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Nuclear Medicine in Pediatric and Adolescent Tumors

Pınar Özgen Kiratli, MD,* Murat Tuncel, MD,* and Zvi Bar-Sever, MD†

Nuclear medicine has an important role in the management of many cancers in pediatric age group with multiple imaging modalities and radiopharmaceuticals targeting various biological uptake mechanisms. 18-Flourodeoxyglucose is the radiotracer of choice especially in patients with sarcoma and lymphoma. ^{18}FDG-PET, for sarcoma and lymphomas, is proved to be superior to conventional imaging in staging and therapy response. Although studies are limited in pediatric population, ^{18}FDG-PET/CT has found its way through international guidelines. Limitations and strengths of PET imaging must be noticed before adapting PET imaging in clinical protocols. Established new response criteria using multiple parameters derived from ^{18}FDG-PET would increase the accuracy and repeatability of response evaluation. Current data suggest that I-123 metaiodobenzylguanidine (MIBG) remains the tracer of choice in the evaluation of neuroblastoma (NB) because of its high sensitivity, specificity, diagnostic accuracy, and prognostic value. It is valuable in determining the response to therapy, surveillance for disease recurrence, and in selecting patients for I-131 therapy. SPECT/CT improves the diagnostic accuracy and the interpretation confidence of MIBG scans. ^{18}FDG-PET/CT is an important complementary to MIBG imaging despite its lack of specificity to NB. It is valuable in cases of negative or inconclusive MIBG scans and when MIBG findings underestimate the disease status as determined from clinical and radiological findings. F-18 DOPA is promising tracer that reflects catecholamine metabolism and is both sensitive and specific. F-18 DOPA scintigraphy provides the advantages of PET/CT imaging with early and short imaging times, high spatial resolution, inherent morphologic correlation with CT, and quantitation. Regulatory and production issues currently limit the tracer's availability. PET/CT with Ga-68 DOTA appears to be useful in NB imaging and may have a unique role in selecting patients for peptide receptor radionuclide therapy with somatostatin analogues. C-11 hydroxyephedrine PET/CT is a specific PET tracer for NB, but the C-11 label that requires an on-site cyclotron production and the high physiologic uptake in the liver and kidneys limit its use. I-124 MIBG is useful for I-131 MIBG pretherapeutic dosimetry planning. Its use for diagnostic imaging as well as the use of F-18 labeled MIBG analogues is currently experimental. PET/MR imaging is emerging and is likely to become an important tool in the evaluation. It provides metabolic and superior morphological data in one imaging session, expediting the diagnosis and lowering the radiation exposure. Radioactive iodines not only detect residual tissue and metastatic disease but also are used in the treatment of differentiated thyroid cancer. However, these are not well documented in pediatric age group like adult patients. Use of radioactivity in pediatric population is very important and strictly controlled because of the possibility of secondary malignities; therefore, management of oncological cases requires detailed literature knowledge. This article aims to review the literature on the use of radionuclide imaging and therapy in pediatric population with thyroid cancer, sarcomas, lymphoma, and NB.
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*Department of Nuclear Medicine, Hacettepe University Medical Center, Ankara, Turkey.
†Department of Nuclear Medicine, Schneider Children's Medical Center, Petah Tikva, Israel.
Address reprint requests to Pınar Özgen Kiratli, MD, Department of Nuclear Medicine, Hacettepe University Medical School, Sıhhiye 06100, Ankara, Turkey. E-mail: pkiratli@gmail.com

Thyroid Cancers in Pediatric and Adolescent Patients

Incidence

The incidence of differentiated thyroid cancer (DTC) has increased over the past decades and became 0.5-0.7/

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million among pediatric patients.[1] Although it is less common compared to the adult population, it has increased gradually and became the fifth most common cancer in children aged between 0 and 14 years.[2-4] Geographic region and iodine insufficiency are considered the most possible reasons for this increase, as well as the availability of the screening tests.[5]

Risk Factors

Previous history of thyroid disease is a risk factor for DTC. Papillary thyroid carcinoma (PTC) has been reported in 9.6% of the patients with thyroid nodules associated with autoimmune thyroiditis.[6] On the contrary congenital hypothyroidism caused by dyshormonogenesis or iodine transporter defect increases the risk of nodules in children which may turn to follicular thyroid cancer.[7] Thyroid cancers originating from follicular cells have a familial association of 5% and 25% for parafollicular cell–originated cancers in children. Radioactive accidents have been considered the primary reason responsible for the increase in DTC incidence[8,9] and the most well known is the Chernobyl accident, where there has been an increased rate of thyroid cancer among the survivors younger than 15.[10] However, the main responsible radiation exposure is caused by imaging procedures using radioactivity and radiotherapy. External radiation therapy used for the treatment of some benign disorders in the past, as well as in some malign diseases, results in an increased rate of DTC.[11] Children, younger than 5 years, are the most sensitive group to radiation. Patients with DTC due to radiation exposure have higher rates of lymph node involvement and distant metastases, with short latency period and worse clinical outcome.[12]

