Nuclear Medicine examinations are integral in the management of children with cancer. Imaging with conventional gamma camera systems, hybrid gamma camera systems and radiopharmaceuticals; and with positron emission tomography (PET) and PET/CT systems and positron emitters can be used for staging, metastatic work-up, surveillance follow-up, therapeutic response assessment and treatment. Tumors that are routinely evaluated include, osteogenic sarcoma, Ewing’s sarcoma, rhabdomyosarcoma, neuroblastoma and lymphoma. Leukemia, brain tumors and thyroid tumors, renal and hepatic tumors may also be imaged using scintigraphic techniques.

The use of image co-registration of functional studies obtained with gamma cameras or PET cameras with anatomic imaging on CT and MRI provide a further level of evidence of the significance and specificity of diagnostic findings. This can be accomplished with sequential acquisition of data in combined PET-CT or gamma-camera-CT machines or by co-registration digitally of individually acquired studies not temporally related. The clinical impact of these combined modalities are becoming established in adults (1-8).

Musculoskeletal Tumors
Primary malignant bone tumors such as osteogenic sarcoma, Ewing’s sarcoma and rhabdomyosarcoma involving bone will appear as intense tracer uptake on skeletal scintigraphy with Tc-99m methylene diphosphonate (MDP) standard bone scans. MDP bone scintigraphy is still the appropriate way to survey the skeleton for extent of disease including metastatic or multifocal disease including skip lesions. Pulmonary metastases of osteosarcoma can show uptake of Tc-99m bone seeking radiopharmaceuticals, but the sensitivity for uptake is much less than the sensitivity for metastatic disease detected with CT scan.

Non-metastatic increased Tc-99m MDP activity may be found after amputation or limb salvage procedures and the various patterns need to be recognized as non-neoplastic. A pattern of non-specific increased activity in the axial skeleton and/or juxtaarticular areas on MDP bone scintigraphy can also be seen in patients who are given colony stimulating factors (CSF).

The gold standard for the assessment of histologic response in osteosarcoma after neoadjuvant chemotherapy has been the evaluation of tumor necrosis on the histologic specimen at the time of definitive surgery; either limb salvage or amputation. Thallium-201 and Tc-99m sestamibi have been used as “surrogate markers” for the non-invasive assessment of this histologic response in osteogenic sarcoma(6). The most important factor in the use of scintigraphy for histologic response assessment and detection of residual tumor is the determination of baseline tumor avidity for the specific radiopharmaceutical. The determination of baseline tumor avidity is best performed at the time of initial staging for all suspected tumors in order to minimize the influence of tissue distortion and inflammation after biopsy or surgery. Histologic tumor response assessment relies on the finding of a decrease in thallium or sestamibi uptake between pre and post treatment scans to indicate good tumor histologic response. Poor tumor histologic response will show persistence of abnormal radiopharmaceutical uptake.

2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) PET may also be helpful in monitoring tumor histologic response. In tumors treated with chemotherapy, FDG-PET accumulation decreased more homogeneously throughout the tumor, in responsive cases. FDG-PET uptake has been shown to more accurately reflect viable
metabolically active tumor. PET may also detect metastatic foci, but occasionally nonspecific uptake not due to malignant disease may show increased uptake on a whole body PET scan. In a study of 18 patients with bone tumors Franzius et al showed on FDG PET imaging tumor to non-tumor ratios in all patients who had good responses ratios decreased more than 30% (7). In patients with poor responses tumor to non-tumor ratios increased or showed less than 30% decrease in contrast to the good responders. Hawkins et al also found FDG-PET with quantitation to correlate with tumor histologic response after neoadjuvant chemotherapy in both osteosarcoma and Ewing’s sarcoma (8). Quantitation by response assessment of maximum standardized uptake values (SUVmax) before and after therapy on PET studies was evaluated in 45 patients. They found that patients with a baseline tumor SUVmax >/= 6 and < 40% decrease in FDG uptake were at 90% risk of systemic disease recurrence at 4 years from the time of initial diagnosis. Patients whose tumors had a >/= 40% decline in the SUVmax in response to chemotherapy were at a significantly lower risk of recurrent disease and death after complete resection and adjuvant radiotherapy (9). FDG PET is also useful in combination with MR imaging to help distinguish viable tumor from post therapeutic changes in patients with bone and soft-tissue sarcomas (10).

MDP bone scintigraphy in Ewing’s sarcoma is important in initial staging of the tumor and for following patients after therapy. Scintigraphy at presentation will commonly show intense uptake of radiopharmaceutical in the lesion. Ewing’s sarcoma may show metastases at diagnosis. Skeletal metastases developing prior to or at the same time as pulmonary metastases can be detected by bone scintigraphy. Soft tissue and pulmonary metastatic disease of Ewing’s sarcoma is not detected on MDP bone scintigraphy. MDP uptake can be affected by nonspecific factors other than tumor activity. There may be marked decrease in uptake 3-4 months after treatment with radiation therapy. Intense focal uptake at tumor site within 3-4 months after treatment may be due to tumor recurrence, or complications such as infection or pathologic fracture.

