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PET/CT in pediatric oncology**AM Samuel**

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India**Abstract**

Radionuclide functional imaging has become a central part of pediatric oncological practice. There have been a number of major advances in imaging technology in recent years, but multislice CT with PET is the modality generating most interest in cancer imaging. In this review, we discuss the common uses and specific issues with regard to PET-CT imaging in pediatric practice. Brain tumors form a significant percentage of pediatric oncology. Use of FDG-PET in brain tumors has helped distinguish viable, residual, or recurrent tumor from post-therapeutic changes and necrosis. High-grade tumors show high uptake of FDG at diagnosis. FDG-PET results may also not accurately correlate with tumor progression after intensive radiation therapy. FDG-PET has been applied to accurate biopsy of infiltrative tumors, tumor grading, and prognostication. Limited available data also suggest that FDG-PET findings correlate well with histopathology and clinical outcome in children. FDG uptake is generally greater in higher grade lymphomas than in lower grade lymphomas. FDG-PET reveals disease sites that are not detected by conventional staging methods, resulting in upstaging of disease with potential therapeutic review. FDG-PET is useful for assessing need for marrow biopsy, residual or recurrent soft tissue masses seen on CT after therapy. The primary role of FDG-PET in neuroblastoma is in non-MIBG concentrating tumors. [11C]-Hydroxyephedrine ([11C]-HED), an analogue of norepinephrine, and [11C]-epinephrine PET have also been used in evaluating neuroblastoma. Uptake of these tracers is demonstrated within minutes after tracer administration, an advantage over MIBG imaging. The exact roles of FDG-PET in osteosarcoma and Ewing's sarcoma are not definitive. FDG-PET may play an important role in monitoring response to therapy. Another diagnostic role may be in assessing patients with suspected metastatic disease.

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Available from: <http://www.indianjancer.com/text.asp?2010/47/4/360/73551>**Full Text****Introduction**

Metabolic imaging with PET and PET-CT has been proving to be an important mode of cancer management in adult and pediatric practice. The potential applications are enormous. This brief review

will describe the role of PET-CT imaging in the present practices of cancer management in children coupled with discussion of specific issues pertinent to this topic. Experimental data of the future possible uses of various PET radiopharmaceuticals and biokinetics are beyond the purview of this communication and will not be described.

Tumor biology and FDG uptake

FDG-PET has been applied to tumor grading and prognostication. Higher grade aggressive tumors have higher FDG uptake than lower grade tumors, which may appear isometabolic or hypometabolic. Increased FDG uptake in a low grade tumor indicates transformation to a higher grade. Shorter survival times have been reported for patients whose tumors show the highest degree of FDG uptake. Limited data also suggest that FDG-PET findings correlate well with histopathology and clinical outcome in children. These are some of the common tenets which belie the use of FDG-PET/CT in oncological evaluation.

Patient preparation protocols: Specific issues related to pediatric population

The preparation of children and parents for nuclear medicine imaging is an important aspect of procedures. In PET-CT imaging, several of these are important but in addition there are a few issues that are specific to this molecular imaging technique.

Immobilization is of utmost importance in imaging and interpretation of data. Sheets wrapped around the body, sandbags, or special holding devices often are sufficient for immobilization. Parents can accompany their child during the course of a study to provide comfort and emotional support. Establishing reliable intravenous access is critical in pediatric imaging. Bladder catheterization also may be needed to avoid reconstruction artifacts in the pelvis and the possibility of spontaneous voiding during image acquisition with resultant radioactive urine contamination. A full bladder also may cause discomfort and lead to patient motion and image degradation. Sedation is indicated when it is anticipated that simple methods will be inadequate to ensure acceptable image quality. Sedation protocols vary from institution to institution. Guidelines such as those advanced by the Society of Nuclear Medicine, the American Academy of Pediatrics, and the American Society of Anesthesiology are useful in developing an institutional sedation program. Although many sedatives may affect cerebral metabolism, they are not known to cause significant changes in tumoral metabolism and can be administered at any time relative to FDG administration for studies of tumors outside the central nervous system (CNS). Oral contrast may be given to outline the bowel without significant untoward effects on image quality, although semiquantitative measures such as the standardized uptake value (SUV) may be altered with such maneuver. The optimum SUV calculation in pediatric patients may be different from that used in adult patients because of body changes that occur during childhood. SUV based on body surface area is a more uniform parameter than an SUV based on body weight in pediatric patients. Intravenous contrast medium is not administered routinely in PET/CT imaging studies because of the need for different contrast protocols for optimal CT imaging of various anatomical regions and potential attenuation correction-related artifacts. However, with new algorithms available PET/CT diagnostic capacity may be improved with little or no compromise of image quality. Procedure guidelines for tumor imaging with PET and PET/CT have been published. [1], [2] Normal patterns of 18 FFDG distribution

