

## **The role of nuclear medicine in malignant endocrine tumors of childhood and especially in well differentiated thyroid cancer.**

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Cancers of the endocrine glands are very uncommon representing about 4-5% of all cancers seen in children. About 40-45% of childhood endocrine tumors arise from the gonads (e.g. germ cell, testicular and ovarian tumors), 30% arise from the thyroid gland and 20% originate in the pituitary. The other, more rare, endocrine cancers affect parathyroids, the adrenal cortex and medulla and the pancreas. Most endocrine tumors of childhood are benign or low-grade malignancies. A small percentage of gonadal and germ cell tumors, thyroid cancers, and adrenocortical tumors are high-grade malignancies. Malignant carcinomas of the parathyroids, the adrenal medulla, and the pancreas are also very rare in childhood.

The main topic of this lecture / manuscript is the role of nuclear medicine in well differentiated thyroid cancer in children.

Ten percent of all cases of thyroid cancer occur in patients younger than 21 years of age. There is an increased incidence in occurrence with puberty, but thyroid cancer can occur at any age. 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.

The biologic behavior of thyroid cancer can differ significantly between adults and children. 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.

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. Unfortunately, children also have higher local and distant recurrence rates for thyroid cancer than do adults.

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. 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.

The majorities of thyroid cancers do not have a known genetic basis and arise sporadically. An increasing understanding of the molecular biology of thyroid cancer, is elucidating some of the biological factors underlying cancer behavior: Some thyroid cancers exhibit aberrant expression of growth factors, activation of RET or TRK signaling pathways, BRAF mutations, or 3p25 rearrangements of peroxisome proliferators-activated receptor gamma gene. Molecular genetic papers suggest that exposure to ionizing radiation is associated with genetic changes that activate oncogenes in thyroid tissue. 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. 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.

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). 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. Technetium-99m 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. However, only a minority of cold lesions are thyroid cancer. The use of thyroid radionuclide scanning for adult patients with thyroid nodules is best reserved for patients with suspected hyperthyroidism or those with extensive multinodular goiters. 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; others suggest removal of all thyroid nodules in children. The accuracy of fine needle aspiration of thyroid nodules in children was found to be less than that reported in adults but similar to that of ultrasound or scintigraphy.

The goals of primary treatment of thyroid cancer in childhood are to eradicate disease and extend not only overall, but recurrence-free survival (RFS). Extending RFS is itself a desirable goal in children because it improves quality-of-life, alleviates anxiety during psychologically formative years, reduces medical resource consumption, and may increase overall survival.

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. Radioiodine scanning remains the mainstay of staging for differentiated thyroid cancer. 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.

Considerable controversy exists as to the choice of diagnostic isotope for thyroid cancer surveys.<sup>65-67</sup> I-131 has traditionally been used. 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 and less probability of stunning. Recombinant human thyrotropin (rhTSH, Thyrogen) can be used instead of hormone withdrawal. Some early studies using FDG-PET for thyroid cancer staging early in the course of treatment have had disappointing results, and FDG-PET is therefore not recommended in the routine staging of thyroid cancer; the well-differentiated, iodine-avid thyroid cancer is less likely to be glycolytic, and therefore FDG-avid, than more aggressive and iodine-negative disease. 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.

Although extensively investigated, treatment of pediatric thyroid cancer remains controversial. 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 recommends lobectomy alone for differentiated thyroid cancer patients with early-stage disease, the American Thyroid Association and the American Association of Clinical Endocrinologists 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. It has to be noticed that after total thyroidectomy, radioactive iodine 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. 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. For these reasons and, particularly in light of their expected life span as compared with the adult with thyroid cancer, in our hospital, a total or near-total thyroidectomy is performed in all children with thyroid cancer. This intensive approach consists not only of total thyroidectomy but also with central lymphadenectomy in all cases, completed by modified lateral lymphadenectomy when necessary. To avoid complications, most surgeons perform a "near-total" thyroidectomy leaving small amounts of remnant tissue near the nerve sites and parathyroid glands. This is especially often for pediatric patients, where size and spacing to critical structures is

much smaller than in adults.

The second 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. 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.

The treatment dose of I-131 administered after thyroidectomy is also a considerable source of controversy in both adult and pediatric thyroid cancer patients. In addition to all thyroid cancer patients important considerations, pediatric thyroid cancer requires some special ones. 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 be more sensitive than adult tissues to I-131. 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. 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 administered dose for pediatric patients. The same dose schema described 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 chemotherapy 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.

Radioiodine therapy is generally safe. Short-term side effects include nausea and vomiting (more frequent in children than in adults), transient neck pain and edema, sialadenitis (<5% incidence), mild myelosuppression (approximately 25%), transient impairment of gonadal function both in females and males (sperm quality in boys), or nasolacrimal obstruction (approximately 3%), with most cases generally being asymptomatic-moderate, self-limiting, or easily prevented or treated. Radioiodine therapy appears not to impair fertility. However, therapeutic I-131 carries a small but definite increase in cancer risk, particularly in the salivary glands, colon, rectum, soft tissue and bone.

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 restaging in cases of recurrence. 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.

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. To better guide primary treatment, different therapeutic combinations should be prospectively compared using RFS as the primary endpoint. Efforts also should be made to identify molecular signatures predicting recurrence, metastasis and mortality.