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PET and PET/CT in Pediatric Oncology

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^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and FDG-PET/computed tomography (CT) are becoming increasingly important imaging tools in the noninvasive evaluation and monitoring of children with known or suspected malignant diseases. In this review, we discuss the preparation of children undergoing PET studies and review radiation dosimetry and its implications for family and caregivers. We review the normal distribution of ^{18}F-fluorodeoxyglucose (FDG) in children, common variations of the normal distribution, and various artifacts that may arise. We show that most tumors in children accumulate and retain FDG, allowing high-quality images of their distribution and pathophysiology. We explore the use of FDG-PET in the study of children with the more common malignancies, such as brain neoplasms and lymphomas, and the less-common tumors, including neuroblastomas, bone and soft-tissue sarcomas, Wilms' tumors, and hepatoblastomas. For comparison, other PET tracers are included because they have been applied in pediatric oncology. Multiple multicenter trials are underway that use FDG-PET in the management of children with neoplastic disease; these studies should give us greater insight into the impact FDG-PET can make in their care. PET is emerging as an important diagnostic imaging tool in the evaluation of pediatric cancers. The recent advent of dual-modality PET-computed tomography (PET/CT) imaging systems has added unprecedented diagnostic capability by revealing the precise anatomical localization of metabolic information and metabolic characterization of normal and abnormal structures. The use of CT transmission scanning for attenuation correction has shortened the total acquisition time, which is an especially desirable attribute in pediatric imaging. Moreover, expansion of the regional distribution of the most common PET radiotracer, FDG, and the introduction of mobile PET units have greatly increased access to this powerful diagnostic imaging technology. Here, we review the clinical applications of PET and PET/CT in pediatric oncology. General considerations in patient preparation and radiation dosimetry will be discussed.

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The preparation of children and parents for nuclear medicine imaging has been thoroughly reviewed elsewhere.[1,2] Sheets wrapped around the body, sandbags, or special holding devices often are sufficient for immobilization. Parents may accompany their child during the course of a study to provide emotional support. Establishing reliable intravenous access is critical in pediatric imaging because patients and parents do not tolerate multiple access attempts. In this regard, the skills of more experienced personnel such as those in pediatric anesthesiology can be quite helpful. Bladder catheterization also may be needed to avoid obscuring lesions attributable to 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.[3] 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.[4-6] Although many sedatives may affect cerebral metabolism, they are not known to cause significant changes in

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Table 1 Radiation Dosimetry for FDG

	Patient Age				
	1 Year	5 Years	10 Years	15 Years	Adult
Mass (kg)	9.8	19.0	32.0	55.0	70.0
Administered activity (MBq)	54.5	105.6	177.8	305.6	389.0
Bladder (mSv)	32.1	33.8	49.8	64.2	62.2
Brain (mSv)	2.6	3.6	5.3	8.6	10.9
Heart (mSv)	19.1	21.1	21.3	24.8	24.1
Kidneys (mSv)	5.2	5.7	6.4	7.6	8.2
Red marrow (mSv)	3.3	3.4	3.9	4.3	4.3
Effective dose (mSv)	5.2	5.3	6.4	7.6	7.4

The doses are reported in mSv [ICRP Report 80] based upon the administered activity of 5.55 kBq/kg (0.15 μCi/kg). Patient masses represent the 50% percentile for that age [ICRP Report 56: Age-dependent doses to members of the public from intake of radionuclides: Part 1, International Commission on Radiation Protection, 1989, p 4].

tumoral metabolism and can be administered at any time relative to FDG administration for studies of tumors outside the central nervous system (CNS).[7]

With combined PET/CT devices, imaging protocols are kept as simple as reasonable to increase patient tolerance of the imaging procedure.[8-12] Oral contrast medium 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 slightly altered.[13-15] The optimum SUV calculation in pediatric patients may be different from that used in adult patients because of body changes that occur during childhood. Specifically, it appears that an SUV based on body surface area is a more uniform parameter than an SUV based on body weight in pediatric patients.[16] Currently, 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 the induction of potential attenuation correction-related artifacts. However, with appropriate imaging protocols, which may include alternative contrast medium application schemes or variations in the attenuation correction procedure, PET/CT diagnostic capacity may be improved with little or no compromise of image quality. Kaste[9] has reviewed the experience of implementing PET/CT at a tertiary pediatric hospital. Issues such as physical location of the PET/CT unit, the roles of CT and nuclear medicine technologists, and the methodology for study interpretation are discussed. Additional important considerations deliberated are the use of intravenous and sugar-free oral contrast media for the CT portion of PET/CT examinations and the management of hyperglycemia. Procedure guidelines for tumor imaging with PET and PET/CT have been published.[17,18]

Radiation Dosimetry

Several factors affect the dosimetry of positron emitters relative to single-photon imaging agents. On one hand, the energy per photon is higher (511 keV, compared with 140 keV for ^{99m}Tc), and there are 2 photons emitted per disintegration, which leads to a much greater energy fluence per unit activity than with most single-photon agents. On the other hand, the higher photon energy also leads to a smaller fraction of the photons being absorbed within the patient. Table 1 summarizes the dosimetry of ^{18}F-fluorodeoxyglucose (FDG) for selected organs as well as the effective dose in the pediatric population.

Because the administered activities were scaled by body weight, the doses were similar across the age range, being slightly greater in adults. The effective dose was 5.1 mSv for a 1-year-old patient and 7.4 mSv for an adult. The critical organ is the bladder wall, with the dose being 6 to 8 times greater than the effective dose (based on a 2-hour voiding; however, patients routinely void before image acquisition starts, which is about 1 hour after FDG injection). Table 2 compares the effective dose from FDG with those of commonly used single-photon imaging agents. In Table 2, it can be seen that the absorbed radiation dose from an FDG-PET scan is very similar to the dose received from other nuclear medicine imaging procedures but considerably less than that from ^{67}Ga citrate.[19,20]

In many cases in pediatric imaging, the parents of the patient prefer to remain with the child during the procedure. The exposure rate constants for ^{18}F and ^{99m}Tc are 0.0154 and 0.00195 mR per hour per MBq at 1 meter, respectively. The difference is primarily attributable to the higher photon energy for ^{18}F than for ^{99m}Tc and the fact that 2 photons are emitted per disintegration. It is therefore prudent to consider

Table 2 Effective Dose in Pediatrics for a Variety of Radiopharmaceuticals

Radiopharmaceutical	Maximum Administered Activity (MBq)	1 Year	5 Years	10 Years	15 Years	Adult
FDG	389	5.2	5.3	6.4	7.6	7.4
^{67}Ga citrate	222	19.9	19.9	20.3	22.7	22.2
^{99m}Tc HMPAO	740	5.1	5.4	5.8	6.4	6.9
^{99m}Tc MDP	740	2.8	2.8	3.7	4.1	4.2
^{99m}Tc sestaMIBI	740	4.7	4.6	5.4	5.8	5.8

The doses are reported in mSv. The maximum administered activity is that which would be administered to a 70-kg adult. The pediatric administered is scaled by the patient's weight as in Table 1 [ICRP Report 80: Radiation dose to patients from radiopharmaceuticals, International Commission on Radiation Protection, 1998, pp 49-110; ICRP Report 56: Age-dependent doses to members of the public from intake of radionuclides: Part 1, International Commission on Radiation Protection, 1989, p 4].

