4 histological types of thyroid cancer: papillary (PTC), follicular (including Hurtle cell), medullary (MTC), and anaplastic. Papillary and follicular (FTC) thyroid carcinomas are commonly referred to as the well-differentiated carcinomas (DTCs) and arise from follicular cells. These cancers are the focus of this review. In adults, the papillary subtype comprises 80% of all thyroid cancers.[1] Mean age at presentation occurs in the third decade of life. The tumor is typically unencapsulated. Cervical lymph node metastases occur in 30% to 40%; distant metastases are present in 2% to 14%. Multifocal disease is common, ranging from 30% to 85% depending on whether on routine versus thin histologic sectioning has been performed; bilateral disease is present in 33%. Overall survival in papillary thyroid cancer is 90% at 20 years.

As medullary and anaplastic thyroid cancer are sometimes mistakenly referred to nuclear medicine departments for treatment, it is important to recognize that radioiodine imaging and therapy are not appropriate for these tumors.[1] Medullary carcinoma arises in the parafollicular or C-cells of the thyroid and manufactures calcitonin.[4] Because these cancers do not arise from cells involved in thyroid hormone production, these cancers are not iodine-avid and, therefore, radioiodine does not play a role in either the diagnosis or manage-

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ment of these patients. Similarly, anaplastic thyroid carcinomas, occurring in 4% to 10% of thyroid cancers, are poorly differentiated and almost never iodine avid.[1] Aggressive chemotherapy and external beam radiotherapy, and not radioiodine, comprise the treatment regimen. Anaplastic thyroid cancer is one of the most aggressive tumor types with death occurring at a mean of 6 months post diagnosis.

Pediatric Thyroid Cancer

Ten percent of all cases of thyroid cancer occur in patients younger than 21 years of age.[3,5] There is an increased incidence in occurrence with puberty, but thyroid cancer can occur at any age.[6-9] In England and Wales, there are 0.19 cases/million/year in those up to age 14 years; this increases to 3 cases/million/year between the ages of 15 and 25 years.[5,6] In the United States, overall incidence rate for pediatric thyroid cancer is 5 cases/million/year in those younger than 19 years with 350 cases of thyroid cancer diagnosed in children each year. Thyroid cancer accounts for less than 1% of all cancers in those younger than 10 years; 3.6% of cancers in those aged 10 to 14 years and 7.8% of cancers in those aged 15 to 19 years.[9-11]

The biologic behavior of thyroid cancer can differ significantly between adults and children.[3,7,8,12,13] The majority of pediatric thyroid cancers are of the well differentiated papillary or follicular subtype. The pediatric cancers are most often iodine-avid and often highly TSH-sensitive. Medullary thyroid carcinoma is uncommon in children and, although typically associated with multiple endocrine neoplasia type 2 (MEN2), can occur sporadically or as familial MTC without other associated endocrine abnormalities.[14]

Female to male incidence ratios in those with pediatric thyroid cancer vary according to age and range from 1.2 to 1.6:1 in those younger 5 to 9 years of age; to 3.3:1 in those ages 10 to 14 years and 5.2:1 in those ages 15 to 19 years of age.[10] Harach[6] concurs citing a female to male ratio of 1.2:1 in children <10 years, increasing to 3.6:1 in the older child with differentiated thyroid carcinoma compared with a 3:1 female to male incidence ratio in adults.

Unlike adults, children typically present with advanced disease at diagnosis. Extensive regional nodal involvement occurs in 60% to 80% of pediatric thyroid cancers; there is a higher incidence of distant metastases as well.[3,6-8,12,13,15-26] Between 10% and 20% of children with thyroid cancer will have lung metastases at diagnosis; bone metastases are rare, accounting for less than 5%. Unfortunately, children also have higher local and distant recurrence rates for thyroid cancer than do adults.[7,12,15]

Children with thyroid cancer have a rapid response to therapy. Prognosis is excellent, with a 10-year mortality of <10% and an overall survival of 95% at 20 years.[3,16] Even in the face of distant metastases, the usually iodine-sensitive disease of children is much less likely to be fatal than comparable disease in adults, where 5 year survival in patients with distant metastases is 40% and 10-year survival is 20%. Although the pediatric disease is not commonly fatal, it can be persistent or recur. Progression free survival in children is only 65% to 70% at 5 years.[27-30]

Pathogenesis; Predisposing Factors

The majorities of thyroid cancers do not have a known genetic basis and arise sporadically. An increasing understanding of the molecular biology of cancer, and more specifically of thyroid cancer, is elucidating some of the biological factors underlying thyroid cancer behavior.[31-33] As in other cancers, aberrant activation of growth-stimulating molecular pathways appears to be an important component of many thyroid cancers, especially those with more aggressive and resistant behavior. Some thyroid cancers exhibit aberrant expression of growth factors, for instance, activation of RET or TRK signaling pathways, BRAF mutations, or 3p25 rearrangements of peroxisome proliferators-activated receptor gamma gene. In some cases, these differences have been exploited to direct targeted therapy for iodine-resistant cancers.[32,34] However, in the vast majority of thyroid cancers, the etiology of these abnormalities is unknown.

Recent molecular genetic papers suggest that exposure to ionizing radiation is associated with genetic changes that activate oncogenes in thyroid tissue. Although the exact mechanism was unknown, the association between the development of thyroid cancer and irradiation (XRT) to the head and neck was first reported by Duffy and Fitzgerald in the 1950s.[13] This association has been confirmed in numerous subsequent studies and well documented in survivors of atomic bomb exposures in Japan and of radioactive fallout in Nevada and the Marshall Islands.[35-38] Winship and Rosvoll,[15] in a review of 878 cases of pediatric thyroid cancer from the world literature and their own observations, determined that the latency period between XRT and the development of thyroid cancer averaged 8.5 years but that the cancer risk continued for up to 30 years after radiation exposure. The risk of development of thyroid cancer was greatest when exposure to ionizing radiation occurred at a younger age, in females, when there were greater thyrotropin (TSH) levels at time of exposure and with higher radiation rates.[39] Some of these risk factors were confirmed in studies after the Chernobyl incident in 1986, which demonstrated a 100-fold increase in the incidence of pediatric thyroid carcinoma in exposed populations.[40,41]

Thyroid radiation exposure can come as a result of radiotherapy of another cancer, for example, Hodgkins disease in the neck or mediastinum, or by accidental exposure to radionuclides, as in the case of Chernobyl. These types of exposures have been shown to be associated with an increased incidence of development of secondary cancers including, but not limited to, thyroid cancer.[42-46] For example, the overall incidence of secondary cancers in those treated with prior XRT or chemotherapy is 3% to 12%. Tucker and coworkers[43] demonstrated a 53-fold increased risk of thyroid cancer in those who had survived 2 or more years from the diagnosis of childhood cancer (Fig. 1). There is also an increased risk of development of secondary tumors in immunosuppressed patients, for instance, after bone marrow (BMT) or organ trans-

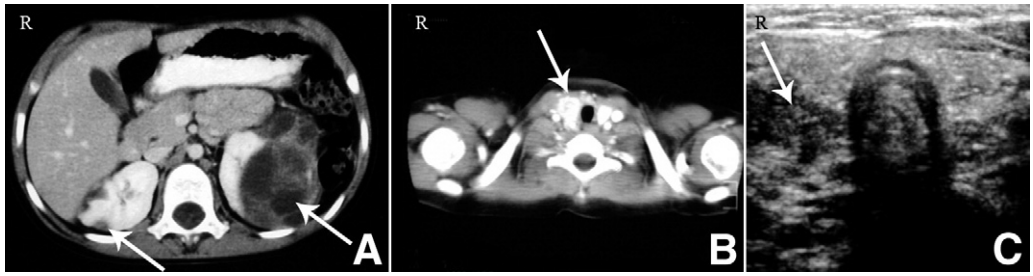

Figure 1 (A) Six years after the diagnosis and treatment of bilateral Wilms tumor (arrows, axial CT) and 2 years after renal transplant, surveillance CT demonstrates a asymptomatic mass in the right lobe of the thyroid (B) (arrow, axial CT). Ultrasound guided biopsy of the hypoechoic solid mass in the right lobe of the thyroid gland (C) (arrow, transverse image from thyroid ultrasound) confirmed papillary thyroid carcinoma. Survivors of childhood cancer, immunosuppressed patients after organ or bone marrow transplant, and those who received thyroid radiation as a result of radiotherapy of another cancer—in this case, whole lung irradiation for pulmonary metastases from bilateral Wilms tumor—are at significantly increased risk for the development of a secondary thyroid cancer.

plant.[47-49] In this patient population, the risk of development of secondary tumors increases to 36 times that of the normal population if patient age was less than 4 years at time of treatment; is 4 times that of the normal population if XRT dose was greater than 10GY, and is 8 times that of the normal population by 10 years after BMT.[47,48]

Clinical Presentation

Pediatric thyroid cancer clinically presents as one or more asymptomatic neck masses.[22,23,25] Although 4% to 7% of adults have palpable thyroid nodules, only 5% of these nodules are malignant. On the other hand, only 1% to 2% of children have thyroid nodules but 33% to 50% of these nodules are malignant. The incidence of cancer in surgically removed solitary thyroid nodules in children ranges from 14% to 61%, averaging about 30%.[50-53] The likelihood of malignancy increases if there has been rapid growth of a thyroid nodule, if the mass is hard, adherent to surrounding tissues, associated with cervical lymphadenopathy, vocal cord paralysis or if there has been a previous history of head and neck irradiation.[54,55]

Diagnosis

In both adults and children, the diagnosis of thyroid carcinoma is based on history, physical examination, laboratory studies, imaging and biopsy-either excisional, or using fine needle aspiration (FNA). FNA is the preferred method of diagnosis, if possible, as it allows for appropriate surgical planning for thyroid cancer.[56] Surgical biopsy most often entails a thyroid lobectomy and may require a second surgery if a diagnosis of cancer cannot be made intraoperatively.