Before reviewing the applications of PET, it is important to consider potential causes of misinterpretation of FDG-PET that relate to physiologic variations in FDG distribution in children. [3],[4],[5] These include:

More extensive distribution of hematopoietic marrow than in adults
The occurrence of high FDG uptake in the thymus, in the adenoids, and tonsils
In the skeletal growth centers, particularly those of the long bone epiphyses
Variable FDG uptake in skeletal muscles, brown fat, myocardium, thyroid gland, and gastrointestinal tract
Accumulation of excreted FDG in the renal pelvis, ureter, and bladder
Tracer accumulation in draining lymph nodes from extravasated tracer at the time of intravenous tracer administration
Diffuse high bone marrow and splenic FDG uptake after the administration of hematopoietic-stimulating factors also may resemble disseminated metastatic disease.

Physiologic Activity

Post- chemotherapy thymic rebound

It is not uncommon to see normal physiologic activity more vividly after completion of treatment than before treatment. Variable physiologic FDG uptake is seen in the brain, digestive tract, liver, skeletal muscles, myocardium, bone marrow, and genitourinary tract. One of the most notable false-positive FDG uptake sites after therapy is the thymus where accumulation has been noted in younger patients, especially children. CT often shows enlargement of the thymus with no abnormal mass.

Brown adipose tissue

There are two types of adipose tissue in the human body: white adipose tissue that stores energy and serves as insulation and brown adipose tissue. Brown adipose tissue plays an important role in cold-induced and diet-induced thermogenesis. The brown color is attributed to the high vascularity and mitochondrial density. The mitochondria in brown adipose tissue exclusively express the thermogenic protein responsible for uncoupling respiration from adenosine triphosphate synthesis, dissipating heat.

FDG uptake in hypermetabolic brown fat can occur as glucose transporters have been shown in brown adipose tissue. Because hypermetabolic brown fat is typically bilateral, symmetric, and elongated in the supraclavicular area on PET the appearance is seldom confused with malignancy. However, when brown fat occurs in the mediastinum, focal FDG uptake in this region can be misinterpreted as primary malignancy or nodal metastases [Figure 1].{Figure 1}

Distribution of brown fat

Hypermetabolic brown fat has been localized to the paratracheal, paraesophageal, prevascular and pericardial regions, azygoesophageal recess, interatrial septum adjacent to the brachiocephalic arteries, and azygos and hemiazygos veins. The appearance of FDG uptake in mediastinal brown fat can be focal and spherical. An elongated appearance of FDG uptake in the mediastinum may be seen. An isolated single focus of hypermetabolic brown fat in the mediastinum-that is, without hypermetabolic brown fat elsewhere in the body may be rarely seen.

The SUV max of the hypermetabolic brown fat ranges from 3.4 to 13 (mean, 5.7). The SUV max of the hypermetabolic brown fat in the extramediastinal may be higher.

Brown fat deposits diminish with age because of reduced demands for thermogenesis. Brown fat is more common in children than in adults. [3],[4],[5],[6]

Radiation dose exposures

The use of low-dose 18 F-FDG-PET/CT scans in pediatric oncology whole body scans has been found to yield high-quality diagnostic information while exposing patients to less than half the radiation of a standard PET/CT procedure [Table 1]. [7] {Table 1}

Radiation Doses (Expressed in mSv) by Standard and Low-Dose Positron Emission Tomography/Computed Tomography (PET/CT)

Many patients are already being exposed to numerous scans because of their diagnosis. Children with cancer and those who are immunocompromised - for example, those who have received bone marrow or other types of transplant - are at higher risk of developing secondary malignancies. In addition, children's bone marrow is much more sensitive to radiation. Some data in the literature show that even exposure to diagnostic X-rays increases children's risk of developing malignancies in the future.