Table 3 Total Exposure to the Parent From a Patient Receiving 260 MBq of ^{18}F for an FDG PET Study

Distance From Patient During Uptake Period (m)	Distance From Patient During Imaging Period (m)	Total Exposure to Parent (mR)
1	1	5.5
1	2	4.0
2	2	1.4
2	3	1.1

It is assumed that the parent stayed with the patient during a 60-minute uptake period and a 60-minute imaging period.

the radiation exposure to the parent during these procedures. As shown in Table 1, pediatric patients receive a range of administered activities depending on patient size. Consider the following assumptions: the patient receives 260 MBq and is considered to be a point source with no self-absorption. The patient sits in a preparatory room for 60 minutes during uptake and then is imaged for 60 minutes. These assumptions are quite conservative, that is, these will probably lead to an overestimation of the radiation dose to the parent. Table 3 estimates the total exposure to the parent during both the uptake and imaging periods, provided the parent maintains the specified distance from the patient.

Even if the parent stayed within 1 meter of the patient during the entire uptake and imaging periods, the exposure to the parent would be no more than 5.5 mR. Therefore, parents can be allowed to stay with the patient during the procedure but are instructed to stay as far from the patient as they feel comfortable. However, in our practices, we do not allow siblings to remain with the patient during the uptake or imaging periods.

Hybrid PET/CT scanners use the CT portion of the examination for attenuation correction. The dose to the patient from CT can vary greatly depending on the tube voltage and current and the size of the patient. Table 4 summarizes the dose to patients of various ages (based on a phantom study using phantoms of various sizes) as a function of tube voltage.

Smaller patients receive a substantially higher dose from use of the same CT acquisition parameters. For example, a 10-year-old patient will receive approximately twice the radiation dose of a medium-sized adult from use of the same CT acquisition parameters. Before the introduction of PET/CT devices, attenuation maps were generated using rotating rod sources. On the basis of a phantom study using phantoms of various sizes, the dose to the patient is between 0.05 and 0.2 mGy for 15 minutes of scanning with a total activity in the rods of 370 MBq. Thus, the dose to the patient from a CT scan used for attenuation correction is substantially greater than that associated with the rotating rod sources. However, the CT scan provides anatomical correlation to the functional images, a feature that is not available using the rod sources, and is considerably quicker.

Comparing the values in Tables 1 and 4, the dose to the patient from the CT portion of the scan can be equal to, if not higher than, the dose received from the radiopharmaceutical. Thus, the acquisition parameters for the CT portion of the scan should be tailored to the patient's size. For diagnostic CT, reduction of exposure by 30% to 50% relative to an adult exposure has been suggested.[21] Reducing the exposure (milliamp-seconds) proportionately decreases the absorbed radiation dose without significant loss in the information provided. In addition, there is the potential to further reduce the tube voltage and current without adversely affecting the quality of the attenuation correction in those cases where precise anatomical correlation is not critical.

Clinical Oncology Applications

Cancer is second only to trauma as a cause of death in children, accounting for approximately 10% of all childhood deaths.[22,23] Of all the adult cancers to which FDG-PET has been most widely applied, only lymphomas and brain tumors occur with an appreciable incidence in children.[3] However, the diagnostic utility of FDG-PET and its impact on patient management have been reported for many pediatric cancers.[24-34] In decreasing order of frequency, PET has led to important changes in the clinical management of lymphoma (32%), brain tumors (15%), and sarcomas (13%).[25] PET/CT also has been shown to be superior to PET alone by allowing precise CT localization of metabolic abnormalities shown on PET and superior to CT alone by allowing metabolic characterization of abnormal and normal findings shown on CT, thereby increasing diagnostic confidence and reducing equivocal image interpretations.[35-38]

Before reviewing the applications of PET in pediatric oncology, it is important consider potential causes of misinterpretation of FDG-PET that relate to physiologic variations in FDG distribution in children. These include a more extensive distribution of hematopoietic marrow than in adults and the occurrence of high FDG uptake in the thymus,[39,40] in the adenoids and tonsils, and in the skeletal growth centers, particularly those of the long bone physes. Other potential pitfalls, similar to those in adults, include variable FDG uptake in working skeletal muscles, brown fat, myocardium, thyroid gland, and gastrointestinal tract, as well as accumulation of excreted FDG in the renal pelvis, ureter, and bladder, and possible tracer accumulation in draining lymph nodes from extravasated tracer at the time of intravenous tracer administration.[41-45] Diffuse high bone marrow and splenic FDG uptake after the administration of hematopoietic-stimulating factors also may resemble disseminated metastatic disease.[46,47]

Table 4 Dose from CT

kvp	Newborn	1 Year	5 Years	10 Years	Med Adult
80	7.0	5.7	4.5	3.8	1.5
100	13.5	11.3	9.0	7.9	3.5
120	21.4	18.2	14.9	12.9	6.0
140	30.1	25.8	21.8	18.9	9.0

All doses are reported in mGy. All data were obtained at 130 mAs and a pitch of helical 1.5:1.