The duration and severity of symptoms, including those of hyper or hypothyroidism; the presence of fever, pain, swelling, or erythema; change in size or shape of the neck mass; and the association with intercurrent acute illness or trauma should be noted. Patient exposure to radiation or goitrogens and familial occurrence of thyroid disease or tumor syndromes should be elicited. Physical examination should document whether the neck mass is tender or hard, located at midline or laterally; its association with the thyroid gland, its mobility, and the presence of lymphadenopathy. Focused evaluation of the thyroid gland should be performed.[57]

Laboratory evaluation should include serum triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), and possibly antithyroid antibody levels. Calcitonin levels are mandated in those with MCT and C-cell hyperplasia; DNA analysis for Ret mutation particularly in those suspected of MEN2 and genetic testing at birth or no later than 1 year for those at risk for MEN2B and MEN2A, respectively.[58]

Anatomic imaging with ultrasound helps to distinguish cystic from solid thyroid lesions without the use of ionizing radiation and is therefore helpful in the evaluation of thyroid nodules. Although cystic thyroid nodules are typically benign, as many as 50% of malignant lesions have a cystic component[59] and as many as 8% of cystic lesions represent malignancies.[60] Ultrasound is also used in detection of nonpalpable nodules and to guide needle biopsies in those with solid nodules. Figures 2 to 4 show some examples of thyroid cancer images at presentation.

Technetium-99m pertechnetate (TcO_4) and Iodine-123 radionuclide scanning are commonly used in the diagnostic evaluation of thyroid nodules, where a "cold" nodule, that is, one with uptake less than normal thyroid tissue, may indicate a thyroid cancer.[51] However, only a minority of cold lesions are thyroid cancer, as opposed to benign lesions. Furthermore, in the absence of clinical or biochemical evidence of hyperthyroidism, most nodules will be either cold or at a similar level to the normal thyroid, and therefore not helpful in ruling out thyroid cancer. The use of thyroid radionuclide scanning for adult patients with thyroid nodules is best reserved for one of two classes of patients[51]: (1) patients with suspected hyperthyroidism or (2) those with extensive multinodular goiters. In the former group, an overactive or "hot" nodule indicates a functioning adenoma, which is only very rarely thyroid cancer, and for which biopsy is not indicated unless there has been evidence of growth. In the latter group, the identification of a "dominant" cold nodule may help direct biopsy in patients with a large number of nodules. I-123 imaging may be indicated in the further evaluation of a "warm" nodule identified on TcO4 scans as discordant nod-

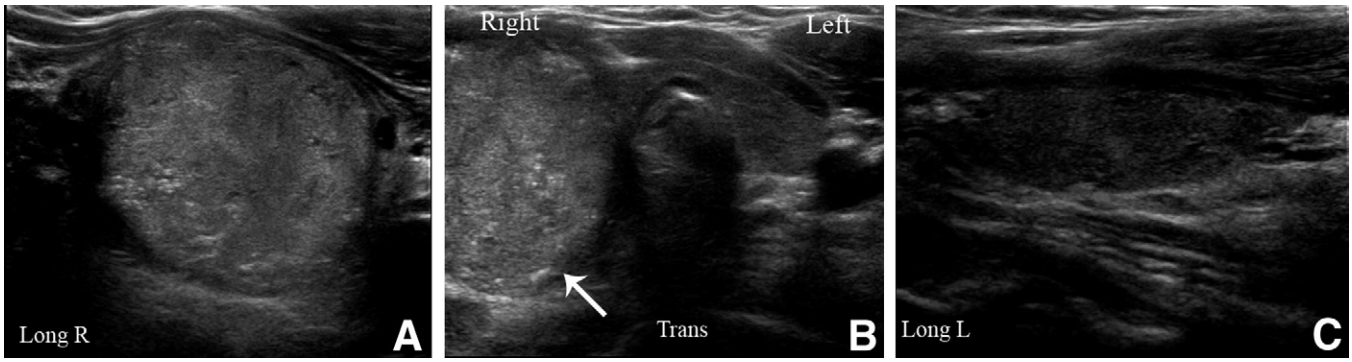

Figure 2 Longitudinal right (A); transverse (B), and longitudinal left (C) views from a thyroid ultrasound in a 15-year-old patient presenting with an 11-month history of weight loss, hoarseness, difficulty swallowing and a palpable right sided neck mass. The right lobe of the thyroid is markedly enlarged and heterogenous with punctuate calcifications (A; arrows B); the left lobe of the gland is normal (C). FNA with ultrasound guidance, the preferred method of evaluating a thyroid nodule, confirmed papillary thyroid carcinoma. The likelihood of malignancy in a palpable thyroid nodule increases if there has been rapid growth, if the mass is hard or adherent to surrounding tissues, associated with vocal cord paralysis or cervical adenopathy.

ules (warm on pertechnetate imaging and cold on iodine imaging) can occur in this setting.[50,52] Outside of these patient subsets, thyroid scanning of nodules is not indicated, and patients should proceed directly to FNA, often with ultrasound guidance, for suspicious lesions.

The best method to evaluate thyroid nodules in children remains debatable. Some recommend surgical resection of scintigraphic "cold" nodules[57]; others suggest removal of all thyroid nodules in children.[55] In adults, the sensitivity, specificity and accuracy of FNA of thyroid nodules has been found to surpass the diagnostic efficacy of sonography, scintigraphy and response to thyroid hormonal therapy in differentiating benign from malignant disease.[51] Dengan and coworkers[61] found the accuracy of fine needle aspiration of thyroid nodules in children to be less than that reported in adults but similar to that of ultrasound or scintigraphy. While emphasizing the safety of the technique, they emphasized that negative FNA results must be viewed with caution and that neither ultrasound, scintigraphy nor FNA was sufficiently accurate to be used as the sole predictor of thyroid malignancy in children.[61,62]

Staging

Because the treatment of thyroid cancer in almost all cases involves surgical resection, extensive presurgical staging is not part of the standard clinical evaluation of thyroid cancer. Neck ultrasound or magnetic resonance imaging (MRI) may be useful in patients with suspected nodal metastasis to help direct surgical debulking of involved lymph nodes. In patients presenting with advanced disease, determination of the presence or absence of pulmonary metastases using noncontrast chest computed tomography (CT) may be helpful in directing the aggressiveness of postsurgical therapy and may identify mediastinal adenopathy that can be sampled, and in some cases debulked, at the time of surgery. Since iodinated contrast interferes with diagnostic and therapeutic radioiodine, CT contrast should be avoided, if at all possible.

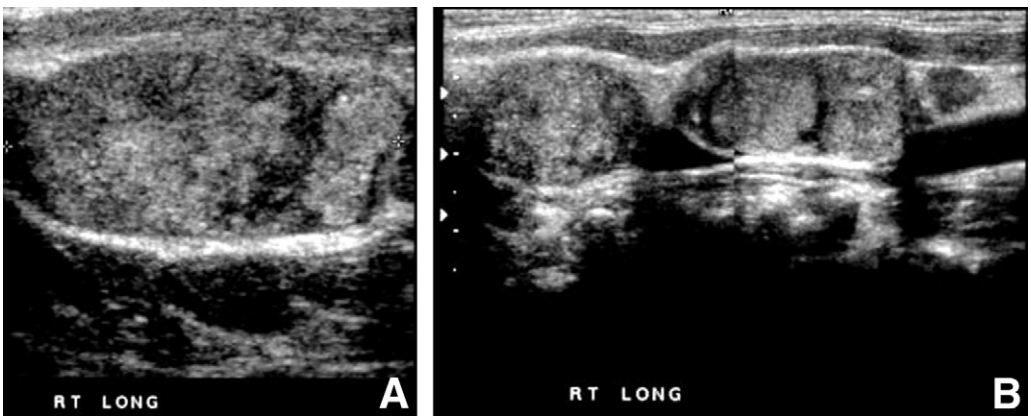

Figure 3 An 11-year-old patient with multiple right sided neck masses. Longitudinal views from a thyroid ultrasound confirm multifocal solid masses in the right lobe of the gland (A) and cervical lymphadenopathy (B) in this patient with extensive metastatic papillary thyroid carcinoma.