Clinical Applications of PET/CT in Children

The currently approved indications for pediatric patients have been developed in consultation with tumor groups and are within the framework of the evidence based guidelines for FDG-PET.

PET/CT referrals are for the following indications in pediatric oncology patients:

Lymphoma

For initial staging of patients to determine extent of disease. To determine response to chemotherapy or radiation therapy [Figure 2]. Post-chemotherapy for patients with advanced stage aggressive non-

Hodgkin's lymphoma and Hodgkin's lymphoma with residual CT abnormalities or initial bulky disease. To plan duration of chemotherapy for patients with Hodgkin's and non-Hodgkin's lymphoma. To plan duration and type of treatment for limited stage aggressive histology lymphoma. Diagnostic CT (full-dose, contrast-enhanced) is the standard of care to follow-up patients with lymphoma. There is evidence that whole body PET/CT imaging is more accurate than diagnostic CT for detection of disease recurrence. These multiple examinations result in large radiation doses to patients, especially of concern in the pediatric population. {Figure 2}

A retrospective study [8],[9] was done to compare the performance of PET/ low-dose CT and diagnostic CT in the follow-up of children with lymphoma. The data collected consisted of nodal and extra-nodal disease in the neck, chest, abdomen, and pelvis, as well as incidental findings. Using region-based analysis (neck, thorax, abdomen, and pelvis), 1.7% sets of paired PET/CT and diagnostic CT were discordant, all false-positives. PET/CT showed FDG uptake in lymph nodes whereas diagnostic CT was negative in 2 patients, biopsy showed follicular hyperplasia.

Diagnostic CT showed pulmonary infiltrates in one patient that was PET/CT negative and it resolved with antibiotics. Neither modality demonstrated false-negatives.

Given the high rate of correlation between the two modalities and lack of false-negative results, PET/CT may suffice for routine follow-up of pediatric patients with lymphoma, with diagnostic CT reserved for selected cases. In addition to being more cost-effective, there is considerably less radiation exposure to patients undergoing PET/CT alone. [8],[9]

Pitfalls in interpretation of PET/CT

Role of PET with F- 18 -(FDG) in staging of Hodgkin disease is well established despite several controversies. A report of Stage III Hodgkin lymphoma patient with false-positive FDG-PET/CT of a seven-year-old male with Hodgkin lymphoma was in remission at end of chemotherapy. At third and fourth month of post-chemotherapy follow-up, increased Gallium uptake and positive FDG-PET/CT in right lower quadrant of abdomen was observed. Open biopsy revealed lymphoid hyperplasia. He has been followed for 21 months without any evidence of disease.

Despite its documented benefit, results of FDG-PET/CT should be interpreted with great caution in order to avoid unnecessary interventions. [9]

Post-treatment FDG PET does not help exclude the presence of minimal residual disease, which may lead to disease relapse.

FDG is not a tumor-specific substance, and increased accumulation may be seen in a variety of benign conditions.

Infection (pneumonia, enterocolitis, cholecystitis, upper respiratory infection, cellulitis) Drug toxicity G-CSF therapy Radiation therapy Physiological activity (thymus, brown fat, bone marrow, brain, myocardium, GIT, urinary tract). Post-operative or biopsy changes Fracture and degenerative changes Injection leakage Nevertheless, recognition of these entities and correlation of FDG PET findings with clinical and other radiologic findings-especially those at combined PET and CT or PET-CT fusion imaging-allows improved diagnostic accuracy. If the interpretation of positive findings is exceptionally difficult, short term follow-up may be helpful. [10]

Achieving complete remission is the main objective of first-line chemotherapy. Complete remission is usually associated with a longer progression-free survival time than is partial remission, which is associated with poorer clinical outcome. However, defining complete remission can be difficult in some patients in whom residual abnormalities remain. Post-therapy residual abnormalities representing the development of fibrosis or tumor necrosis are seen in up to 64% of patients with lymphoma. [11]