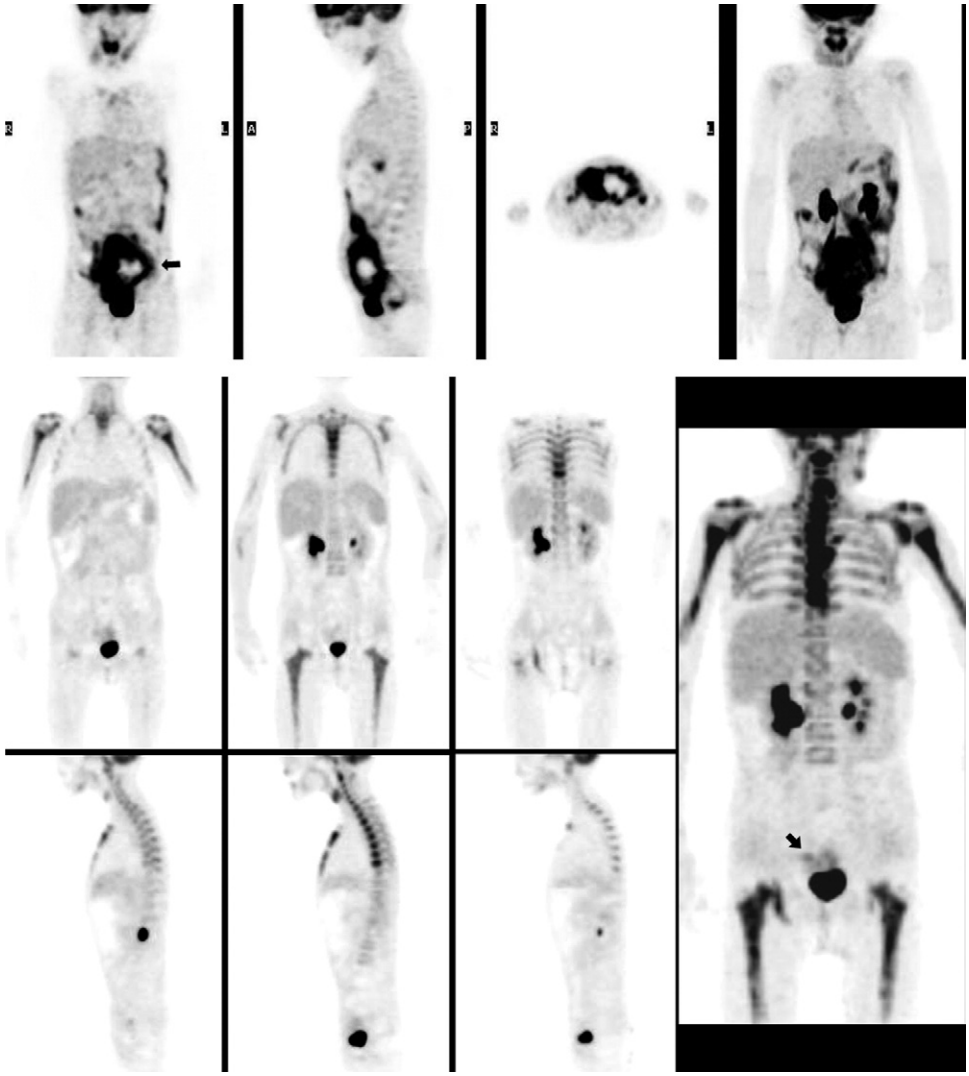

Figure 1 Effects of granulocyte colony-stimulating factor and radiation. High [^{18}F]fluorodeoxyglucose uptake is shown in a large pelvic mass and at multiple sites within the abdomen of a 7-year-old girl with embryonal rhabdomyosarcoma and omental metastases (top row PET coronal, sagittal, transverse, and anterior projection views). The patient received chemotherapy and radiotherapy (2,250 cGy to the whole abdomen and a boost of 2,490 cGy to the pelvis). Three months after completing radiotherapy, a restaging PET scan (middle and bottom rows) was obtained while the patient was receiving 5 μg/kg of granulocyte-colony stimulating factor daily for chemotherapy-induced neutropenia. Low-grade uptake was shown in the mass (arrow on anterior projection image, far right lower image). Uptake was high throughout the hematopoietic marrow, except in the regions that had been included within the radiation port. (Reprinted with permission from Drubach LA, Dubois S, Frazier L, Connolly LP: Combined Effects of Granulocyte Colony Stimulating Factor and Radiation. Clin Nucl Med 32:39-41, 2007.)

Increased bone marrow FDG uptake has been observed in patients as long as 4 weeks after completion of treatment with granulocyte colony-stimulating factor (Fig. 1).[46] Thymic activity also may occasionally be increased in a minority of young adults after chemotherapy because of reactive thymus hyperplasia (Fig. 2).[39,48] Physiologic thymic hypermetabolism also may be seen in younger children before chemotherapy. With the introduction of PET/CT imaging systems, it has been recognized that elevated FDG uptake in the normal brown adipose tissue also may be a source of false-positive findings.[42,45,49] The common anatomical areas involved include the neck and shoulder region, axillae, mediastinum, and the paravertebral and perinephric regions. Neck brown fat hypermetabolism is seen significantly more in the pediatric population than in the adult population (15% versus 2%, $P < 0.01$) and appears to be stimulated by cold temperatures.[42,45] Recent data have shown that brown fat metabolic activity may be suppressed pharmacologically (eg, by propranolol or fentanyl)[50,51] or by the simpler measure of controlling environmental temperature in the hours before injection and during the uptake phase.[52] High FDG uptake also may occasionally be observed in some benign lesions. Among these, fibro-osseous defects,[53] which are very common in the growing skeleton, and osteochondromas,[54] which can develop secondary to radiation therapy, are particularly important to note (Fig. 3).

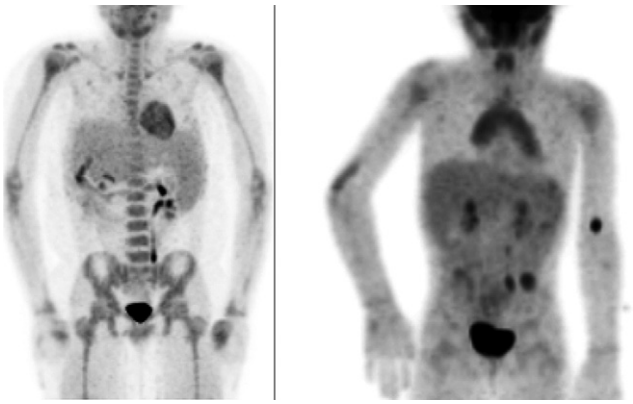

Figure 2 Anterior maximal intensity projection images of a 12-year-old boy undergoing therapy for embryonal sarcoma of the liver shows no discernible thymic uptake (left panel). Six months after completion of therapy, there is markedly increased uptake in the thymus, which appears enlarged (right panel).

Some artifacts are unique to the hybrid PET/CT imaging systems. These artifacts may be attributable to metallic objects, respiration, and oral and intravenous contrast agents. Overcorrection of dense metallic objects may result in hot spot artifacts in attenuation-corrected PET images.[55] Transient hot spot artifacts also may be found on PET images as a result of the bolus passage of undiluted intravenous contrast material. This is uncommon with proper contrast medium infusion protocols. The overestimation bias is modest (less than 15%) on PET images of organs other than the kidneys, which may display higher bias.[56] Examination of nonattenuation-corrected images can be helpful in distinguishing this technical artifact from physiologic/pathologic hypermetabolism. It is also important to note that attenuation correction of PET emission data using an artifactual CT map can yield false semiquantitative indices in the regions adjacent to metallic artifacts and probably in the presence of oral and intravenous contrast media.[13]

CNS Tumors

Tumors of the CNS account for approximately 20% of all pediatric cancers, second only to hematologic malignancies. Most pediatric brain tumors arise from neuroepithelial tissue. CNS tumors are subclassified histopathologically by cell type and graded for degree of malignancy using criteria that include mitotic activity, infiltration, and anaplasia.[57,58]

The distribution of the most common CNS tumors may be categorized according to the major anatomical compartment involved. In the posterior fossa, the most common tumors are medulloblastoma, cerebellar astrocytoma, ependymoma, and brain stem gliomas. Tumors about the third ventricle include tumors that arise from suprasellar, pineal, and ventricular tissue, and the most common are optic and hypothalamic gliomas, craniopharyngiomas, and germ cell tumors. Supratentorial tumors are most often astrocytomas, many of which are low-grade.[58]

Magnetic resonance imaging (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 ^{99m}Tc methoxyisobutylisonitrile have proven valuable for this determination in several pediatric brain tumors, generally demonstrating tracer uptake in the tumor and not in the scar tissue.[59-62]

The use of FDG-PET in brain tumors has been widely reported in adult patients, for whom FDG-PET has helped distinguish viable tumor from post-therapeutic changes.[63-65]

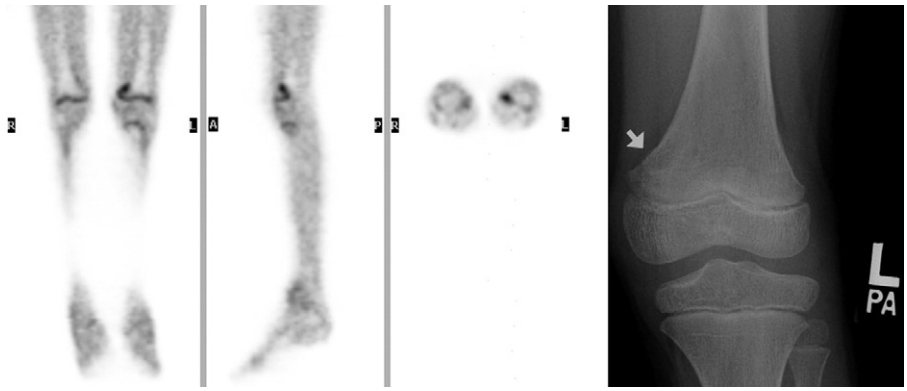

Figure 3 Avulsive cortical irregularity. PET performed as a surveillance study to detect unsuspected malignancy in a 9-year-old boy with a history of bilateral retinoblastomas and a pineal tumor consistent with the rare syndrome of familial retinoblastoma and an intracranial neuroblastic tumor (trilateral retinoblastoma), shows focal marked uptake in the posteromedial left distal femoral metaphysis extending to the linear zone of physiologically high physeal uptake. An anteroposterior radiograph shows a subtle radiolucency (arrow) at the site of high uptake in the medial left distal femoral metaphysis. The radiographic appearance allayed fears of the possibility of osteosarcoma, which is among the more common malignancies that develop in patients with familial retinoblastoma, and was consistent with an avulsive cortical irregularity. That diagnosis was subsequently supported by MRI (not shown). (Reprinted with permission from Connolly SA, Davies KJ, Connolly LP: Avulsive Cortical Irregularity and F-18 FDG-PET. Clin Nucl Med 31:87-89, 2006.)