MDP bone scan of primary lesion site provides little information to predict long-term survival or disease progression in patients with non-metastatic Ewing’s sarcoma. Scintigraphy with thallium-201 will more reliably show histologic tumor response. Ewing’s sarcoma exhibits similar findings to osteogenic sarcoma on thallium-201 scintigraphy. Pretreatment uptake of thallium-201 is found in all extremity tumors. Because of splanchic uptake, pelvic tumors may have equivocal uptake. Because there is not often surgical resection of the primary site, thallium may potentially provide more specificity for the presence of viable tumor compared with follow-up bone scintigraphy. Metastatic disease can be seen with thallium-201 but sensitivity data is not available. Indications for FDG-PET in Ewing’s sarcoma are for detection of osseous metastases of Ewing’s sarcoma, therapy monitoring and the diagnosis of recurrences (11, 12).

While some osseous pulmonary metastases can be visualized on MDP bone scans, no other single photon scintigraphic agents are useful for this diagnosis. FDG-PET in one series of 71 combined adult and pediatric patients with osteosarcoma or Ewing’s sarcoma identified FDG-PET had a sensitivity of 0.50, a specificity of 0.98, and an accuracy of 0.87 on a patient based analysis with comparable spiral CT values of 0.75, 1.00, and 0.94 respectively. Their conclusion was that at present a negative FDG-PET cannot be used to exclude lung metastases. But, because the specificity of FDG-PET is high, a positive FDG-PET result can be used to confirm abnormalities seen on thoracic CT scans as metastatic (13).

The staging and non-invasive response assessment is rhabdomyosarcoma is challenging due to this tumor’s multifocal behavior. The tumors will often accumulate Tc-99m MDP due to hypervascularity. Local bony involvement can be distinguished with 95% accuracy. Bone scans alone however do not detect soft tissue involvement by primary and metastatic disease in all cases. Thallium-201 tumor scintigraphy can be helpful in soft tissue tumors for assessment of primary and metastatic disease and response to therapy. Mild to marked thallium-201 uptake in rhabdomyosarcoma has been described in (14, 15). FDG-PET can help in distinguishing benign soft tissue masses from
malignant lesions of soft-tissue sarcoma. FDG-PET has also been reported to be helpful in detection of unsuspected metastatic sites in patients with what is believed to be isolated disease.\(^\text{16}\)

153- Samarium EDTMP has been reported to provide bone-specific therapeutic irradiation when used for palliation of painful bone metastases in patients with osteoblastic bone metastases from osteosarcoma.\(^\text{17}\) Hematologic toxicity requires peripheral blood stem cell grafts to overcome myeloablative effects of the skeletal irradiation. Nonhematologic side effects are minimal. In addition this radiopharmaceutical can be imaged using a conventional gamma camera.\(^\text{18}\)

**Lymphoma**

In Lymphoma, Ga-67 imaging is well established in the staging and monitoring of response to therapy of patients with Hodgkin Disease and non-Hodgkin lymphoma (NHL). Failure to convert to a negative scan post-treatment signals a poor prognosis. In one study of 139 adult and pediatric patients with aggressive NHL, positive Ga-67 after the first cycle of treatment predicted 64% of patients who had failure of treatment. A positive study at mid-treatment predicted 77% of patients who had treatment failure.\(^\text{19}\)

PET-FDG can be used to accurately stage, assess therapeutic response and assess for residual or recurrent disease in adults with lymphoma. Uptake in lymphoma corresponds to grade of tumor and prognosis. FDG has been shown to be more sensitive and accurate than Ga-67 in detecting splenic involvement at time of staging.\(^\text{20}\) Tumors which are aggressive and resistant to treatment tend to show high uptake of FDG and a lower survival rate. Recent publications are identifying a similar utility of FDG-PET and PET/CT imaging in children with lymphoma.\(^\text{21}\) Using FDG-PET as compared to CT, resulted in a higher staging in 4 of 25 patients and in a lower staging in 2 of 25 patients in a retrospective study of FDG-PET in 25 children with lymphoma.\(^\text{22}\) As with gallium, persistent abnormal FDG-PET uptake after chemotherapy in NHL is highly predictive for residual or recurrent disease. In relapsing patients, progression free survival was significantly shorter after a positive scan than after a negative scan.\(^\text{21-26}\) Awareness of normal uptake patterns, variants and artifacts on PET-FDG imaging in children is important in accurate disease assessment.\(^\text{25}\) Standardization of protocols for pediatric patients is not yet defined. The use of premedication to prevent brown fat uptake is also being evaluated as more centers perform these studies on pediatric patients.\(^\text{27}\)

In lymphoma, residual anatomic masses are often present that cause uncertainty for the need for salvage or alternate therapy. CT and MR have limited ability to distinguish between active residual or recurrent disease or fibrosis or scar. Gallium scintigraphy is reported to be superior to CT and MR for evaluating response to therapy. Combining Ga-SPECT with MR has been reported to improve diagnostic accuracy for disease detection. PET-FDG studies can be useful to assess residual masses after chemotherapy.\(^\text{28}\)

One of the differential diagnoses of residual anatomic mass after therapy is thymic rebound. This physiologic thymic regeneration following chemotherapy is more common in children than in adults. Increased thymic gallium localization due to thymic regeneration and not tumor involvement has been well described with a characteristic bilobed appearance.\(^\text{29}\) FDG-PET accumulation can also occur in normal thymus.\(^\text{30-32}\) The natural history of thymic rebound uptake seen scintigraphically is that it regresses after a few months and usually with 6-12 months.