Conventional imaging (CT, ultrasonography, magnetic resonance [MR] imaging) cannot reliably help differentiate between active tumor and fibrosis or necrosis. Metabolic FDG PET offers the advantage of functional tissue characterization. Currently, FDG PET may be more accurate than anatomic imaging modalities in assessing treatment effects to correctly identify patients with residual disease and predict therapy outcomes. [12]

In patients with persistent FDG uptake, it might be appropriate to use salvage therapy and possibly hematopoietic stem cell transplantation before a clinically overt relapse occurs.

Nevertheless, after completion of chemotherapy, FDG PET cannot help exclude the presence of microscopic residual disease, which may lead to a later relapse. [13],[14],[15]

PET after one to three cycles of chemotherapy

There is growing interest in patient response early during treatment. Less than 50% of patients with newly diagnosed aggressive non-Hodgkin lymphoma can expect prolonged disease-free survival with current treatment regimens. [16]

Patients who do not respond to initial chemotherapy are candidates for salvage chemotherapy or autologous bone marrow transplantation. Recognition of resistant or nonresponding tumor early during chemotherapy may result in lower cumulative treatment toxicity and tumor burden at the start of salvage therapy, thereby potentially improving clinical outcome and prognosis. However, the usefulness of these strategies has yet to be established, and further studies are warranted. Usually, metabolic changes following therapy tend to precede anatomic changes, a phenomenon that allows early response evaluation with functional imaging. [17],[18],[19] Effective treatment sharply reduces metabolic tumor activity within days, whereas persistent abnormal uptake is usually associated with treatment failure. In addition, PET performed after one or two cycles of chemotherapy may help predict long-term freedom from relapse more accurately than post-treatment PET, which does not help exclude the presence of microscopic residual disease. [20],[21],[22],[23],[24]

PET before autologous stem cell transplantation

Treatment consisting of high-dose chemotherapy combined with stem cell transplantation has been shown to be effective in patients who experience a relapse of lymphoma after undergoing conventional chemotherapy, but remain chemotherapy sensitive. It has been reported that FDG PET performed after salvage chemotherapy and before a combination of high-dose chemotherapy and stem cell transplantation can help predict patient outcome. That is, whereas patients with negative pre-transplantation FDG PET findings are unlikely to experience relapse, abnormal uptake at pre-transplantation FDG PET is associated with tumor progression after transplantation.

PET during or after radiation therapy or radioimmunotherapy

The relationship between radiation therapy and changes in tumor FDG uptake is yet to be established. Generally, FDG uptake 6 months after radiation therapy is associated with tumor recurrence. Radioimmunotherapy with iodine-labeled anti-B1 antibody developed against the surface antigen CD20 has been recognized as a promising approach for treatment of low-grade non-Hodgkin lymphoma. [19],[20]

Tumor response to radioimmunotherapy may be more gradual than response to chemotherapy. In a study, [21] FDG PET metabolic data obtained 1-2 months after radioimmunotherapy correlated well with the ultimate response of non-Hodgkin lymphoma to radioimmunotherapy.

Restaging and surveillance

Another study [25] demonstrated that FDG PET is a useful diagnostic tool in the follow-up of asymptomatic treated patients and the evaluation of symptomatic patients with suspected disease recurrence. Detection of residual tumors at a subclinical level or within a small volume might be beneficial for optimizing the efficacy of subsequent therapy.

False positive interpretations

FDG PET is very useful in the evaluation of treatment response in lymphoma patients. FDG is not a tumor-specific substance, and increased accumulation may be seen in a variety of benign conditions, which may give rise to false-positive results. In the post-therapy setting, it has been reported that up to 40% of FDG uptake occurs in nontumor tissues. Although several of these imaging pitfalls are easily recognizable, and therefore, unlikely to present diagnostic problems; others are potentially confusing.

Correlation with findings at anatomic imaging such as CT is important and could help identify changes resulting from treatment; PET with CT and PET-CT fusion imaging are especially helpful in this setting. If interpretation is exceptionally difficult, short-term follow-up may be helpful.