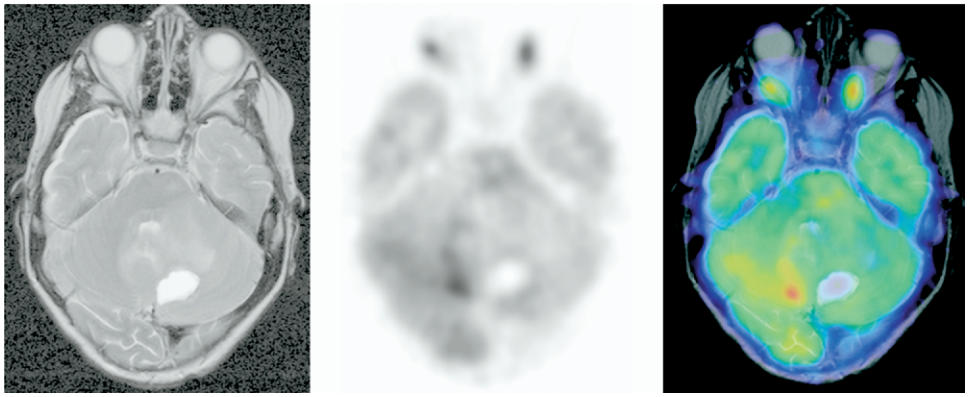

Figure 4 A 7-year-old boy with recent resection of anaplastic astrocytoma of the cerebellum. T2 MRI with contrast medium (left), FDG-PET (middle), and fusion image (right) from FDG-PET, CT scan, and MRI. Abnormally increased uptake is seen along the medial aspect of the right cerebellar hemisphere. Most of the abnormal signal on MRI shows FDG uptake similar to that of normal gray matter. Fusion images created using Hermes Medical Systems software.

High FDG uptake relative to adjacent brain indicates residual or recurrent tumor, whereas low or absent FDG uptake is observed in areas of necrosis (Fig. 4). This distinction is most readily made with high-grade tumors that show high uptake of FDG at diagnosis. FDG-PET does not, however, exclude microscopic tumor foci. FDG-PET results also may not accurately correlate with tumor progression after intensive radiation therapy.[66] Moreover, elevated FDG uptake may persist in the immediate post-therapy period.[67]

The 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.[68] In addition, 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.[69,70] 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.[71] 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.[72] Limited available data also suggest that FDG-PET findings correlate well with histopathologic findings and clinical outcome in children.[73-78] 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.[79] In that series, high tumoral glucose metabolism shown by FDG-PET was a more accurate predictor of tumor behavior than was histologic analysis. Combining FDG-PET and MRI in the planning of stereotactic brain biopsies has been reported to improve the diagnostic yield in infiltrative, ill-defined lesions and to reduce sampling in high-risk functional areas.[68] The combined imaging also facilitates tumor resection planning.[80]

Another positron-emitting radiotracer that has been used to study pediatric brain tumors is the radiolabeled amino acid [^{11}C]methionine (^{11}C-Met), which localizes to only a minimal degree in normal brain tissue. Uptake of this radiotracer reflects transmethylation pathways that are present in some tumors. However, as with FDG, some low-grade gliomas may escape detection without clear limits of tumor-to-normal brain tissue ratios that can accurately assess malignancy grade.[81-84] ^{11}C-Met PET has been reported to be useful in differentiating viable tumor from therapy-induced changes.[81,85-87] However, it is worth noting that, similar to FDG, ^{11}C-Met is not tumor-specific, as it has been shown to accumulate in some nontumoral CNS diseases, probably as a result of blood–brain barrier disruption.[88] Both FDG-PET and ^{11}C-Met PET have been shown to be independent predictors of event-free survival.[83,89] ^{11}C-Met, because of the short 20-minute half-life of the ^{11}C label, must be produced locally for administration and is currently not commercially available. Potential uses of [^{18}F]3′-deoxy-3′-fluorothymidine, [^{11}C]methyl-L-tryptophan, and [^{18}F]fluoroethyl-L-tyrosine in assessing brain tumors recently have been described.[90-94]

Lymphoma

Non-Hodgkin's and Hodgkin's lymphomas account for between 10% and 15% of pediatric malignancies (Fig. 5). Non-Hodgkin's lymphoma occurs throughout childhood. Lymphoblastic and small-cell tumors, including Burkitt's lymphoma, are its most common histologic types, and the disease usually is widespread at diagnosis. Mediastinal and hilar involvement are common with lymphoblastic lymphoma, whereas Burkitt's lymphoma most often occurs in the abdomen. In contrast, Hodgkin's disease has a peak incidence during adolescence and accounts for about 6% of all childhood cancers.[95] Nodular sclerosing and mixed cellularity are the most common histologic types. The disease is