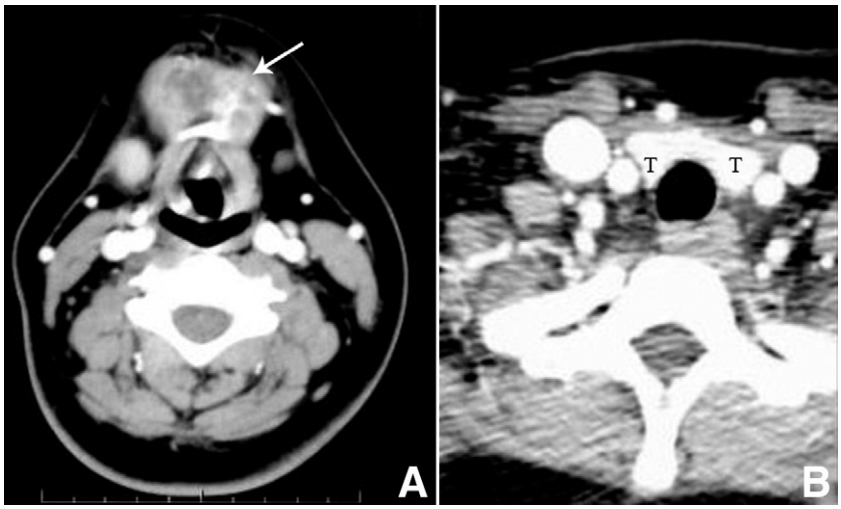

Figure 4 An 18-year-old patient with persistent, slowly enlarging midline neck mass. (A) Axial CT reveals a heterogenous multicystic and solid midline mass at the level of the hyoid bone (arrow) cephalad to and separate from a normal appearing thyroid gland (B, area T). Excisional biopsy confirmed papillary thyroid carcinoma arising in a thyroglossal duct cyst. It is important to avoid administration of iodinated contrast in the CT evaluation of a patient with suspected thyroid carcinoma as its administration precludes the subsequent use of I-131 or I-123 in complete staging evaluation following total thyroidectomy for a minimum of 12 weeks.

In patients that present with extensive lung metastases, there is a finite chance of cerebral metastases. In this case, it is important to determine the presence of any cerebral metastases before the tumor stimulation that occurs with preparation for radioiodine scanning and therapy. In these patients, screening brain MRI may be appropriate to exclude cerebral metastasis before proceeding to radioiodine scanning and/or therapy.

Radioiodine scanning remains the mainstay of staging for differentiated thyroid cancer.[63] Unlike iodine scintigraphy for benign thyroid disease, thyroid cancer metastatic surveys require extensive patient preparation. Almost all thyroid cancers, though iodine-avid, are considerably less iodine-avid than normal thyroid tissue, that is, they are "cold" compared with the normal thyroid. When substantial thyroid tissue is present at the time of the scan, it will therefore limit visualization of thyroid cancer sites. Thyroid cancer surveys are therefore possible only after near-total thyroidectomy and are not appropriate for patients who have only undergone hemithyroidectomy. Substantial thyroid remnants can have quite prominent uptake and cause a "star" artifact along lines of preferential septal penetration, which can limit the visualization of cancer sites in the neck and upper chest.

Pediatric thyroid cancer patients typically undergo a radioiodine thyroid cancer survey 8 to 12 weeks after their total thyroidectomy to allow time for surgical healing and clearance of iodine-containing material used at surgery. It is advisable for the referring pediatric endocrinologist, oncologist, or the nuclear medicine physician to have an office visit with the patient and family at the time of procedure scheduling to discuss issues like preparation, radiation precautions, the side effects of therapy, and other topic related to diagnostic and therapeutic radioiodine procedures. In preparation, patients are counseled to avoid interfering materials such as radiographic contrast agents, seafood, and high iodine content foods. If there has been exposure to radiographic contrast, most centers advocate waiting at least 2 to 3 months before radioiodine thyroid cancer imaging to allow adequate iodine clearance. For patients on levothyroxine at the time preparation is begun, discontinuation begins 4 to 6 weeks before scheduled imaging to allow clearance and compensatory rise in TSH. Most centers will supplement patients with T3 (liiothyronine, Cytomel) up to 2 weeks before scanning to help alleviate symptoms and minimize the time in full withdrawal and TSH stimulation. A low-iodine diet is instituted 1 to 2 weeks before imaging. These extensive preparations are necessary to maximize the iodine-avidity of residual thyroid cancer and are important for both diagnostic imaging and radioiodine therapy.

As many pediatric thyroid cancers will come from a referral population some distance from the performing center, the time of thyroid cancer imaging presents a convenient time to have patient follow-up and final discussions of considerations for treatment. Shortly before I-131 scanning, in addition to physical examination by the pediatric oncologist or endocrinologist, the following laboratory studies are obtained: TSH, thyroglobulin, urinary iodine (if there has been a significant iodine exposure), complete blood count, calcium, and a pregnancy test in all females of menstrual age. TSH level is necessary to assure adequate stimulation for scanning and possible therapy and preferably should be greater than 30 mIU/L. TSH can be insufficiently stimulated in cases of noncompliance with the preparation regimen or if there is a substantial thyroid remnant still making thyroid hormone. For patients being considered for therapy, a complete blood count is important to exclude marrow dysfunction or hematologic disorders that might increase sensitivity to I-131 therapy. The postsurgical thyroid cancer survey is

also a convenient time to measure serum calcium; transient parathyroid dysfunction associated with surgery will typical have resolved by 6 to 8 weeks after surgery. The absence of pregnancy must be assured in all females of child-bearing age.

The measurement of thyroglobulin just before diagnostic dose administration is a key component of the study, as blood thyroglobulin is an important marker of disease presence and burden. Thyroglobulin is a protein associated with production of thyroid hormone by the thyroid and its sources are limited to thyroid and thyroid cancer.[64] In the absence of thyroid tissue, it provides a highly sensitive screen for disease recurrence. Although thyroglobulin levels vary from patient to patient, serial thyroglobulin levels in the same patient provide an estimate of disease burden. It is important to note that levels increase after TSH stimulation, therefore measuring the thyroglobulin level at the time of scanning, when there has been TSH stimulation, is an important component of staging and surveillance. Since the normal thyroid remnant can produce some thyroglobulin, levels of up to 20 to 30 ng/mL may be seen in the first postsurgery scan; however, after remnant ablation levels should be close to zero. Higher thyroglobulin levels often indicate sites of disease outside the thyroid, such as regional lymph nodes or distant metastases.[64] Because a substantial fraction of patients have autoantibodies to thyroglobulin, which may interfere with the assay, antithyroglobulin antibody levels should be measured as part of the thyroglobulin assay.

Considerable controversy exists as to the choice of diagnostic isotope for thyroid cancer surveys.[65-67] I-131 has traditionally been used, since its longer half-life allows for adequate background clearance to reach optimal target/background levels at 48 to 72 hours after dose administration. On the other hand, because only 10% of radioactive emissions are imagable, and emitted gammas are high energy that is not well suited for standard gamma cameras, image quality is poor and radiation burden is relatively high. There is some concern the diagnostic I-131 will stun thyroid remnants and thyroid cancer, leading to reduced uptake and efficacy of the subsequent therapeutic radioiodine dose, although the importance of stunning is debated.[68] This concern has lead some practitioners to suggest skipping the diagnostic image altogether, to proceed immediately to I-131 therapy, and take only a post-therapy scan. This approach has the disadvantage of not being able to adjust I-131 dosing for either a large remnant or unexpected disease sites and also means that diagnostic surveillance scans will need to be compared only to post-therapy scans, rather than to more appropriately matched pretherapy diagnostic scans. We have continued to use the pretherapy diagnostic scan at our center.

An increasing number of nuclear medicine centers use I-123 to perform thyroid cancer surveys. I-123 has the advantage of much lower radiation burden and, at 159 keV, gamma emission much more amenable to imaging on standard gamma cameras.[65] The chief disadvantage is the short half-life, which requires imaging at 24 hours or sooner after dose administration, less than optimal time for background clearance. Considerable literature has been devoted to the comparison of I-123 and I-131, and it is not at all clear that one method is superior to the other, suggesting that both approaches are equally valid. In our center, especially given the need for the longer half-life to measure iodine clearance for dosimetry studies, we have preferred I-131.

On the day of administration of the diagnostic dose (I-131 in our case), it is incumbent on the pediatric radiologist or nuclear medicine specialist to review the antecedent patient history and laboratory results. Results of recent serum laboratory studies should be reviewed. In particular, the serum TSH level should be >30 mIU/L to indicate adequate thyroid hormone withdrawal. The nuclear medicine physician and technologists should verify the I-131 dose and patient identification before dose administration. The nuclear medicine staff should ensure that the patient and family have the appropriate educational materials and understand appropriate radiation precautions.

In our center, diagnostic I-131 postsurgical scanning with iodine uptake is performed at 72 hours after the oral administration of an adult equivalent dose of 1 to 3 mCi (37-111 MBq) of I-131 scaled to patient weight in those who have undergone a standard thyroid hormone withdrawal protocol (Fig. 5). The low dose is chosen to avoid "stunning" as discussed previously. Anterior and posterior whole-body images are obtained with patient in the supine position using a large field of view and a high-energy collimator. Additional spot scintiphotos of the head, neck, chest, and abdomen are obtained for 5 to 10 minutes per view as needed. For those centers with high-energy pinhole collimators, an anterior pinhole view of the neck should be used to try to differentiate thyroid remnant from nodal metastases. The former tends to highly-iodine avid and appearing entirely within the normal thyroid bed. Nodal metastases tend to be more punctate, less iodine-avid, and often at the edge or outside the thyroid bed. In practice it can be difficult to differentiate small thyroid remnant sites from residual cancer of nodal metastases.