Infection

One of the well-known side effects of chemotherapy is bone marrow suppression, which leads to neutropenia, anemia, and thrombocytopenia. Affected patients are at increased risk for infections such as upper respiratory infection, pneumonia, enterocolitis, and cholecystitis. Anti-inflammatory cells such as activated macrophages or granulation tissue that are present in areas of inflammation have been shown to actively take up FDG.

Drug toxicity

Drug toxicity of the lung is not uncommon during or after chemotherapy. Bleomycin is one of the most commonly used drugs for the treatment of Hodgkin disease, with up to 5% of patients to whom it is administered developing pulmonary drug toxicity. Diffuse increased FDG accumulation in the lungs has been reported with this conditions.

Granulocyte colony-stimulating factor therapy

G-CSF is a glycoprotein hormone that primarily regulates proliferation and differentiation of granulocyte precursors. G-CSF has been used increasingly to correct chemotherapy-induced neutropenia and has reduced infections. Increased FDG uptake is often observed in bone marrow and spleen during and after G-CSF therapy. In patients with a prior history of lymphomatous infiltration of bone marrow, normal bone marrow may demonstrate increased activity due to G-CSF therapy, whereas previously infiltrated bone marrow may demonstrate reduced FDG uptake due to resolution of tumor cell uptake.

Radiation therapy

The accumulation of FDG in tumor cells may be enhanced following radiation therapy, since radiation therapy may cause inflammation in normal structures such as the lungs and mucous membranes, thereby inducing pneumonia, pharyngitis, and esophagitis. After radiation therapy, normal physiologic uptake (e.g., in the bone marrow and salivary glands) may be decreased.

Post-operative changes

Healing involves an inflammatory reaction even in the absence of infection. Leukocytic infiltration is present in the granulation tissue associated with wound repair and the resorption of necrotic debris and hematoma. Recent surgery can result in spurious increased FDG uptake in areas of resolving inflammation. Focal FDG uptake associated with ostomies or various indwelling stents (e.g., tracheostomy gastrostomy) is not uncommon.

Fracture and degenerative change

Fractures are often seen in patients with malignant disease due to metastasis or radiation therapy and are frequently associated with increased FDG uptake. In addition, focal uptake associated with degenerative change is not uncommon.

Injection leakage

Leakage at the injection site or residual radiotracer in the indwelling catheter used for injection causes accumulation of FDG. Abnormal FDG accumulation in lymph nodes can be as a consequence of delivery of the radiotracer by means of lymphatic drainage, when the radiotracer extravasates into tissue drained by a regional lymph node group.

FDG uptake in axillary lymph nodes due to partial subcutaneous injection into the antecubital fossa has been reported. In patients who receive an injection of FDG through a central venous catheter that has a thrombus at the tip, FDG could become trapped at the thrombus site and mimic mediastinal adenopathy.

False-negative findings

Because the spatial resolution of PET is not perfect, lesions less than 1 cm often go undetected. Although FDG PET is sensitive in most low-grade lymphomas (e.g., follicular lymphoma), some types of indolent lymphoma such as peripheral T-cell lymphoma are not well visualized.

Physiologic uptake can obscure the uptake by lymphoma, especially in the gastrointestinal tract and bone marrow.

Sarcoma

To evaluate the primary soft tissue mass prior to biopsy to identify high grade areas and guide biopsy. For staging of locally advanced high grade soft tissue sarcomas. For detection of suspected local recurrence of soft tissue sarcoma after definitive treatment. For staging of Ewing's sarcoma. For initial staging and evaluation of potential recurrence in osteogenic sarcoma.

Identification of an Unknown Primary Site

Although most sarcomas are evident on physical examination, it is estimated that 4% of rhabdomyosarcomas and 3–5% of all cancers present with metastatic disease and an unknown primary site. The imaging evaluation of such patients is focused on identifying the primary site and is guided by both clinical suspicion and the pathologic type of metastatic disease.