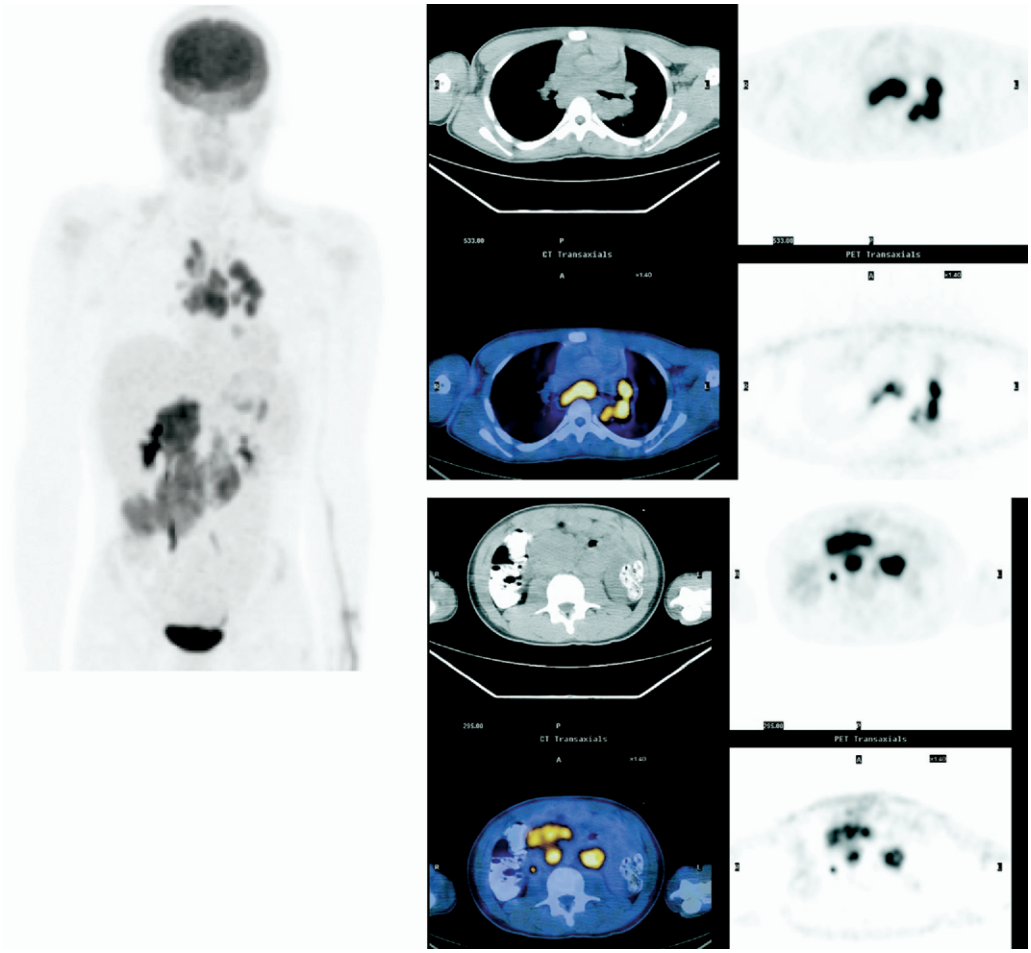

Figure 5 A 14-year-old boy with recent fevers and weight loss. Biopsy showed nodular sclerosing Hodgkin's lymphoma. Left panel: Anterior maximal intensity projection image shows extensive abnormal uptake in the chest and abdomen. Upper center and upper right panels: Cross-sectional views of the mid-chest show markedly increased uptake in subcarinal and left hilar masses. Lower center and lower right panels: Cross-sectional view of the mid-abdomen shows markedly increased uptake in mesenteric, para-aortic, and paracaval lymph node masses.

rarely widespread at diagnosis, and most cases have intrathoracic nodal involvement.[22,96]

^{67}Ga citrate scintigraphy has proven useful in staging and monitoring therapeutic response in patients with non-Hodgkin's and Hodgkin's lymphomas.[97-101] For nearly 2 decades, this was the best functional imaging agent available for the evaluation of lymphomas. FDG-PET has several features that make it preferable to ^{67}Ga citrate scintigraphy, including a shorter injection to imaging interval, completion of the study in a few hours instead of multiple days, higher image quality, and more favorable dosimetry (Table 2) In numerous studies that predominantly included adult patients, FDG has been shown to accumulate in non-Hodgkin's and Hodgkin's lymphomas.[41,102-125] Similar to Gallium-67 citrate, FDG uptake generally is greater in the higher-grade lymphomas than in lower-grade lymphomas.[109,111] FDG-PET has been reported to reveal disease sites that were not detected by conventional staging methods, resulting in upstaging of disease with potential therapeutic ramifications.[106,107,112-114] FDG-PET, when performed at the time of initial evaluation, also has been shown to change disease stage and treatment in 10% to 23% of children with lymphoma.[126-130] Identification of areas of intense FDG uptake within the bone marrow can be particularly useful in directing the site of biopsy or even eliminating the need for biopsy at staging.[107,120] FDG-PET is also useful for assessing residual soft-tissue masses shown by CT after therapy. Absence of FDG uptake in a residual mass is predictive of remission, whereas high uptake indicates residual or recurrent tumor (Fig. 6).[114,122,131] A negative FDG-PET scan after completion of chemotherapy, however, does not exclude the presence of residual microscopic disease.[132] FDG-PET can predict clinical outcome with a higher accuracy than conventional imaging (91% versus 66%, $P < 0.05$) in patients previously treated for Hodgkin's disease.[133]

Levine and coworkers[134] reported on the frequency of false-positive results with PET-only systems after completion of therapy. Scans were considered positive if the interpretation was most consistent with malignancy. Diagnostic validation was by pathologic evaluation, resolution on follow-up scan, or absence of disease progression over at least 1 year without intervention. A false-positive rate of 16% was observed with etiologies such as fibrosis, progressive transfor-

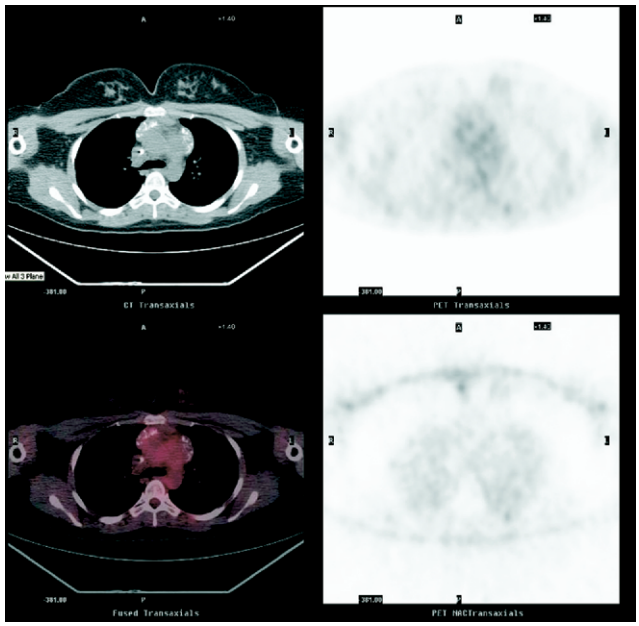

Figure 6 A 20-year-old woman with a history of Hodgkin's lymphoma 1 year after completion of therapy. Areas of calcification in the mediastinum show no elevated FDG uptake, indicating successful treatment. The patient remained in clinical and radiographic remission 2 years later.

mation of germinal centers, abdominal wall hernia, appendicitis, thymus, and HIV-associated lymphadenopathy. Positive PET scans after treatment should be interpreted cautiously, and therapeutic decisions should not be made without histologic confirmation. Similar recommendations have been adapted by others.[135] Despite this, however, hybrid systems that incorporate both structural and metabolic information will provide a more accurate assessment.[136] In fact, in a recent German study, it was demonstrated that a correlative imaging strategy that included FDG-PET provided the most accurate imaging evaluation, improved diagnostic confidence, and improved therapeutic management.[137] Another study from Israel that used PET/CT in 24 Hodgkin's and 7 non-Hodgkin's lymphoma patients showed that PET/CT resulted in a stage change in 32% of patients (22% upstages and 10% downstages).[138] In general, however, it is suggested that a negative PET/CT during routine follow-up for lymphoma in children strongly suggests the absence of recurrence (high negative predictive value), but a positive finding should be interpreted with caution (low positive predictive value).[139] The potential role of FDG-PET in radiation treatment planning for pediatric oncology including lymphoma has also been recently described.[140-142]

FDG-PET has been compared with ^{11}C-Met PET in a small series of 14 patients with non-Hodgkin's lymphoma. ^{11}C-Met PET provided superior tumor-to-background contrast, but FDG-PET was superior in distinguishing between high- and low-grade lymphomas.[105] In summary, the existing large body of evidence indicates that PET will play an increasingly important role in staging, evaluating tumor response, planning radiation treatment fields, and monitoring after completion of therapy in pediatric lymphoma.[24,142]

Neuroblastoma

Neuroblastoma is the most common extracranial solid malignant tumor in children. The mean age of patients at presentation is 20 to 30 months, and it is a rare occurrence after the age of 5 years.[96] The adrenal glands are the most common site of neuroblastoma. Other sites of origin include the paravertebral and presacral sympathetic chain, the organ of Zuckerkandl, posterior mediastinal sympathetic ganglia, and cervical sympathetic plexuses. Gross or microscopic calcification often is present in the tumor. Disseminated disease is present in up to 70% of neuroblastoma cases at diagnosis and most commonly involves cortical bone and bone marrow. Less frequently, there is involvement of liver, skin, and lung. A primary tumor is not detected in up to 10% of children with disseminated neuroblastoma or in those who present with paraneoplastic syndromes.[143]

Surgical excision is the preferred treatment for localized neuroblastoma. When local disease is extensive, intensive preoperative chemotherapy may be administered. When distant metastases are present, the prognosis is poor, but high-dose chemotherapy, total-body irradiation, and bone marrow reinfusion are beneficial for some children with this presentation.