More recently, diagnostic radioiodine thyroid cancer surveys have been performed using recombinant human thyrotropin (rhTSH, Thyrogen) instead of hormone withdrawal.[69] This drug is a genetically engineered version of TSH identical to human TSH. After intramuscular injection of 0.9 mg rhTSH, TSH levels in adults reach peak levels on the order of 100 mIU/L, declining to baseline with a half-life of 20 to 30 hours.[70-72] The side effects are minimal with headache and nausea reported in approximately 10% of patients. The recommended regimen for radioiodine scanning is 0.9 mg IM daily on each of the two days before diagnostic dose administration.[71] With this regimen, adult peak levels are 132 ± 89 mIU/L at 24 hours and 16 ± 12 mIU/L at 72 hours after the second injection.[70] Postinjection TSH levels in pediatric patients appear to be quite similar.[72] Because iodine clearance is faster in euthyroid patients receiving rhTSH compared with hypothyroid patients, likely due to reduced renal function in the hypothyroid state, there is lower uptake per mCi of administered radioiodine. Therefore, current practice recommendations are for 4 to 5 mCi (148-185 MBq) of I-131 (versus 1-3 for withdrawal studies), and a 48-hour imaging delay from dosing. A typical schedule calls for rhTSH injections on

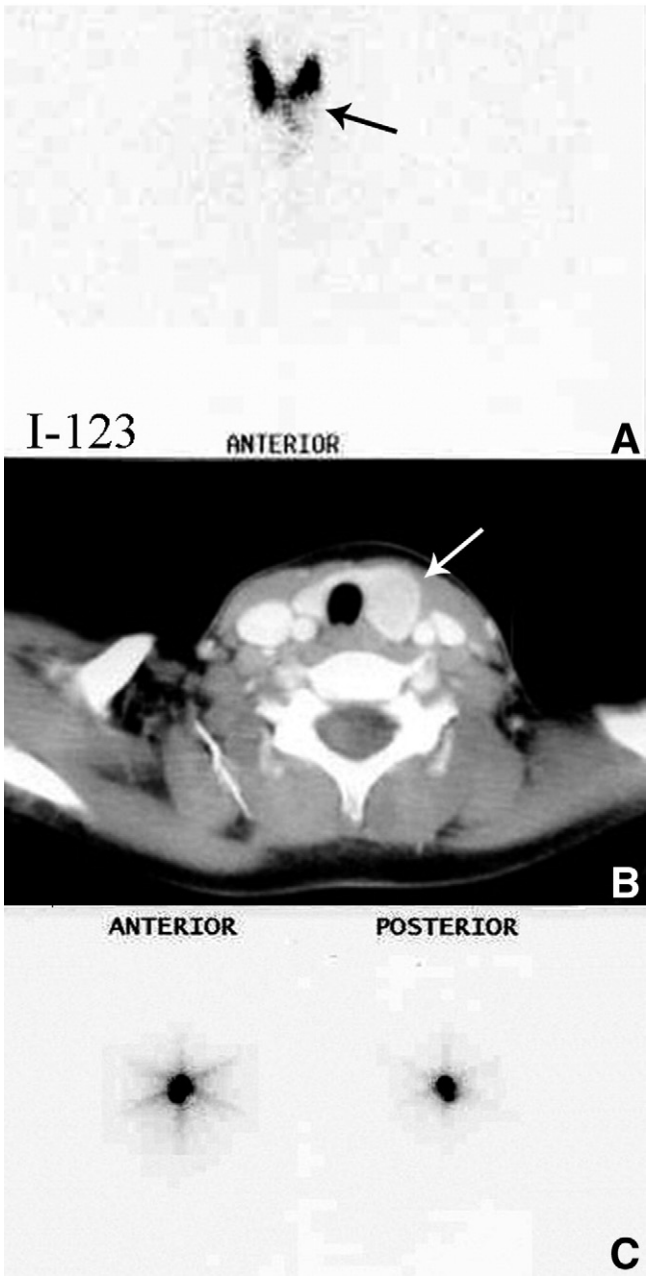

Figure 5 Previously healthy 4-year-old patient with enlarging left neck mass. (A) I-123 thyroid scan shows a cold nodule in the lower lobe on the left (arrow), also demonstrated on subsequently performed contrast enhanced axial CT (B, arrow). (C) Anterior and posterior views of the head and neck from a I-131whole body scan staging scan obtained 18 weeks after initial lobectomy and subsequent completion thyroidectomy for metastatic follicular variant of papillary thyroid carcinoma revealed residual remnant or node in the left neck with typical "star" pattern consistent with 72-hour iodine uptake of 32%. Some suggest surgical re-exploration and debulking when iodine uptake is greater than 20%. Given history of 2 prior neck surgeries and known metastatic disease in the neck, we elected to perform a remnant ablation using age and weight adjusted dose of oral I-131 in the outpatient setting.

Monday and Tuesday, diagnostic dosing on Wednesday, and scanning on Friday. Early phase III trials of rhTSH-driven scanning suggested that the sensitivity for thyroid remnant or thyroid cancer by scanning using rhTSH was reduced by 15-20% compared with withdrawal scanning.[70,71] For this reason, the recommended protocol includes measurement of thyroglobulin pre-rhTSH injection and 72 hours after the second injection, for use as an adjunct to scanning for detecting thyroid cancer. Using a cut-off of less than 2.5 ng/mL for thyroglobulin levels post-rhTSH and no significant increase pre- to post-rhTSH as additional criteria for a negative study, the rhTSH-driven studies showed equivalent sensitivity to withdrawal scanning, especially in the detection of metastatic thyroid cancer.[71] The approach using rhTSH stimulation is the increasingly preferred method for purely-diagnostic studies, with no anticipated therapy, especially for low-risk patients who have low or undetectable suppressed thyroglobulins and have previously undergone I-131 therapy. It has recently been studied in pediatric patients with good results,[72,73] although its use is not yet approved for children by the FDA.

Previous studies have investigated the use of other radiopharmaceuticals for thyroid cancer diagnostic imaging, including thallium-201, technetium-99m-sestamibi (MIBI), and fluorine-18-fluorodeoxyglucose (FDG). Although some early studies showed efficacy, thallium and MIBI are not recommended for thyroid cancer imaging. FDG-positron emission tomography (PET) has been increasingly used for thyroid cancer, but mostly in the setting of post-therapy surveillance, in particular for patients with negative iodine scans and positive thyroglobulin levels (discussed later).[74] Some early studies using FDG-PET for thyroid cancer staging early in the course of treatment have had disappointing results,[75] and FDG-PET is therefore not recommended in the routine staging of thyroid cancer. It appears the well-differentiated, iodine-avid thyroid cancer is less likely to be glycolytic, and therefore FDG-avid, than more aggressive and iodine-negative disease.[76] Our anecdotal observations have noted some pediatric patients with rapidly growing adenopathy that is both iodine and FDG-avid, where FDG-PET may be helpful in directing surgery; however, this application remains to be prospectively tested.

Surgery

Although extensively investigated, treatment of pediatric thyroid cancer remains controversial. The overall number of patients with the disease is small, making it difficult to obtain a large, single institution series. Moreover, differences in treatment methods at different as well as at the same institution over time has prevented a large retrospective study of pediatric patients with a well defined treatment protocol. Finally, there has been no controlled, randomized prospective study of these patients to date.

One of the first controversies encountered in treatment of the pediatric thyroid cancer patient is the extent of the thyroidectomy to be performed in those patients with a solitary thyroid cancer. Although the Society of Surgical Oncology[77] recommends lobectomy alone for differentiated thyroid cancer patients with early-stage disease, the American Thyroid Association[78] and the American Association of Clinical Endo-

crinologists[79] recommend total or near total thyroidectomy in all patients except those with T1M0N0 disease. For multifocal, bilateral or advanced thyroid cancer (including local infiltration of surrounding tissues, local or distant metastases), total thyroidectomy is mandated.

Those undergoing lobectomy have been found to have an excellent overall prognosis and suffer a lower risk of surgical complications. Proponents of lobectomy also note that less than 5% of recurrences occur in the thyroid bed and of these, greater than 50% of local recurrences can be cured with additional surgery. As noted, however, patients with a thyroid lobe remaining are not candidates for diagnostic radioiodine imaging.[80,81]

Newman and coworkers[82] found the recurrence rate of well-differentiated thyroid cancer in children after total or subtotal thyroidectomy to be identical to that of lobectomy alone. Unfortunately, surgical reintervention for recurrent disease in children initially treated with lobectomy alone is often associated with a higher complication rate.[83] Other groups[84-86] have demonstrated a positive effect of total thyroidectomy on recurrence free survival.

On the other hand, after total thyroidectomy, radioactive iodine (I-131) can be used to detect and treat residual thyroid tissue, local and distant metastases. Serum thyroglobulin levels are more sensitive in the detection of persistent or recurrent disease when all normal thyroid tissue has been removed, especially after remnant ablation. Recurrence develops in the contralateral lobe in 7% of patients; 50% of these patients die of their disease. Because as many as 85% of those with PTC have microscopic foci of disease in the contralateral lobe, total thyroidectomy eliminates these foci as sites of possible disease recurrence.[81] For these later reasons and, particularly in light of their expected life span as compared with the adult with thyroid cancer, we, like other groups[22,63,81,83-89] perform total or near-total thyroidectomy in all children with thyroid cancer at our institution.