PET/CT was found useful in identifying an unknown primary site in a child with widely metastatic alveolar rhabdomyosarcoma. [26]

Initial Staging of a Sarcoma

The baseline imaging evaluation of bone and soft tissue sarcomas in children currently includes MRI of the primary tumor, CT of the chest to evaluate pulmonary metastases, and technetium-99m-labeled methyldiphosphonate (^{99m}Tc MDP) nuclear scintigraphy to identify bony metastatic disease. In tumors with a propensity for regional nodal spread, as in rhabdomyosarcoma, MRI or CT of the draining lymph nodes must also be performed. PET-CT was useful in identifying and localizing unusual sites of soft tissue and bony metastases not appreciated on physical examination or imaging performed during the conventional metastatic workup. PET/CT has had limited specificity in distinguishing benign and malignant nodal disease.

Monitoring Response to Therapy

Evaluating response to neoadjuvant chemotherapy is crucial in the management of childhood sarcomas, particularly osteosarcoma, for which tumor response is highly predictive of patient outcome and may impact surgical planning for amputation or limb salvage procedures. Currently, the therapeutic response of sarcomas in children is assessed by morphologic changes seen on CT and MRI. These imaging techniques can be limited by distorted normal anatomy, indistinct tumor border, and a lack of reproducible quantitative information about tumor viability. Radiation therapy and chemotherapy may invoke significant changes in tumor viability, whereas only minimal change in morphology is apparent on conventional imaging.

It has been reported that measurement of the standard uptake value of primary osteosarcoma, on serial FDG PET images is an accurate indicator of tumor response to preoperative chemotherapy.

PET/CT to be a useful adjunct in assessing the adequacy of surgical tumor resection.

Although the value of PET in the evaluation of a number of solid tumors in adults has been validated, further prospective clinical trials are necessary to determine the role of PET and PET/CT in the management of pediatric sarcomas. [26]

Neuroblastoma

For evaluation of the extent of viable tumor tissue in primary tumor. For staging and disease evaluation of MIBG-negative tumors. Post-treatment, to evaluate residual mass or primary site for recurrent or residual tumor, particularly if conventional studies are not helpful or equivocal. Post-treatment or marrow transplantation, to evaluate for local recurrence or distant metastases. The published experience on

neuroblastoma is limited, scan findings correlate well with disease status as determined by MIBG scans, CT (or MRI), bone marrow tests, urine catecholamine levels, and clinical history.

Sequential scans depict treatment effects and disease evolution.

Because of the higher spatial resolution and the tomographic nature of PET images, it is better than routine ^{123}I - or ^{131}I -MIBG scintigraphy for identifying small lesions and for delineating the extent or localizing anatomic sites of disease. An advantage over MIBG scans for detecting metastases in liver, where the normally intense accumulation of MIBG can obscure disease. PET shows more osteomedullary abnormalities than $^{99\text{m}}\text{Tc}$ -MDP scans in extracranial structures, and in this regard, it matches or surpasses MIBG scans. PET and MIBG scans show similar patterns of diffusely abnormal skeletal findings in patients with extensive bone marrow involvement but neither imaging modality reliably detects minimal bone marrow. A major drawback of PET is lack of visualization of lesions in the cranium because of high physiologic activity in brain. PET might provide insights into the proliferative or malignant potential of disease. Whether the degree of uptake at diagnosis has prognostic significance, especially with localized tumors, has not been studied. The findings in patients with metastatic neuro-blastoma can influence treatment decisions. For example, in patients receiving cytotoxic therapy, but with persistence of measurable lesions by standard staging studies, PET scans with normal or with faintly abnormal distribution of FDG might be indicative of quiescent or responding, rather than actively proliferating or aggressive, disease; the impact would be support for continuation of the treatment program. The current primary role of FDG-PET in neuroblastoma is in the evaluation of known or suspected neuroblastomas that do not demonstrate MIBG uptake. ^{11}C Hydroxyephedrine (^{11}C -HED), an analog of norepinephrine, and ^{11}C epinephrine PET also have been used in evaluating neuroblastoma. [27],[28],[29],[30]