Delineation of local disease extent is achieved with MRI, CT, and scintigraphy. These tests also are used to localize the primary site in children who present with disseminated disease or with paraneoplastic syndrome. Metaiodobenzylguanidine (MIBG, an analog of guanethidine and norepinephrine) and [^{111}In]pentetreotide (a somatostatin type 2 receptor agonist) scintigraphy have been used in these settings with a sensitivity of greater than 85% for detecting neuroblastoma. Uptake of MIBG into neuroblastoma is by a neuronal sodium and energy-dependent transport mechanism. The localization of [^{111}In]pentetreotide in neuroblastoma reflects the presence of somatostatin receptors on some neuroblastoma cells.[144]

Bone scintigraphy has been most widely used for detection of skeletal involvement for staging but is unable to distinguish active disease from bony repair on the basis of tracer uptake. Patients with residual unresected primary tumors are periodically evaluated with MRI or CT. These studies, however, cannot distinguish viable tumor from treatment-related scar tissue. Specificity in establishing residual viable tumor can be improved with MIBG or [^{111}In]pentetreotide imaging when the primary tumor has been shown to accumulate one of these agents. These agents also are useful in assessing residual skeletal disease in patients who have skeletal metastases with a high affinity for MIBG- or [^{111}In]pentetreotide. Neuroblastomas are metabolically active tumors (Fig. 7). Neuroblastomas and their metastases avidly concentrated FDG before chemotherapy or radiation therapy in 16 of 17 patients studied with FDG-PET and MIBG imaging.[145] Uptake after therapy was variable but tended to be lower. FDG and MIBG results were concordant in most instances; how-

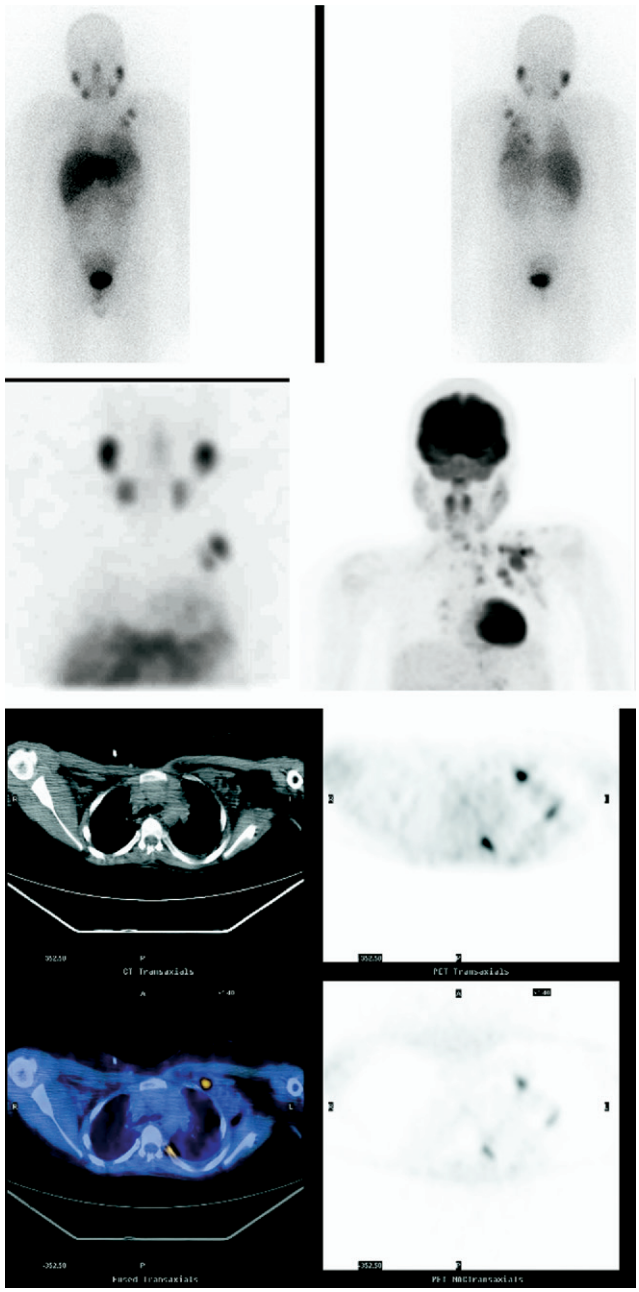

Figure 7 A 12-year-old boy with recurrent neuroblastoma. Upper panel: Anterior and posterior whole body images from a ^{123}I-MIBG scan show multiple foci of abnormal uptake in the left hemithorax and left thoracic paraspinal region. Middle panel: (Left) Anterior maximal intensity projection ^{123}I-MIBG image of the neck and chest for comparison with anterior maximal intensity projection FDG-PET image of the torso (right). Lower 2 panels: Transverse cross-sectional views of the upper chest show elevated uptake in a left pectoral lymph node, in a left posterior rib, and within left axillary fat.

ever, there were few discordant cases in which one tracer accumulated at a site of disease and the other did not. MIBG imaging was overall considered superior to FDG-PET, particularly in the delineation of residual disease. An advantage of FDG-PET is the initiation of imaging 30 to 60 minutes after FDG administration, whereas MIBG imaging is performed 1 or more days after tracer administration.

FDG-PET may be of limited value for the evaluation of bone marrow involvement in neuroblastoma due to mild FDG accumulation by the normal bone marrow.[145] Pitfalls resulting from physiologic FDG uptake in the bowel and the thymus are additional factors that may limit the role of FDG-PET in neuroblastoma. 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. All 7 neuroblastomas studied showed uptake of ^{11}C-HED[146] and 4 of 5 neuroblastomas studied showed uptake of [^{11}C]epinephrine.[147] A recent study reported a greater sensitivity for ^{11}C-HED PET/CT than that for [^{123}I]MIBG single-photon emission CT (99% versus 93%).[148] Uptake of these tracers is demonstrated within minutes after tracer administration, which is an advantage over MIBG imaging. However, practical current limitations regarding cost and the need for on-site synthesis of short-lived ^{11}C (half-life of 20 minutes) hinder their clinical utility. Compounds labeled with ^{18}F, such as fluoronorepinephrine, fluorometaraminol, and fluorodopamine, also may be useful tracers.[149] PET using 4-[fluorine-18]fluoro-3-iodobenzylguanidine[150] and ^{124}I-labeled MIBG[151] has also been described.

Wilms' Tumor

Wilms' tumor is the most common renal malignancy of childhood. Wilms' tumor is predominantly found in younger children and is rarely encountered after the age of 5 years.[22] Bilateral renal involvement occurs in approximately 5% of all cases and can be identified synchronously or metachronously.[96,152] An asymptomatic abdominal mass is the typical mode of presentation. Nephrectomy with adjuvant chemotherapy is the treatment of choice. Radiation therapy is used in selected cases when resection is incomplete.