Complications of thyroidectomy are rare in the hands of experienced surgeons.[63,81] The most common side effect other than postsurgical pain is parathyroid dysfunction, resulting in low PTH and calcium levels after surgery and associated symptoms of circum-oral numbness, extremity tingling, and occasionally tetanus in severe cases. Hypoparathyroidism typically resolves within several weeks after surgery and can be managed by calcium and, occasionally, vitamin D supplementation. A more serious complication is damage to the recurrent laryngeal nerves, which run close to the thyroid, resulting in vocal cord paralysis. To avoid complications, most surgeons perform a "near-total" thyroidectomy leaving small amounts of remnant tissue near the nerve sites and parathyroid glands. Given the delicacy of the surgical site and potential complications, thyroidectomy should be reserved for surgeons with considerable experience in the procedure. This is especially true for pediatric patients, where size and spacing to critical structures is much smaller than in adults.

Radioiodine (RAI); I-131 Radiotherapy

First introduced by Seidlin[90] in 1946, RAI produces short range (2 mm) B radiation with a half-life (T1/2) of 8 days. In adults, RAI uptake is found in 80% of those with FTC, in 70% of those with PTC, and in 10% of those with HCT. The high degree of uptake in the differentiated thyroid cancers and its physical properties led to the use of RAI as a therapeutic agent in this disease. Numerous authors have reported improved survival, decreased disease progression and lower recurrence rates in those with DTC who received postoperative RAI.[63,91-94] Mazzaferri and coworkers[93] found a recurrence rate of 6.4% and a 5-year disease-free survival rate of 97% in those with DTC who underwent total thyroidectomy and RAI as opposed to a 11% recurrence rate and 40% to 60% relapse rate between 5 and 10 years after surgery alone. Others concur demonstrating a decrease in recurrence rate from 17% to only 6% after postsurgical RAI treatment.[94] Despite these findings, for some, the use of postoperative RAI remains controversial in the treatment of thyroid cancer.

The goal of radioiodine treatment is 2-fold[63,94]: (1) to ablate the thyroid remnant in the postsurgery setting with the goal of facilitating follow-up by both imaging and thyroglobulins and (2) treatment of residual thyroid cancer or thyroid cancer metastases. The former goal is relatively easily accomplished because the thyroid remnant is highly iodine-avid. A recent study showed 100% efficacy for remnant ablation with an adult equivalent dose of 100 mCi (3.7 GBq), using either hormone withdrawal or rhTSH stimulation.[95] Thus, only modest doses are needed for remnant ablation. However, iodine uptake in thyroid cancer is variable and almost always considerably lower than the normal thyroid. There are many factors that influence I-131 uptake, including the serum iodide and TSH levels, tumor type, degree of tumor differentiation, and patient age. Furthermore, thyroid cancer is relatively radio-resistant compared with other cancer such as lymphoma. For these reasons, higher doses are needed to treat thyroid cancer, and dosing levels are empirically adjusted to the expected disease burden and risk of recurrence and progression. In adults, risks factor for disease progression include tumor size, older patient age, thyroid capsular penetration by the tumor, and especially the presence of distance metastases. Lymph node metastasis is quite common, especially for papillary thyroid cancer, and not necessarily associated with a higher risk of death from thyroid cancer. Lymph node metastasis noted by surgical pathology or possibly by scanning is, however, a marker for likely residual small-volume disease and has been associated with a higher rate of local recurrence. This must be considered in choosing a radioiodine dose for patients with thyroid cancer.

One consideration in the postsurgical setting is the concept of "adjuvant" radioiodine. In other tumors such as breast and colon cancer, adjuvant systemic therapy is used to treat likely microscopic disease sites, even if they are too small to visualize, to decrease the risk of disease recurrence, particularly at distant sites. Because radioiodine is systemically delivered, the same concept may hold for radioiodine treatment of thyroid cancer. Certain factors such as the presence of macropscopic lymph node metastases at the time of surgery, capsular penetration, or large tumor size increase the likelihood of thyroid cancer metastases, which are often small-

volume sites of disease, not visualized on either anatomic or radioiodine imaging. Thus, in choosing the aggressiveness of radioiodine therapy, it is important to consider strongly data obtained from surgical pathology in choosing a radioiodine dose.

The treatment dose of I-131 administered after thyroidectomy is a considerable source of controversy in both adult and the pediatric thyroid cancer patients.[3,63,89,96,97] In addition to the considerations that are important in all thyroid cancer patients, discussed previously, pediatric thyroid cancer requires some special considerations. Pediatric patients may be more sensitive to the side-effects of I-131, including the possibility of inducing a second cancer. Some studies have suggested that, per unit absorbed dose, pediatric organs such as bone marrow may more sensitive than adult tissues to I-131.[89,96] On the other hand, studies have shown that the effect of radioiodine in reducing distant recurrences of thyroid cancer can take 20 to more years to be manifest.[97] With a nearly full lifetime for disease recurrences to occur, it is highly desirable to eradicate small-volume residual disease on initial presentation, especially for more advanced disease, where micrometastases are more likely. These competing considerations are important when choosing radioiodine dosing levels for pediatric patients.

The first consideration is whether or not to treat with radioiodine. For patients with small primary tumors, often incidentally discovered in surgery for a benign nodule, some practitioners advocate not undergoing thyroid remnant ablation, even if a near-total thyroidectomy has been performed.[63] Most agree that tumors that are at increased risk for recurrence and spread, including larger tumors, those with lymph node metastasis, and those with capsular penetration, deserve radioiodine ablation.

If the initial post-thyroidectomy I-131 scan shows uptake confined to the thyroid bed but greater than or equal to 20% at 48 to 72 hours, surgical re-exploration and resection of residual tumor or thyroid remnant may be considered. For low risk patients (tumor size less than 2 cm, no capsular invasion, no nodal or distant metastases, T1, NO, MO), if uptake is confined to the thyroid bed and less than 10% at 48 to 72 hours, I-131 dosing with the goal of thyroid remnant ablation is chosen. For low risk patients, many consider an appropriate "outpatient" dose of I-131 to be an adult dose of 30 mCi (1.1 GBq). This dose was not based on success rate, but largely on regulations that permitted patients to receive therapy as an outpatient if they received 30 mCi (1.1 GBq) of I-131 or less. These regulations have largely changed, and in the US, most states allow outpatient treatment of thyroid cancer patients for doses up to considerably more than 30 mCi (1.1 GBq). Nevertheless, several studies[93,98] have demonstrated that there is little difference in efficacy between low (<30 mCi [<1.1 GBq]) and high (up to 100 mCi [3.7 GBq]) dose radio-ablation with I-131. Mazzafferi and Jhiang[93] concur, demonstrating that there is greater than an 80% to 90% chance that 30 mCi (1.1 GBq) of I-131 will produce ablation. More recently, studies using 100 mCi (3.7 GBq) for remnant ablation in adults, using either withdrawal or rhTSH stimulation showed 100% efficacy in remnant ablation.[95] Balancing considerations include the lower side effect profile with lower doses, particular to organs such as salivary glands versus the possible need to readminister radioiodine in the case of a failed ablation. Most centers prefer to err on the side of lower doses for low-risk pediatric patients.

In adults with higher risk disease, inpatient therapy with I-131 doses ranging from 100 to 200 mCi (3.7-7.4 GBq) is performed. There are no "standard" doses for treatment and few prospective studies to set dosing guidelines.[63] At our center, guidelines are based on the adult practice, adapted to the pediatric population and adjusted to weight. Adult-equivalent doses are as follows: For patients with minimal risk factors (T1-2, N0, M0), an ablative dose of up to 100 mCi (3.7 GBq) is given. For higher-risk patients, particular those with nodal metastases (T1-2, N1, M0), doses of 150 to 175 mCi (5.6-6.5 GBq) are given, depending on the extent of nodal disease and the anticipated residual nodal burden. In the highest risk patients, especially those with very large tumors or penetration of the thyroid capsule and growth into adjacent structures (T3-T4), extensive nodal disease, or distant metastases (M1), empiric adult-equivalent doses of 200 mCi (7.4 GBq) are used. In patients with known distant metastases, who may have life-threatening disease at some point in their lives, aggressive radioiodine therapy based on iodine dosimetry, rather than empiric dosing, may be appropriate. In this approach, whole body and blood iodine clearance measurements, in addition to tumor surveys, serve to provide estimates of the maximum tolerated dose by critical organs, typically the bone marrow or the lungs in the case of extensive pulmonary metastases.[99,100] This approach allows dosing based on patient tolerance, rather than on empiric estimates, and in pediatric patients has the advantage of dose estimates to sensitive organs such as bone marrow. However, dosimetry procedures are more complex, require considerable experience at the center performing them, and require patients' visits for typically 4 to 5 days in a row after diagnostic dosing. Dosimetry is likely therefore best reserved for referral centers with experience in the technique.

The same dose schema described previously for adults is used in children, but the actual I-131 dose administered is adjusted by weight and by additional safety factors dependent on age or antecedent treatment. Radiation dosimetry estimates are typically performed in those patients under age 10 years; in patients who have undergone prior chemo- or radiation therapy; in those that have distant metastases; in those in whom thyroid cancer is a secondary tumor; or when cumulative doses for thyroid cancer treatment approach 250 to 500 mCi (9.3-18.5 GBq).