Bone Tumors

The exact roles of FDG-PET in osteosarcoma and Ewing's sarcoma are unclear. However, current experience suggests that in patients with bone sarcomas, FDG-PET may play an

important role in assessing the extent of disease [Figure 3], monitoring the response to therapy, and predicting the long-term outcome after therapy. In comparison with bone scintigraphy, FDG-PET may be superior for detecting osseous metastases from Ewing's sarcoma but may be less sensitive for those from osteosarcoma. Its role is in assessing patients with suspected or known pulmonary metastasis, which is particularly common with osteosarcoma. [31],[32] One of the first well-described applications of ^{18}F -fluoride PET was the imaging of primary bone tumors. Using projection and tomographic images, both malignant and benign skeletal lesions were identified by ^{18}F -fluoride PET. [33],[34] Subsequent clinical use has demonstrated the utility of ^{18}F -fluoride PET in detecting primary bone tumors. {Figure 3}

Rare Tumors in Children

Adrenocortical tumors in children are usually endocrinologically active and very aggressive clinically. A germline mutation is a major predisposing factor. Most patients present with virilization. Two-thirds of patients have resectable tumors.

Preliminary experience indicates that these tumors are quite active metabolically, and FDG has been used to monitor them. Hepatoblastoma is quite rare, accounting for less than 1% of childhood tumors. With chemotherapy and surgery as primary treatment modalities, the prognosis has improved considerably over the past 20 years. The 5-year survival rate has increased from 30% to 70%. These tumors are also metabolically active. In contrast to FDG uptake in hepatocellular carcinomas, hepatoblastomas accumulate and retain FDG much more reliably. FDG-PET is useful in monitoring hepatoblastomas during and after therapy. [35],[36],[37]

Brain

To evaluate for recurrent tumor [Figure 4]. To differentiate between recurrent tumor and post-treatment necrosis. For localization of areas of high grade disease to guide biopsy and treatment planning. {Figure 4}

The most common tumors are medulloblastoma, cerebellar astrocytoma, ependymoma, brain stem gliomas, optic and hypothalamic gliomas, craniopharyngiomas, and germ cell tumors.

Supratentorial tumors are most often astrocytomas, many of which are low grade.

MRI and CT are the principal imaging modalities used in staging and follow-up for children with CNS tumors.

Their main limitation is distinguishing viable recurrent or residual tumor from post-therapy alterations.

Single-photon emission CT with ^{201}Tl and $^{99\text{m}}\text{Tc}$ methoxyisobutylisonitrile has proven valuable for this determination in several pediatric brain tumors, generally demonstrating tracer uptake in the tumor and not in the scar tissue.

The use of FDG-PET in brain tumors has widely helped distinguish viable tumor from post-therapeutic changes.

FDG uptake relative to adjacent brain indicates residual or recurrent tumor, whereas low or absent FDG uptake is observed in areas of necrosis. FDG-PET does not exclude microscopic tumor foci. FDG-PET results also may not accurately correlate with tumor progression after intensive radiation therapy. Elevated FDG uptake may persist in the immediate post-therapy period. Combined anatomical (MRI) and metabolic (PET) image information has been shown to improve the diagnostic yield of stereotactic brain biopsy in children with infiltrative, ill-defined brain lesions while reducing tissue sampling in high-risk functional areas. FDG-PET has been applied to tumor grading and prognostication. Higher-grade, aggressive tumors typically have greater FDG uptake than do lower-grade tumors, which may appear isometabolic or hypometabolic in comparison with normal brain tissue. The development of hypermetabolism, as evidenced by increased FDG uptake in a low-grade tumor that appeared hypometabolic at diagnosis, indicates progression to a higher grade. The degree of FDG uptake appears to correlate with the biological behavior of the tumor. Shorter survival times have been reported for patients whose tumors show the highest degree of FDG uptake. Limited available data also suggest that FDG-PET findings correlate well with histopathologic findings and clinical outcome in children. A potential pediatric application of this arises from a reported excellent correlation between FDG-PET findings and clinical outcome in children affected by neurofibromatosis and low-grade astrocytomas. Both FDG-PET and $^{11\text{C}}$ -Met PET have been shown to be independent predictors of event-free survival. $^{11\text{C}}$ -Met, because of the short 20-minute half-life of the $^{11\text{C}}$ label, must be produced locally for administration and is currently not commercially available. Potential uses of ^{18}F -3'-deoxy-3'-fluorothymidine, $^{11\text{C}}$ -methyl-L-tryptophan, and ^{18}F -fluoroethyl-L-tyrosine in assessing brain tumors recently have been described. [38],[39],[40]

Thyroid carcinoma

For detection and localization of suspected recurrence after definitive therapy, in patients with elevated or rising thyroglobulin levels and negative radioiodine scan (papillary and follicular carcinomas).