Presentation

DTC in pediatric age group presents with a relatively advanced stage at the time of diagnosis and shows higher rate of recurrence.[13] Mazzaferri and Kloos[14] reported that cervical lymph node metastases were seen as high as 79%, and distant organ metastases in 15% of these patients. The recurrence rate was reported in 37% of the pediatric patients, but fortunately the mortality rate is lower (1%) compared to adults.[12] The reasons for this better prognosis and overall survival in pediatrics still remain unclear.[15]

Gene rearrangement is common, and point mutations are rare in pediatric PTC. Besides, studies have shown that *BRAF* mutations are rare, but *RET/PTC* relocations are common in children with DTC. Point mutations of RAS and BRAF lead to genomic instability and dedifferentiation causing diminished expression of the sodium iodide symporter, but *RET/PTC* relocations do not cause genomic instability.[16,17] Sodium iodide symporter expression is a strong marker for differentiation, and it is higher in both primary tumor and metastases.[18] These molecular differences might be the reason for better response to radioiodine in children and may explain low mortality and low progression rate.

The incidence of DTC is lower in prepubertal children, but the course is more aggressive.[15] Extrathyroidal extension and lung metastases are commonly seen in prepubertal period compared to pubertal period (80% and 70% vs 35.5% and 23.5%, respectively).[15,19]

Histopathology

PTC is the most common DTC in pediatric age group including Turkey.[20] The size of the tumor is generally more than 1 cm, multifocal and bilateral, and presents with metastases to the lungs in approximately 25% of cases generally with substantial local lymph node metastases.[19] It was hypothesized that invasion of the thyroid capsule and adjacent tissues is due to the smaller size of the thyroid gland in children.[15] Histologic subtypes of PTC in pediatrics are classic, solid, follicular, and diffuse sclerosing. On the contrary, follicular type DTC is frequently seen in pubertal children.[21] It is often unifocal and shows hematogenous metastases to the lungs and bones. Hurtle cell (oncocytic), clear cell, and insular (poorly differentiated) carcinoma are histologic variants of follicular type DTC.

Medullary thyroid cancer (MTC) is seen in 5% of childhood thyroid carcinoma. It arises from parafollicular C cells of the thyroid gland[2] and is often associated with multiple endocrine neoplasia type 2, where sporadic MTC and anaplastic thyroid cancer are almost only seen in adults. In patients with hereditary MTC, RET proto-oncogene mutation is always seen. RET mutation screening is more sensitive than traditional biochemical markers. As MTC is a functional neuroendocrine tumor, it secretes calcitonin, carcinoembriogenic antigen, and other peptides.[22] Calcitonin level is correlated with the tumor volume, recurrence, and carcinoembriogenic antigen is correlated with the lymph node involvement and distant metastases.[23] Prophylactic thyroidectomy is suggested once this mutation is detected.

Diagnosis

Patients generally present with palpable thyroid nodule or mass. Ultrasonography (US) is very valuable in the assessment of thyroid nodules. Signs of benign course are cystic or hyperechoic nodules with good demarcation and external vascularization,[24] whereas solid hypoechoic nodules, irregular borders, internal vascularization, and the presence of microcalcification are associated with malignancy. Thyroid scintigraphy has a role in the evaluation of the nodules' function. Nonfunctional thyroid nodules with suspicious US findings have higher risk for malignancy.[24] Once a nodule is found, it should be evaluated with fine-needle aspiration biopsy. Although fine-needle aspiration biopsy has a high sensitivity and specificity for the diagnosis of malignancy, the relatively low rate for positive predictive value (PPV) for benign diagnosis made surgery a preferable method for children younger than 10 years.[25]

Surgery is the primary treatment for thyroid cancer. Near-total or total thyroidectomy is the preferred operation for DTC. If the surgery is performed by experienced hands, children with DTC have lower rates of complications. The multifocal nature of PTC and better disease-free survival in children, made surgeons favor total thyroidectomy or near-