The care and treatment of the child with thyroid cancer benefits from a team approach involving pediatric specialists in nursing, oncology, surgery, radiology and nuclear medicine. When a child with thyroid cancer is identified at our institution, the first step after thyroidectomy is discussion of the patient at tumor board. It is at this time that surgical and pathology findings are reviewed by the entire care team and plans for I-131 RAI discussed. If hospitalization is warranted for I-131 therapy, ensure that inpatient nursing staff and the radiation safety officer are informed and updated and that the

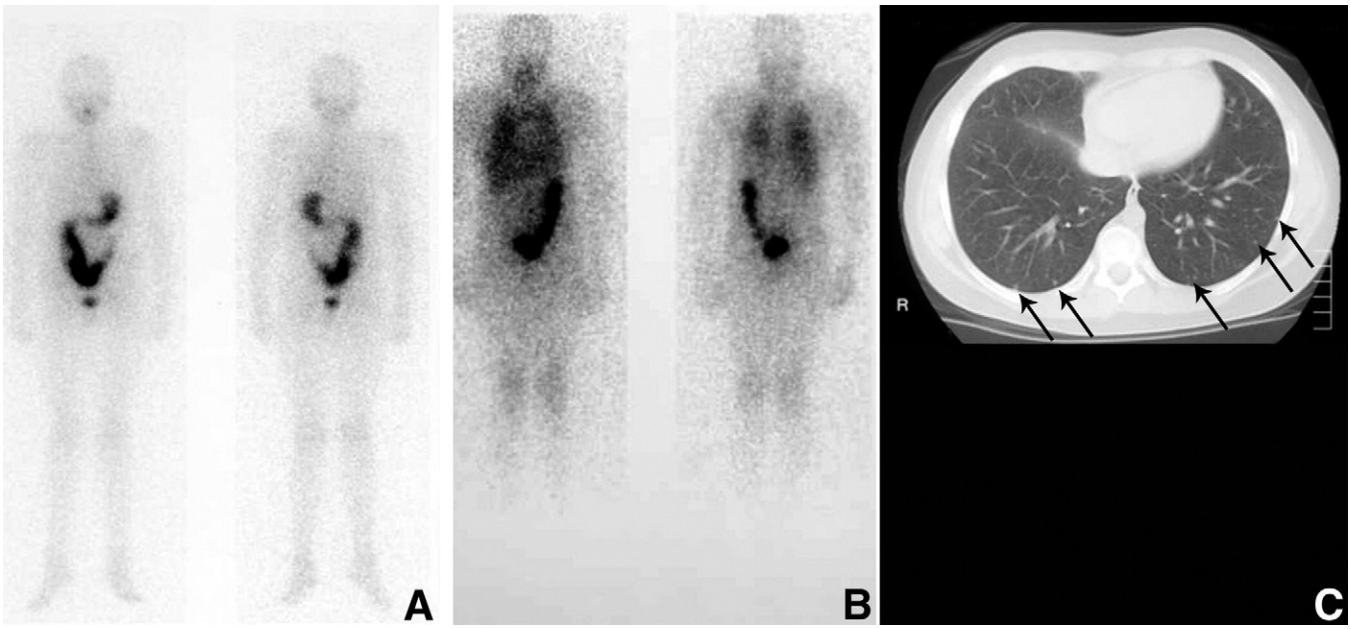

Figure 6 An 11-year-old s/p total thyroidectomy and lymph node dissection for papillary thyroid carcinoma with metastatic nodal involvement. (B) Anterior and posterior whole body images obtained 7 days after oral I-131 therapy clearly show diffuse lung metastases confirmed on noncontrast CT (C, arrows) but not seen on diagnostic (staging) postthyroidectomy I-131 scan (A). Dose related sensitivity of I-131 for detection of metastatic thyroid disease as seen in this case is well documented in the literature. Post-therapy I-131 whole body imaging at 7 to 10 days is mandatory in all patients as this may detect new or unexpected lesions in as many as 46% of patients.

lead lined room and other equipment are appropriately prepared.

On the day of therapy, the pediatric radiologist or nuclear medicine specialist should ensure that the patient has complied with the preparatory regimen to maximize therapeutic efficacy. Next, the patient is admitted to the lead-lined room. Patient identity is verified using 2 forms of identification, including either a state-issued or other photo ID. Witnessed, written informed consent for the procedure is obtained from the parent or from the patient if he or she is an emancipated minor or older than 18 years of age; assent is also obtained from children older than 12 years. Elements of the consent should include short- and long-term risks of the procedure, including but not limited to sialadinitis, gastritis, neck pain or swelling, thrombocytopenia; the possibility of decreased fertility, infertility; and the development of secondary cancers. Admonition to avoid becoming pregnant in the 9 to 12 months immediately after I-131 radiotherapy should be stressed. Alternatives to the procedure should be discussed and any patient questions answered. Educational materials and radiation safety procedures should be reviewed.

Subsequently, a prophylactic intravenous line is placed for fluid hydration if adequate oral liquids cannot be tolerated. The need for oral hydration is emphasized to the patient and the use of lemon drops in decreasing sialadinitis discussed. After verification of the I-131 dose, the pediatric radiologist or nuclear medicine specialist personally witnesses and/or administers the dose. Standard hospital orders are written by the admitting pediatric oncologist. Baseline patient radiation emissions are obtained by the radiation safety officer or nuclear technologist immediately following the oral administration of the I-131 dose and at least twice daily thereafter. The patient is hospitalized until their external dose rate is less than acceptable rates (7mR/h at 1 m in the state of Washington). If air travel is anticipated, a letter verifying recent treatment with I-131 signed by the discharging physician should be given to the patient. This may also be necessary for patients crossing borders, where radiation detectors are increasingly in use.

All patients should be reimaged 7 to 10 days after I-131 treatment. Several publications have demonstrated a dose-related sensitivity of I-131 in disease detection.[101-103] Specifically, as the dose of I-131 administered increases, so does the number of lesions detected. In fact, post-therapy scans may detect new lesions in as many as 46% of patients. Diffuse liver uptake is a common feature on the post-therapy scan, likely as a result of metabolism of iodinated proteins and should not be mistaken for metastases, unless more focal uptake is seen. Figures 6 to 8 show examples of whole body I-131 post-therapy scans.

Reinstitution of thyroid hormone supplementation and of normal diet begins at time of patient discharge. Patients are screened for hematologic effects at 4 to 6 weeks after ablation or therapy during routine visit with the pediatric oncologist. At this time, thyroid hormone replacement serum levels should also be evaluated and replacement doses adjusted if necessary.

Radioiodine Therapy: Special Situations

Considerable controversy exists regarding patients who are post-thyroidectomy and previously treated with radioiodine

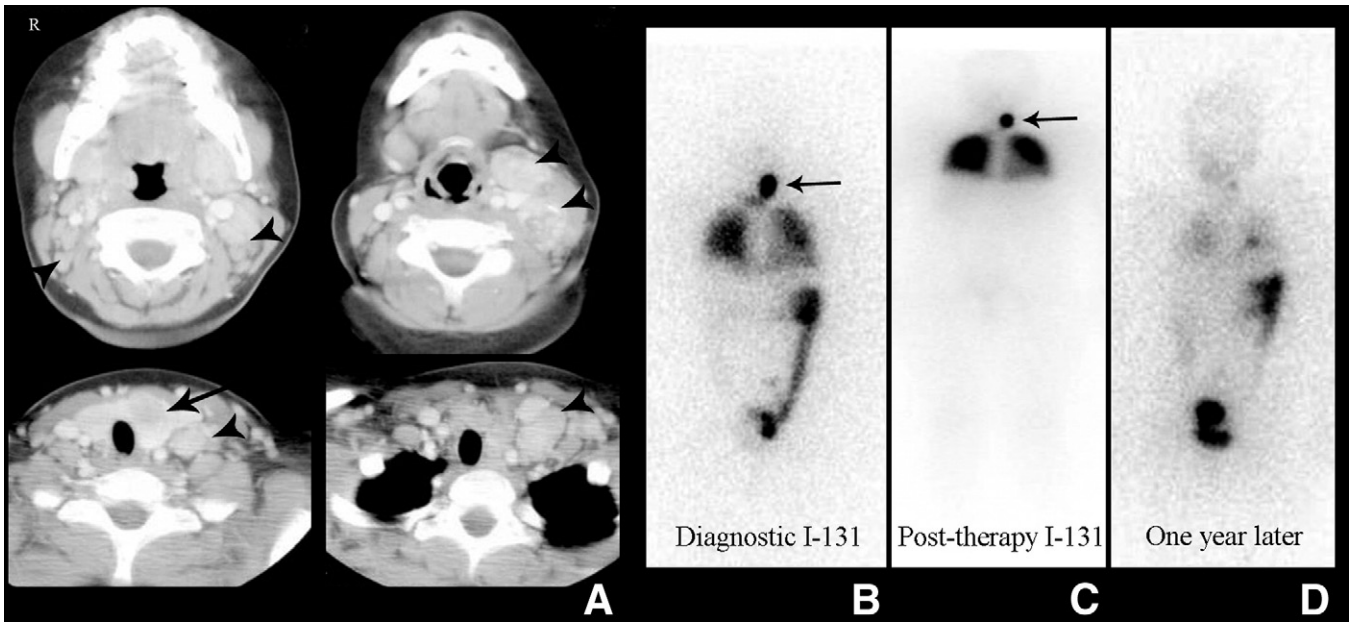

Figure 7 (A) Axial CT scans of a 12-year-old patient with "neck mass" reveals a low attenuation lesion in the left lobe of the thyroid (arrow) associated with bilateral cervical and supraclavicular lymphadenopthy (arrowheads). (B) Anterior whole body image from a I-131 scan obtained 12 weeks post total thyroidectomy and lymph node dissection for metastatic papillary thyroid carcinoma demonstrates residual uptake in large thyroid remnant or nodal conglomerate (arrow) in the left neck as well as diffuse lung metastases. These findings are better visualized on scan (C) obtained 10 days following treatment with an empiric dose of 200 mCi (7.4 GBq) of I-131, adjusted for patient weight/body surface area and age. Response to treatment is confirmed on anterior image from I-131 study performed 1 year later (D).