Principles of functional imaging of endocrine tumors

^{18}F FDG is taken up into cells via glucose transporters, and after conversion to ^{18}F deoxyglucose-6-phosphate (^{18}F FDG-P), catalyzed by hexokinase (HK), is trapped in the cells because ^{18}F deoxyglucose-6-phosphate is not a substrate for glucose-6-phosphatase (G6P). ^{18}F Fluorodopamine (^{18}F FDA) is taken up by chromaffin cells via the cell membrane norepinephrine transporter (NET) and translocated into storage vesicles via the vesicular monoamine transporter (VMAT), before undergoing slow conversion to 6- ^{18}F fluoronorepinephrine (^{18}F FNE) catalyzed by dopamine- α -hydroxylase (DBH). $^{11\text{C}}$ Metomidate binds to 11β -hydroxylase ($11\beta\text{OHase}$) in adrenocortical cells. $^{11\text{C}}$ Estradiol binds to nuclear receptors and ^{111}In pentetreotide (^{111}In octreotide) to cell membrane somatostatin receptors. In patients with known thyroid cancer following thyroidectomy, serum thyroglobulin levels, at baseline or after administration of recombinant human TSH, provide useful diagnostic information for detecting recurrence or metastases.

Some patients with metastatic thyroid cancer have undetectable or uninterpretable thyroglobulin levels,

due to circulating thyroglobulin antibodies or minimal thyroglobulin secretion. In this setting, radioiodine whole body scanning and other radiological imaging studies are appropriate.

About 20% of patients with well-differentiated thyroid cancer have postoperative recurrence or cervical metastases. Radioiodine scanning fails to detect one third to one half of such cases due to poor iodine uptake or small tumor size.

Neck ultrasound (often followed by ultrasound guided biopsy) is therefore usually recommended when a cytological diagnosis is important. Anatomic distortion by prior surgery may interfere with interpretation of CT and MRI imaging results. If elevated thyroglobulin levels lead to suspicion of recurrence or metastasis, then 18 FDG scanning is useful.

In patients with negative radioiodine scans after thyroidectomy, but with serum thyroglobulin levels above 2 ng/ml, 18 FDG scanning can detect metastases in cervical lymph nodes not evident by CT or MRI. Thus, thyroid imaging using 18 FDG should be restricted to postoperative thyroidectomy patients; in such patients, the sensitivity and specificity of 18 FDG scanning for detecting residual tumor, recurrence, or metastases are 82-95% and 83-95%, respectively, depending on the site of metastasis. 18 FDG scanning may also enable detection of Hurthle cell carcinoma, which radioiodine usually fails to visualize. [41],[42], [43]

Medullary thyroid cancer is often invasive and progressive over years, with a high potential for metastasis. Because of their hypermetabolic state, 18 FDG scanning offers a potential approach to detect such lesions and improve identification of involved lymph nodes, surgical resection of which can result in complete or prolonged remission.

Thyroid "incidentalomas" found on 18 FDG scanning appear to have a high rate of malignancy and should be assessed by fine-needle aspiration.

PET scanning may also be useful in patients with anaplastic thyroid cancer.

Radiolabeled monoclonal antibodies in PET imaging

Imaging of tumors with radiolabeled mAbs seeks to enhance the sensitivity and specificity of disease detection. More important, it provides vital pharmacokinetic information as well as dosimetry measurements not easily available by conventional radiologic imaging modalities. The use of SPECT and PET has added greatly to precision in quantifying radioactivity targeted by radiolabeled antibodies in vivo. Nevertheless, few antibodies are currently available for radioimmunodetection in pediatric patients.

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