Radiography, sonography, CT, and MRI are commonly used for anatomical staging and detection of metastases, which involve predominantly lung, occasionally liver, and only rarely other sites. Anatomical imaging, however, is of limited utility in the assessment of residual or recurrent tumor.[152] Uptake of FDG by Wilms' tumor has been described,[153] but a role for FDG-PET in Wilms' tumor has not been established. Normal excretion of FDG through the kidney is also a limiting factor. However, careful correlation with anatomical cross-sectional imaging usually allows distinction of tumor uptake from normal renal FDG excretion. We have found FDG-PET most useful in identifying active tumor in residual masses that persist after radiation, chemotherapy, or both, and for evaluating the effects of treatment on metastatic disease (Fig. 8).

Bone Tumors

Osteosarcoma and Ewing's sarcoma are the 2 primary bone malignancies of childhood. Osteosarcoma is more common

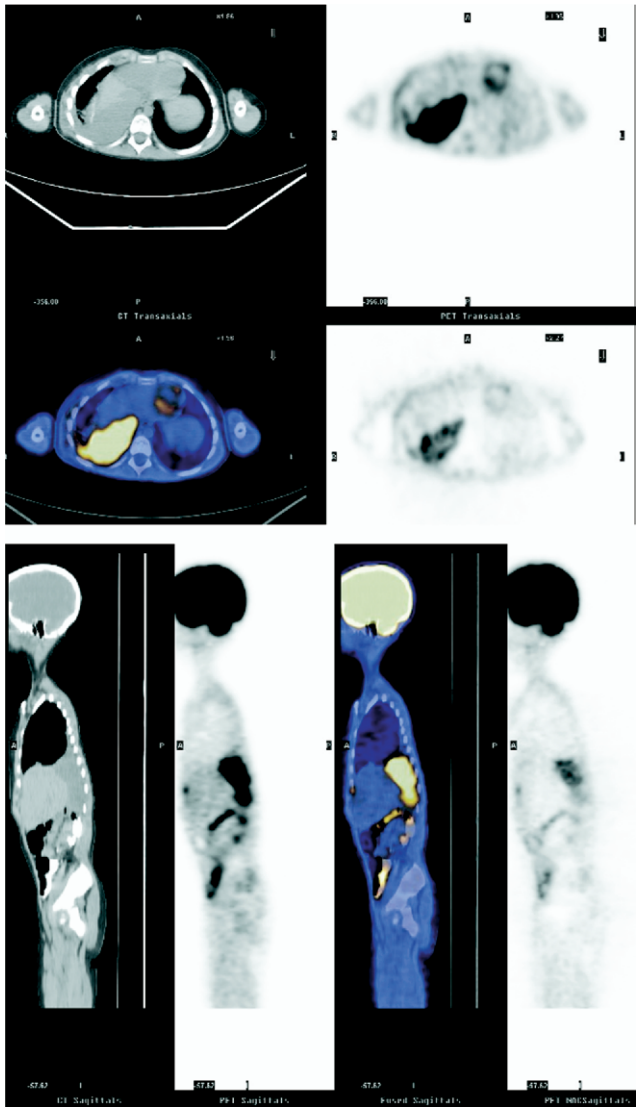

Figure 8 A 4-year-old boy with recurrent Wilms' tumor after radiotherapy and bone marrow transplantation. Transverse images (upper 2 panels) show markedly increased uptake in the right lung mass and pleural effusion. Sagittal images (lower panel) show that this uptake and mass extend inferiorly into the mid-abdomen.

and affects predominantly adolescents and young adults with a second peak in older adults, particularly individuals with a history of radiation to bone or Paget's disease. This tumor rarely affects children younger than 7 years. Osteosarcoma typically is a lesion of the long bones. The treatment of choice for osteosarcoma of an extremity is wide resection and limb-sparing surgery, which involves resection of the tumor with a cuff of surrounding normal tissue at all margins followed by skeletal reconstruction. Limb-sparing procedures can be appropriately performed in 80% of patients with the current chemotherapeutic regimens pre- and postoperatively and imaging to define tumor extent and viability.[154]

Almost all cases of Ewing's sarcoma occur between the ages of 5 and 30 years, with the highest incidence being in between the ages of 10 and 19 years. In patients younger than 20 years, Ewing's sarcoma most often affects the appendicular skeleton. Beyond that age, pelvic, rib, and vertebral lesion predominate. The tumor is believed to be of neuroectodermal origin and, along with the primitive neuroectodermal tumor, to be part of a spectrum of a single biological entity.[155] Therapy for Ewing's sarcoma involves radiation, surgery, or both for control of the primary lesion and multiagent chemotherapy for eradication of metastatic disease.[156]

MRI is used to define the local extent of osteosarcoma and Ewing's sarcoma in bone and soft tissue. However, signal abnormalities caused by peritumoral edema can result in an overestimation of tumor extension.[157] Scintigraphy has been used primarily to detect osseous metastases of these tumors at diagnosis and during follow-up. With osteosarcoma, skeletal scintigraphy occasionally demonstrates extraosseous metastases, most often pulmonary, due to osteoid production by the metastatic deposits. Because of the nonspecific appearance of viable tumor on MRI, variable results have been reported for assessing chemotherapeutic response in planning for limb-salvaging surgery.[158-163] Scintigraphy with ^{201}Tl has been shown to be useful for assessing therapeutic response in osteosarcoma and Ewing's sarcoma.[164-169] A marked decrease in ^{201}Tl uptake by the tumor indicates a favorable response to chemotherapy. A change in therapy may be needed when ^{201}Tl uptake does not decrease within weeks of chemotherapy. ^{99m}Tc methoxyisobutylisonitrile may also be useful in osteosarcoma but appears not to be with Ewing's sarcoma.[170,171]

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, monitoring the response to therapy, and predicting the long-term outcome after therapy (Fig. 9).[172-180] The post-therapy level of FDG uptake may underestimate the extent of tumor necrosis compared with histologic assessment, probably due to some increase in the metabolic activity in response to therapy-induced inflammation and healing.[181] 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.[182] A second potential role is in assessing patients with suspected or known pulmonary metastasis, which is particularly common with osteosarcoma. In a recent retrospective study of 55 patients with bone tumors, PET detected metastases in 22% of patients, with 67% of those harboring disease outside the lung; 7% of patients were upstaged to stage IV, with the most important alteration in treatment decisions being the use of radiation in lieu of surgery for local control.[183]

Soft-Tissue Tumors

Rhabdomyosarcoma is the most common soft-tissue malignancy of childhood. The peak incidence occurs between 3 and 6 years of age. Rhabdomyosarcomas can develop in any organ or tissue, and contrary to what the name implies, do not usually arise in muscle. The most common anatomical locations are the head, particularly the orbit and paranasal sinuses, the neck, and the genitourinary tract. CT and MRI are important for establishing the extent of local disease.

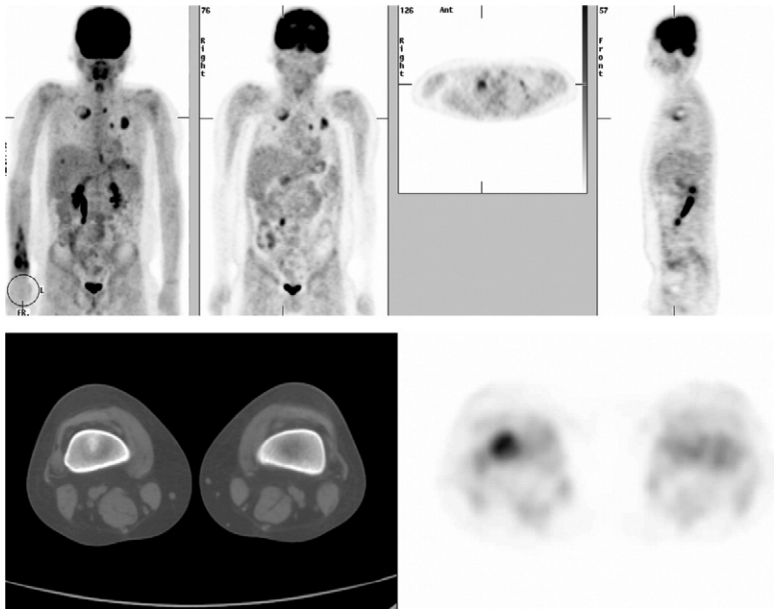

Figure 9 An 11-year-old boy with progressive Ewing's sarcoma of the right radius. Upper panel: Projection and cross-sectional images show many foci of abnormal uptake in the lungs and the right forearm. Lower panel: Increased uptake in the distal right femur corresponds with a sclerotic lesion on CT scan.