who have absent I-131 uptake but elevated thyroglobulin levels on surveillance studies.[104,105] Some advocate an empiric dose of 100 to 150 mCi (3.7-5.6 GBq), largely to detect the site of disease on post-therapy scanning. Kebebew[81] suggests a treatment dose of 100 mCi (3.7 GBq). Interestingly, on post-treatment scans performed at 7 days, one third of these same patients will demonstrate I-131 uptake and will have resultant decrease in thyroglobulin levels on follow-up. Others question what is being treated in these patients; they question the dose administered and are concerned about the

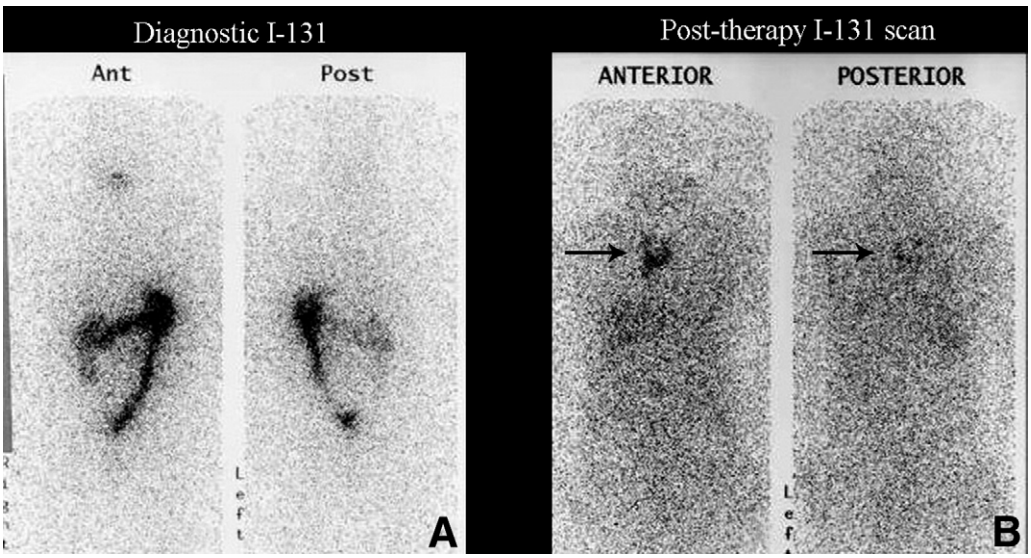

Figure 8 (A) Anterior and posterior whole body images from I-131 scans obtained 12 weeks after thyroidectomy for papillary thyroid carcinoma in a 15-year-old patient reveal no evidence of residual or recurrent disease. (B) Whole body scan obtained 10 days after I-131 therapy (with a empiric dose of 150 mCi (5.6 GBq) of I-131 adjusted for patient weight/body surface area) shows uptake in the thymus and in the liver. CT scan (not shown) identified the presence of a small residual thymic gland and confirmed the absence of mediastinal disease. Diffuse liver uptake, commonly seen on post-therapy scans, should not be mistaken for metastatic disease unless more focal uptake is present.

risk/benefit ratio for this form of therapy. Increasingly, PET or PET/CT imaging with F-18 FDG is being used in such cases for diagnosis and to make therapeutic decisions based on tumor location and expected behavior.[76] This is discussed in more detail below.

Although hormone withdrawal remains the standard and most tested preparation for I-131 therapy for thyroid cancer, there are emerging data on the use of rhTSH to prepare patients for therapy.[106] The chief advantages are fewer side effects and likely less tumor stimulation compared with hormone withdrawal. The chief difference is altered clearance of iodine in patients who receive rhTSH and are not hypothyroid. Studies suggest a factor of 1.5 to 2 times faster clearances, and similar less iodine uptake, in patients undergoing rhTSH-stimulated therapy compared with hormone withdrawal.[107] Therefore, direct application of empiric dosing schema based on withdrawal scanning to rhTSH-drive therapy is incorrect and will undoubtedly result in under-dosing.

I-131 therapy driven by rhTSH has been tested in two settings.[106] One is in adults with low-risk disease, empirically treated with 100 mCi (3.7 GBq) with goal of thyroid remnant ablation. Here rhTSH-driven therapy resulted in 100% remnant ablation and was as effective as withdrawal-based treatment.[95] The other setting has been in the case of compassionate use, for patients who cannot tolerate hormone withdrawal. A preliminary report by Robbins[108] pointed to the potential efficacy of this approach, which can be combined with dosimetry to choose appropriate dosing levels.

Early experience[109] suggests a third possible patient group, namely those pediatric patients with highly TSH-sensitive tumors that experience growth of disease, typically at nodal sites, during withdrawal. In these patients, use of rhTSH instead of hormone withdrawal may minimize tumor stimulation and growth before adjuvant I-131 therapy. This approach has only preliminary experience and remains to be tested in more formal studies.

Risks of I-131 Radiotherapy

There are both short and long term risks associated with I-131 RAI. Short-term or acute risks are those that occur during or shortly after therapy. These include mild nausea and/or emesis from radiation gastritis in as many as 50% of patients.[81,94,110-112] Acute sialadinitis is seen in approximately 30% of those treated and can be decreased by use of lemon drops or other substances at the time of dose administration that stimulate the production of saliva. Despite this precaution, permanent reduction of salivary gland function can occur in up to 40% of patients. Xerostomia (4%) and altered taste sensation are usually mild and self-limited. Painful swelling of thyroid remnant or of nodal metastases is seen in 10% to 20% of cases, usually associated with higher I-131 uptake levels on post-thyroidectomy diagnostic scans. Transient, mild thrombocytopenia occurs in up to 66% of patients, typically at 4 to 6 weeks after treatment. Transient amenorrhea, lasting up to 10 months in some, has been documented in 8%; menstrual irregularities are slightly more common, reported in between 12% and 30%.[113,114] In males, transient elevation of follicular-stimulating hormone has been noted.[115]

In contrast to short term effects, the potential long-term hazards of I-131 therapy which are of greatest concern to parents of children and young adults being treated include genetic damage (decreased or infertility; birth defects) and the induction of secondary malignancies. These are considered to be stochastic effects with no threshold; thus any patient receiving any dose of I-131 will be exposed to some potential risk.[116] Unfortunately, assessing hazards like genetic mutations and carcinogenesis that are infrequent and which have long latency periods before manifestation has resulted in a paucity of data which, when available is often confusing and contradictory.

Vini and coworkers[113] in a study of almost 500 women younger than the age of 40 who underwent I-131 radiotherapy for thyroid cancer found no cases of permanent ovarian failure. More to point, Sarker and coworkers,[117] evaluating 40 patients younger than age 20 (20 females) found no overt evidence of genetic damage in children and adolescents treated with high doses of I-131 for thyroid carcinoma. Smith and coworkers,[118] evaluating 154 children (age <20 years; 68 females) concurred, demonstrating that I-131 doses up to 250 mCi (9.3 GBq) were not associated with a long-term risk of infertility. However, Schlumberger[119,120] did note an increased risk of miscarriage in women with thyroid cancer treated with I-131. Finally, I-131 RAI is associated with an earlier onset of menopause compared with the general female population.[121]

Numerous authors have shown that I-131 therapy does not result in adverse effects in subsequent pregnancies if conception occurs greater than 12 months after treatment.[122-125] Unfortunately, birth defects were encountered in those patients who conceived within 6 months of I-131 RAI.[118,126]

In males, azoospermia, oligospermia, and increased follicle-stimulating hormone levels have been described.[115,127-129] Damage to spermatogenesis, although usually transient, has been demonstrated to be dose dependent. Consequently, treatment with high activity I-131 should be at the lowest level possible to achieve disease control.

