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Nuclear Medicine investigations in urinary system malignancies in children

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In the most of developed countries, cancer is the second most common cause of death among children between the ages of 1 and 14 years. Leukemia is the most common cancer in this age group. During the past 25 years, there have been significant improvements in the 5-year relative survival rate for all of the major childhood cancers. This is mainly due to early diagnosis and better management of pediatric cancer. In this chapter, we describe role of various nuclear medicine investigations used for the management of urinary system pediatric malignancies. Various malignancies involving the urinary system in pediatric age group are Wilm's tumours, renal cell carcinoma, mesoblastic nephroma, rhabdoid cell tumors, rhabdomyosarcoma, neuroblastoma and teratoma.

Wilm's Tumor

Wilm's tumor also called as nephroblastoma. It is the most common pediatric urologic tumor and comprises 6% of all childhood cancers. It is recognized as a part of many congenital malformation syndromes like WAGR, Denis-Drash and Beckwith-Wiedmann etc. Most commonly associated with mutation involving chromosome 1p13 (WT1) and 11p15 (WT2). Wilm's tumor most commonly present as an abdominal swelling or mass, abdominal pain, gross hematuria and fever. Hypertension may also be noted in these patients. Most common differential diagnosis is neuroblastoma, which is also common in this age group. They occur most commonly from age 2-3 years and 5% of cases have bilateral disease but can occur throughout childhood. Management depends on presence and function of opposite kidney, whether one or both kidneys are affected. In addition, it also depends on presence of any intravascular thrombus and regional lymph node metastasis. The tumor is also staged to see if there is any spread of the tumor away from the kidney to other parts of the body. If only one kidney is involved, it is usually removed to confirm the diagnosis and provide surgical treatment. If both kidneys are involved, a biopsy or sample of the tumor is taken, and chemotherapy is planned to shrink the tumors down to allow surgical removal at a second operation. Based upon the pathology of the tumor and stage, or extent of the tumor, chemotherapy and possibly radiation therapy are also added to treat the tumor. This allows combinations of therapy to maximize treatment but also attempts to minimize side effects of the therapies.

Conventional Imaging Modalities

Various diagnostic studies impart different important roles. The diagnosis is usually suggested by anatomic imaging and established by biopsy or resection. Commonly employed diagnostic modalities are x-rays, renal ultrasonography (USG), computed tomography (CT) and megnectic resonance imaging (MRI). USG examination reveals the solid or cystic nature of mass, the renal origin and gross measurement. Contrast enhanced computed tomography (CECT) also reveals the nature of mass, invasion of adjacent organs like spleen, liver and colon, any nephrogenic tumor rest in opposite kidney and intravascular thrombus.

Renal and bone Scintigraphy

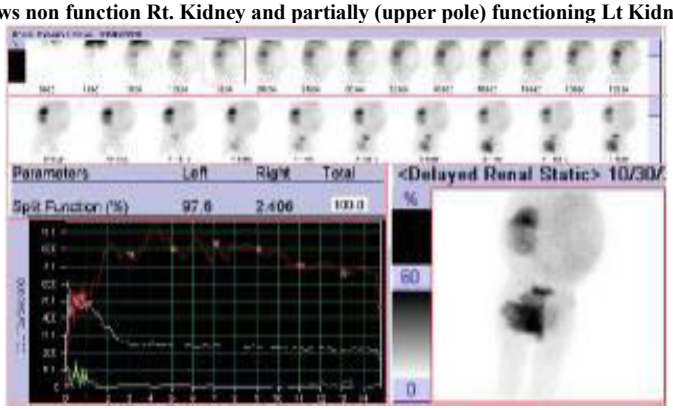
Nuclear medicine studies play important role in the management of Wilm's tumor. The principal roles of functional imaging have been the evaluation of renal function and search for skeletal metastases. Renal dynamic scintigraphy plays important role in evaluating the presence and function of opposite kidney, whether one or both kidneys are affected. In case of unilateral Wilm's tumor, if contralateral kidney shows normal renal function, usually nephrectomy is done. While in cases of bilateral involvement, depending on renal functions, a decision of partial and total nephrectomy is being made (**Fig 1**). Bone scintigraphy can be used to detect bone metastasis.