Radiography and CT are used for detecting pulmonary metastases, and skeletal scintigraphy is used to identify osseous metastases. Radiation therapy and surgery are used for local disease control and chemotherapy for treatment of metastatic disease. Rhabdomyosarcomas show variable degrees of FDG accumulation. Although there are reports of diagnostic utility, the exact clinical role of FDG-PET in rhabdomyosarcoma has not yet been established (Fig. 10).[7,172,184-186] A recent study showed that, in patients with soft-tissue sarcomas, the pretreatment tumor standardized uptake value and the change in the value after neoadjuvant chemotherapy independently identified patients at high risk for tumor recurrence.[187]

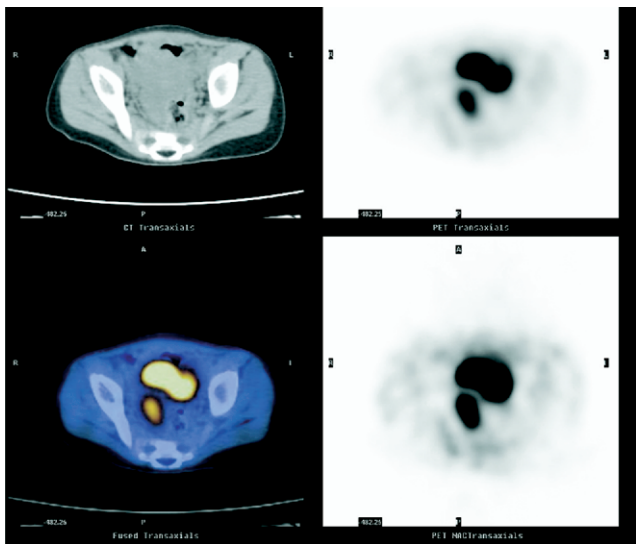

Figure 10 A 2-year-old girl with newly diagnosed pelvic rhabdomyosarcoma. Transverse images of an FDG-PET/CT scan show markedly increased uptake in a retrovesicular mass. Uptake is well seen despite the intense concentration of tracer in the excreted urine.

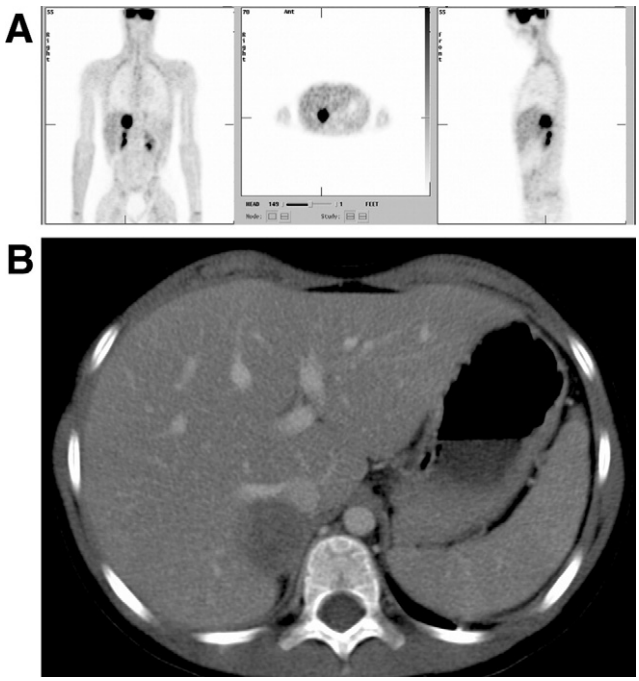

Figure 11 An 8-year-old girl with locally recurrent and metastatic adrenocortical carcinoma. (A) Cross-sectional images from an FDG-PET scan show markedly increased uptake in the adrenal bed. A small focus of activity seen on the coronal image in the mid-right chest represents a small pulmonary metastasis. (B) Contrast-enhanced CT shows a low attenuation mass in the right adrenal bed.

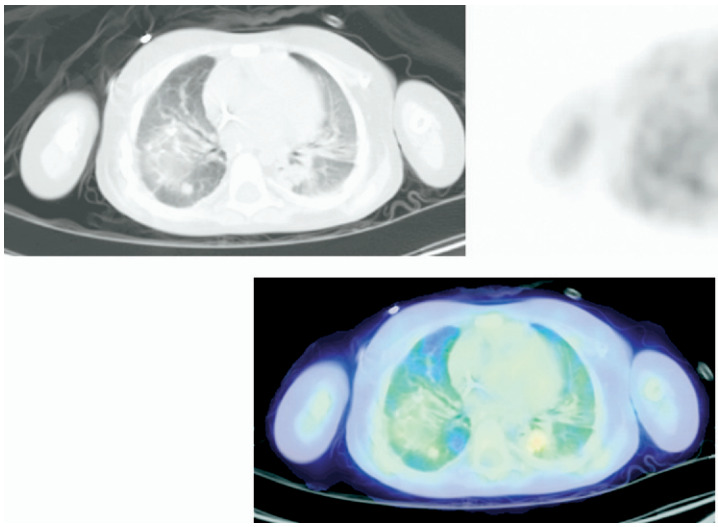

Figure 12 A 4-year-old boy with metastatic hepatoblastoma. FDG-PET/CT images show abnormal uptake in a left lower lung metastasis. A smaller right lung metastasis has only slightly elevated uptake.

Rare Tumors in Children

Adrenocortical tumors in children are usually endocrinologically active and very aggressive clinically.[188] A germline mutation is a major predisposing factor. Most patients present with virilization. Two-thirds of patients have resectable tumors. For these patients, surgery currently holds the only realistic hope for cure. Preliminary experience indicates that these tumors are quite active metabolically, and FDG has been used to monitor them (Fig. 11).[33]

Hepatoblastoma is quite rare, accounting for less than 1% of childhood tumors.[189] 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 (Fig. 12). FDG-PET is useful in monitoring hepatoblastomas during and after therapy.[190]

Summary

FDG-PET and FDG-PET/CT are being increasingly applied to pediatric conditions, particularly in oncology. Most children in the United States who have tumors are studied under protocols developed by the Children's Oncology Group. Patients are treated in multiple institutions that conform to strict treatment and evaluation regimens. This presents the opportunity to critically and scientifically evaluate the use of FDG-PET in the management of childhood tumors in multiinstitutional, cooperative efforts. Though these tumors are rare, cooperative group studies allow national and international efforts to objectively determine the impact of FDG-PET and FDG-PET/CT in patient management. Most tumors in children are metabolically active and thus concentrate and retain FDG. We fully expect that future data will show not only that FDG-PET and FDG-PET/CT provide useful diagnostic and staging information in individual tumor types, but they also will play a pivotal role in the clinical management and care of children with cancer.

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