Although radioiodine therapy has been used in the treatment of hyperthyroidism and thyroid cancer for close to 60 years, controversy persists regarding the carcinogenic risks of its use. On the molecular level, Gutierrez and coworkers[130] have demonstrated that I-131 treatment for hyperthyroidism and thyroid cancer induces cytogenetic damage in peripheral blood leukocytes that can be measured using the micronucleus assay. Two large studies suggest that an increase in chromosome alterations frequency could predict an increased cancer risk.[131,132]

On a more clinical level, Brinker[133] in 1973 reported a 2% frequency of leukemia in patients following I-131 RAI. Holm[134] in 1980 declared that there was no evidence of increased risk of development of malignant thyroid cancers after I-131 therapy for Graves disease. Hoffman[135] in 1982 found that there was an increased risk of developing cancers in salivary glands, gut, and urinary bladder, organs that con-

centrate iodine, after I-131 RAI. Smith and Edmonds[110] concurred, citing a small-but-significant excess of deaths from leukemia and bladder cancer in those who underwent I-131 therapy. Hall,[136,137] in studies performed in 1991 and 1992, disputed those results, claiming that no specific cancer or groups of cancers could be linked to high-dose I-131 RAI. Despite this, isolated reports of leukemia in those undergoing I-131 radiotherapy continued to surface.[138,139] Additionally, Green and coworkers[140] in 1995 demonstrated an increased risk of breast cancer after I-131 treatment. Most recently, Rubino and coworkers[141] studying a large cohort of 6841 thyroid cancer patients, demonstrated a significantly increased risk of development of secondary primary malignancies, including both solid tumors and leukemias, in those undergoing I-131 radiotherapy for their disease. Risk of secondary primary malignancy increased with increasing cumulative doses of I-131 administered. Pediatric patients are younger at time of I-131 treatment and have a significantly longer life expectancy than adults with thyroid cancer. On the basis of data from Chernobyl and from experience with chemo and radiation therapies in other types of childhood cancers, as well as the data cited previously, it seems prudent to consider the possibility that there is an unknown-but-increased risk of development of secondary cancers in children treated with I-131. This risk should be discussed with patients and their parents before I-131 treatment.

A final-but-significant late effect of I-131 radiotherapy is the development of pulmonary fibrosis. Pulmonary fibrosis occurs in those thyroid cancer patients who have lung metastases. The risk of pulmonary fibrosis correlates with the intensity of I-131 uptake[94,111] and varies inversely with the age of the patient. Consequently, pulmonary fibrosis occurs in only 1% of adult but 10% of pediatric thyroid cancer patients.

Long-Term Follow-Up

Long-term follow-up of these children includes periodic physical examinations and disease surveillance based on laboratory testing and diagnostic whole body radioiodine scan. It is important to verify that TSH is suppressed and to monitor serum thyroglobulin levels. As discussed, differentiated thyroid carcinomas secrete thyroglobulin, which is the most important biochemical test to detect disease recurrence. Consequently, after total thyroidectomy and ablation of normal thyroid tissue, serum thyroglobulin levels greater than 2 to 3 ng/mL with rhTSH stimulation or greater than 8 ng/mL following thyroid hormone withdrawal are diagnostic of tumor recurrence.

Assessment of thyroglobulin levels is more sensitive in the setting of TSH stimulation, where thyroglobulin levels can increase considerably. This stimulation was traditionally performed by withholding thyroid hormone, often in conjunction with iodine scanning. More recently, stimulation of thyroglobulin with recombinant human thyrotropin (rhTSH) has been shown to be an effective alternative to thyroid hormone withdrawal that has been proven effective in adults.[142] Some authors advocate the use of rhTSH-stimulated thyroglobulin measurements without radioioidine scanning for routine surveillance.[142-144]

Stimulation with rhTSH also has been shown to be an effective alternate to hormone withdrawal for radioiodine scanning.[71] This methodology avoids the often debilitating effects of hypothyroidism, which include impaired school performance in children. Hoe[73] and coworkers have published preliminary results demonstrating that rhTSH can be used successfully and without adverse effects to stimulate thyroglobulin secretion and radioiodine uptake for diagnostic whole body radioiodine scans in children with thyroid cancer who have undergone prior thyroidectomy and either RAI remnant ablation or therapy.

The frequency of radioiodine scanning in long-term follow-up of children with differentiated thyroid cancer has not been well established and also remains controversial. Current indications include verification of ablation and re-staging in cases of recurrence. Hung and Sarlis[89] evaluate patients every 6 months after thyroidectomy and I-131 ablation with diagnostic I-131 whole-body scan and serum thyroglobulin measurements for the first 18 months, readministering I-131 therapy if disease is encountered. If patients are disease free, they perform neck ultrasound and noncontrast chest CT at 18 months and follow annually for 2 more years with TSH stimulated diagnostic I-131 scans and serum thyroglobulin levels. Assuming the patient remains disease free, evaluations are performed at 5-year intervals until adulthood when the patient's care is transferred to an adult endocrinologist or internist to ensure life-long monitoring. Our practice has been to verify thyroid remnant ablation with at least one thyroid metastatic survey 9 to 12 months after initial treatment, often using a rhTSH driven approach. In some high-risk patients, 1 to 2 additional scans can be considered at yearly or biyearly intervals. No standard recommendations have yet evolved. Thyroid cancer surveys are also used in the setting of suspected recurrence, on the basis of physical examination, thyroglobulin levels, or other imaging such as ultrasound.

A special case occurs in the setting of elevated thyroglobulins and a negative diagnostic radioiodine scan. In this setting, it is important to verify that radioiodine scanning was done with proper preparation, including low-iodine diet and avoidance of iodine-containing contrast for 2 to 3 months before scanning. Although iodine-negative, thyroglobulin-positive findings can occur in the setting of false-positive tumor markers, elevated thyroglobulin after thyroid remnant ablation is fairly specific for recurrent cancer and occurs in 1 of 2 settings: (1) the recurrent disease is no longer iodine avid or (2) the recurrent disease of sufficiently small volume that it is no visualized on diagnostic thyroid metastatic surveys. The latter case can occur, for example, in the case of micronodular lung metastases, which are often missed on diagnostic iodine scans, only to be seen later of post-therapy scans. Although some advocate empiric therapy with 100 to 150 mCi (3.7-5.6 GBq) of I-131, an alternative and increasingly used approach relies on additional imaging. This imaging should include neck ultrasound or MRI to identify macroscopic, noniodine-

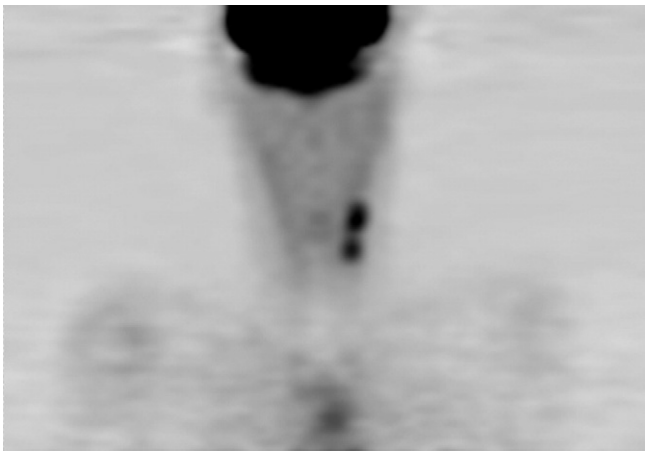

Figure 9 Patient with history of T3N1 papillary thyroid cancer treated with near-total thyroidectomy and 200 mCi I-131. Hormone withdrawal I-131 diagnostic scan obtained 9 months after I-131 therapy was negative but stimulated thyroglobulin levels were greater than 100 ng/mL. F-18 FDG-PET scan (coronal images of neck) shows 2 left cervical foci suggestive of lymph node metastases, confirmed by pathology at targeted neck dissection. This case illustrates the utility of FDG-PET in the setting of elevated thyroglobulin with negative iodine scans.

avid nodal disease and a noncontrast chest CT to identify possible pulmonary parenchymal metastases.

Increasingly, FDG-PET is added to this scanning regimen for several reasons.[76] First, FDG-PET identifies recurrent disease in up to 70-80% of iodine-negative, thyroglobulin-positive cases (Fig. 9).[145-147] This can help direct further therapy, especially surgical excision. Equally importantly, the presence or absence of FDG uptake is a prognostic factor. Robbins[69] recently showed that in the setting of elevated thyroglobulin, the presence of FDG uptake predicted a poor outcome, with less than 50% 5-year survival, compared with patients without FDG uptake, who had greater than 90% survival to more than 7 years. In our practice, we have used these data to help make decisions in patients with elevated thyroglobulins and negative iodine scans. In the absence of evidence of regional nodal disease or pulmonary metastases, and with a negative FDG-PET scan, it may be reasonable to closely follow patients with serial thyroglobulins, ultrasound or MRI, and CT rather than undertake empiric treatment. It should be noted that like radioiodine scanning, FDG-PET may be insensitive for micronodular lung metastasis, and therefore the presence of lung metastases by CT together with an elevated thyroglobulin may be an indication for systemic therapy with I-131 or other agent, even if both FDG and radioiodine scans are negative.

Conclusion

Despite the aggressive nature of pediatric thyroid cancer, overall survival—even in those with distant metastases—is 100% at 10 years. Although recurrent disease may not manifest until after the first decade post-therapy, it is important to remember that 5% to 7% of children succumb to progressive disease. More importantly, 5% to 7% develop lethal treatment related complications or secondary malignancies. Consequently, lifelong surveillance for pediatric thyroid cancer patients is mandatory and is a delicate balance between the side effects of treatment and the lifelong possibility of recurrence.

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