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

I. Iakovou
Assist. Professor

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 allcancers in those younger than 10 years; 3.6% of cancers inthose aged 10 to 14 years and 7.8% of cancers in those aged15 to 19 years.

The biologic behavior of thyroid cancer can differ significantlybetween adults and children. The majority ofpediatric thyroid cancers are of the well-differentiated papillaryor follicular subtype. The pediatric cancers are most often iodine-avid and often highly TSH-sensitive. Medullarythyroid carcinoma is uncommon in children and, althoughtypically associated with multiple endocrine neoplasia type 2(MEN2), can occur sporadically or as familial MTC withoutother associated endocrine abnormalities.

Unlike adults, children typically present with advanceddisease at diagnosis. Extensive regional nodal involvementoccurs in 60% to 80% of pediatric thyroid cancers; there is ahigher incidence of distant metastases as well.Unfortunately, children alsohave higher local and distant recurrence rates for thyroidcancer than do adults

Children with thyroid cancer have a rapid response totherapy. Prognosis is excellent, with a 10-year mortality of10% and an overall survival of 95% at 20 years. Even inthe face of distant metastases, the usually iodine-sensitivedisease of children is much less likely to be fatal than comparabledisease in adults, where 5 year survival in patientswith 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 isonly 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 whenexposure to ionizing radiation occurred at a younger age, infemales, when there were greater thyrotropin (TSH) levels at time of exposure and with higher radiation rates. Some ofthese 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 inexposed 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 thyroidnodules. 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 lesionsare thyroid cancer. The use of thyroid radionuclidescanning for adult patients with thyroid nodules is best reservedfor patients withsuspected hyperthyroidism or those with extensive multinodulargoiters. Outside of these patientsubsets, thyroid scanning of nodules is not indicated,and patients should proceed directly to FNA, often with ultrasoundguidance, for suspicious lesions.

The best method to evaluate thyroid nodules in children remains debatable. Some recommend surgical resection ofscintigraphic “cold” nodules; otherssuggest removal of allthyroid nodules in children. The accuracy of fine needle aspiration ofthyroid nodules in children was found to be less than that reported inadults 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 casesinvolves surgical resection, extensive presurgical staging isnot part of the standard clinical evaluation of thyroid cancer.Radioiodine scanning remains the mainstay of staging fordifferentiated thyroid cancer. Unlike iodine scintigraphyfor benign thyroid disease, thyroid cancer metastatic surveysrequire extensive patient preparation. Almost all thyroid

cancers,though iodine-avid, are considerably less iodine-avidthan normal thyroid tissue, that is, they are “cold” comparedwith the normal thyroid. When substantial thyroid tissue ispresent at the time of the scan, it will therefore limit visualizationof thyroid cancer sites. Thyroid cancer surveys aretherefore possible only after near-total thyroidectomy and arenot appropriate for patients who have only undergone hemithyroidectomy.

Considerable controversy exists as to the choice of diagnosticisotope for thyroid cancer surveys.65-67 I-131 has traditionallybeen used, An increasing number of nuclear medicine centers useI-123 to perform thyroid cancer surveys. I-123 has the advantageof much lower radiation burden and, at 159 keV,gamma emission much more amenable to imaging on standardgamma 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 stagingearly in the course of treatment have had disappointing results,and FDG-PET is therefore not recommended in theroutine 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 havenoted some pediatric patients with rapidly growing adenopathythat is both iodine and FDG-avid, where FDG-PET maybe helpful in directing surgery.

Although extensively investigated, treatment of pediatric thyroidcancer remains controversial. One of the first controversies encountered in treatment ofthe pediatric thyroid cancer patient is the extent of the thyroidectomy to be performed in those patients with a solitarythyroid cancer. Although the Society of Surgical Oncologyrecommends lobectomy alone for differentiated thyroid cancerpatients with early-stage disease, the American ThyroidAssociation and the American Association of Clinical Endocrinologistsrecommend total or near total thyroidectomyin all patients except those with T1M0N0 disease. For multifocal,bilateral or advanced thyroid cancer (including localinfiltration 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 thyroidtissue, local and distant metastases. Serum thyroglobulin levelsare more sensitive in the detection of persistent or recurrentdisease when all normal thyroid tissue has been removed,especially after remnant ablation. Recurrencedevelops in the contralateral lobe in 7% of patients; 50% ofthese patients die of their disease. As many as 85% ofthose with PTC have microscopic foci of disease in the contralaterallobe, total thyroidectomy eliminates these foci assites of possible disease recurrence.For these reasonsand, particularly in light of their expected life span as comparedwith the adult with thyroid cancer, in our hospital, a total or near-total thyroidectomy is performedin 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 remnanttissue near the nerve sites and parathyroid glands. This is especially often for pediatricpatients, where size and spacing to critical structures is

muchsmaller than in adults.

The second consideration is whether or not to treat with radioiodine.For patients with small primary tumors, often incidentallydiscovered in surgery for a benign nodule, somepractitioners advocate not undergoing thyroid remnant ablation,even if a near-total thyroidectomy has been performed.Most agree that tumors that are at increased risk forrecurrence and spread, including larger tumors, those withlymph node metastasis, and those with capsular penetration,deserve radioiodine ablation.

The treatment dose of I-131 administered after thyroidectomyis also a considerable source of controversy in both adultand pediatric thyroid cancer patients. In additionto all thyroid cancer patients important considerations,pediatric thyroid cancerrequires some special ones. Pediatric patientsmay be more sensitive to the side-effects of I-131, includingthe possibility of inducing a second cancer. Some studieshave suggested that, per unit absorbed dose, pediatric organssuch as bone marrow may more sensitive than adult tissues toI-131. On the other hand, studies have shown that theeffect of radioiodine in reducing distant recurrences of thyroidcancer can take 20 to more years to be manifest. Witha nearly full lifetime for disease recurrences to occur, it ishighly desirable to eradicate small-volume residual disease on initial presentation, especially for more advanced disease,where micrometastases are more likely. These competingconsiderations are important when choosing radioiodineadministereddose for pediatric patients. The same dose schema described for adults isused in children, but the actual I-131 dose administered isadjusted by weight and by additional safety factors dependenton age or antecedent treatment. Radiation dosimetryestimates are typically performed in those patients under age 10 years; in patients who have undergone prior chemo- orradiation therapy; in those that have distant metastases; inthose in whom thyroid cancer is a secondary tumor; or whencumulative 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 131I 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 notbeen well established and also remains controversial. Currentindications include verification of ablation and restaging incases of recurrence. Our practice hasbeen to verify thyroid remnant ablation with at least onethyroid metastatic survey 9 to 12 months after initial treatment,often using arhTSH driven approach. In some highriskpatients, 1 to 2 additional scans can be considered atyearly or biyearly intervals. No standard recommendationshave yet evolved. Thyroid cancer

surveys are also used in thesetting of suspected recurrence, on the basis of physical examination,thyroglobulin levels, or other imaging such asultrasound.

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 manifestuntil after the first decade post-therapy, it is important toremember that 5% to 7% of children succumb to progressivedisease. More importantly, 5% to 7% develop lethal treatmentrelated complications or secondary malignancies. Consequently,lifelong surveillance for pediatric thyroid cancerpatients is mandatory and is a delicate balance between theside 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.