**Neuroblastoma**

MDP bone scintigraphy in children with neuroblastoma may show uptake in the primary tumor in 35-100% with an average occurrence of 70%.\(^\text{33-39}\) The intensity of uptake does not correlate with grade of malignancy, prognosis, or the presence and amount of calcification present in the tumor. Metastatic uptake includes focal areas of increased radiopharmaceutical accumulation, photopenic or “cold” lesions, and symmetrical metaphyseal increased uptake. Metastatic disease detected on bone scintigraphy is often abnormal before radiographic changes are apparent. Later in the disease, however, lesions may be seen radiographically which may not be abnormal on bone scintigraphy. This reduction in uptake of
the bone-seeking radiopharmaceutical causing a false negative scan may be an altered biodistribution affect from chemotherapy.

Accurate staging is important for therapy considerations. Stage IV disease can be distinguished scintigraphically from stage IVs disease by performing MIBG scintigraphy to assess extent of disease including primary tumor, and bone disease. The better detection of metastases can upstage the disease. Tc-99m MDP bone scintigraphy is required if MIBG scan is negative or unavailable and radiographs of positive scintigraphic lesions are recommended. Sensitivity and specificity for MIBG scintigraphy are 94% and greater than 95%, respectively. Abnormal activity can be seen in the primary tumor site, and in bone, bone marrow and soft tissue metastases. In post chemotherapy evaluation of advanced neuroblastoma, MIBG scintigraphy can show tumor response appearing as a decrease in MIBG uptake and can also detect new lesions. MIBG often will detect more bone and bone marrow disease at diagnosis and in follow-up not demonstrated by bone scintigraphy, radiographs or marrow biopsy. A negative MIBG scan after induction chemotherapy is reported to be a good predictor of better disease free survival.

Uncommonly, neuroblastoma may be non-avid on MIBG scintigraphy or less avid than disease detected on bone scintigraphy. More mature forms of neural crest histology such as ganglioneuroblastoma and ganglioneuroma may have some but variable uptake of MIBG. False negative MIBG bone uptake compared to positive MDP bone uptake has been reported possibly because MDP bone scintigraphy will better reflect cortical bone disease as compared with marrow disease, suggesting a complementary role for MIBG and MDP scintigraphy (40).

Octreotide somatostatin receptor imaging is sometimes used as an alternative to MIBG scintigraphy in children with neuroblastoma, but with a lower sensitivity of 77%. MIBG negative tumors, which are positive on somatostatin scintigraphy, are described. FDG-PET has been utilized in children with neuroblastoma. FDG accumulated in primary neuroblastoma lesions and in metastatic disease and in disease that was MIBG non-avid (12, 41-43). Other PET radiopharmaceuticals are also being evaluated in neuroblastoma (44).

Radionuclide Therapy In Neuroblastoma

MIBG labeled to I-131 has a relatively long half-life which varies from 2.8-8.0 days and this allows therapeutic doses of irradiation to be delivered with acceptable hemotoxicity (46). The therapeutic use of I-131 MIBG in the treatment of neuroblastoma is well tolerated in the pediatric patient. With respect to hematologic toxicity, thrombocytopenia is the main side effect and is dependent on the status of the bone marrow at the time of treatment. Patients who have extensive bone marrow invasion and have been treated with chemotherapy at the time of treatment are much more likely to develop toxicity, and bone marrow suppression may be permanent. Patients who receive MIBG therapy as front line therapy are much less likely to suffer this complication since they do not yet have substantial marrow involvement (46-49). Post therapy whole body I-131 MIBG scans may demonstrate sites of marrow involvement not appreciated on pre-treatment scans.

Initially treatment of neuroblastoma with I-131 was limited to patients with advanced disease who had failed to achieve any significant success with other more established treatment modalities. Most series consisted almost exclusively if not exclusively of patients with progressive stage IV disease. Despite that, early cumulative results in 276 patients demonstrated a positive response in 35% (50). MIBG had proven itself to have potential in palliation and improvement in the quality of life in these seriously ill children. I-131 MIBG therapy has also been used as a front line therapy in patients with advanced neuroblastoma at the time of diagnosis. In a series of 49 patients with stage 3 and 4 neuroblastoma one year survival was 65% and 5 year survival was 38% (61). Toxicity was not severe with thrombocytopenia being the main complication. A recent study using multiple infusion of I-131 MIBG showed increasing response but did show hematologic toxicity (62). Studies for treatment with I-131MIBG in combination with myeloablative chemotherapy and hematopoietic stem-cell rescue has also proven feasible with acceptable toxicity (62, 53).
References