FDG PET/PET-CT

There are not many studies in literature regarding FDG PET in Wilm's tumors. This is mainly because of physiological excretion of FDG through kidney. However, the usefulness of FDG-PET has been documented in

the detection of distant metastasis from urologic malignancies in adults. Initial study by Shulkin *et al*[1] with F-18 fluorodeoxyglucose positron emission tomography/ computed tomography (F18-FDG PET/CT) demonstrated that FDG PET can be a useful modality in management of Wilm's tumors. There was a good correlation of standardized uptake value (SUV) and histological differentiation of Wilm's tumors. However, contrary to previous studies, in recent study, Misch *et al*[2] showed FDG-PET does not provide additional information to the traditional imaging work-up for staging Wilm's tumor patients, preoperative response assessment and clinical outcome. FDG-PET was advantageous in ruling out residual disease after completion of first line treatment and in pretherapeutic staging of relapse patients. Study by Owens *et al*[3] emphasized that fused PET-CT allows accelerated metabolic activity to be accurately anatomically localised and so is potentially useful for staging, assessment of treatment response, and for surgical and radiotherapy planning.

Fig. 1 **A 3-years old Male child presented with abdominal lumb and respiratory distress. Investigations revalued B/L wilm's tumor. A RDS shows non function Rt. Kidney and partially (upper pole) functioning Lt Kidney**



Neuroblastoma

Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy. Close to 50 percent of neuroblastoma cases occur in children younger than two years old. It is a neuroendocrine tumor, arising from any neural crest element of the sympathetic nervous system or SNS. It most frequently originates in one of the adrenal glands, but can also develop in nerve tissues in the neck, chest, abdomen, or pelvis. Neuroblastoma is one of the few human malignancies known to demonstrate spontaneous regression from an undifferentiated state to a completely benign cellular appearance. The first symptoms of neuroblastoma are often vague making diagnosis difficult. Fatigue, loss of appetite, fever, and joint pain are common. Symptoms depend on primary tumor locations and metastases if present. Neuroblastoma often spreads to other parts of the body before any symptoms are apparent and 50 to 60% of all neuroblastoma cases present with metastases. The most common location for neuroblastoma to originate (I e the primary tumor) is on the adrenal glands. This occurs in 40% of localized tumors and in 60% of cases of widespread disease. Neuroblastoma can also develop anywhere along the sympathetic nervous system chain from the neck to the pelvis. Frequencies in different locations include: neck (1%), chest (19%), abdomen (30% non-adrenal), or pelvis (1%). In rare cases, no primary tumor can be discerned.

Conventional imaging modalities

Plain radiograph shows the calcification in primary tumor tissue. USG is noninvasive and provides size criteria. CT and MRI provide better anatomic details, discerning tumor size and surrounding tissue and tumor operability. MRI is particularly useful in spinal cord and marrow involvement by the tumor.

Metaiodobenzylguanidine (MIBG)

I-131-metaiodobenzylguanidine (I131-MIBG), I-123-metaiodobenzylguanidine (I123-MIBG) and Tc99m - methylene diphosphonate have been the radiopharmaceuticals used for neuroblastoma assessment. Recently, the use of F18-FDG PET is increasing for the management of neuroblastoma. Functional imaging like bone scan being highly sensitive provides better information about the skeletal involvement but lacks the specificity of MIBG scan. MIBG being an analogue of norepinephrine is internalized by amine uptake type 1 mechanism and concentrated by many neuroendocrine tumors including neuroblastoma **(Fig 2,3)**. So also it reliably depicts all the metastatic sites **(Fig 4)**. It can be labeled with I-123 or I-125 or I-131. Therefore, any tumors that are derived from the neural crest and exibit an amine uptake 1 mechanism can concentrate MIBG and thus can be detected.

MIBG, with a sensitivity of about 90% and specificity of nearly 100%, is the radiopharmaceutical conventionally used for imaging neuroblastoma. MIBG was originally used for the localization of pheochromocytoma[4] with its use in neuroblastoma evolving shortly thereafter.[5,6] MIBG takes advantage of the adrenergic origin of neuroblastoma, using the type 1 catecholamine uptake mechanism for transport into tumor cells.

Fig. 2. **A 3-years old male child underweight MIBG scan to characterize left adrenal mass. The scan shows intense MIBG uptake suggestive of Neuroblastoma**

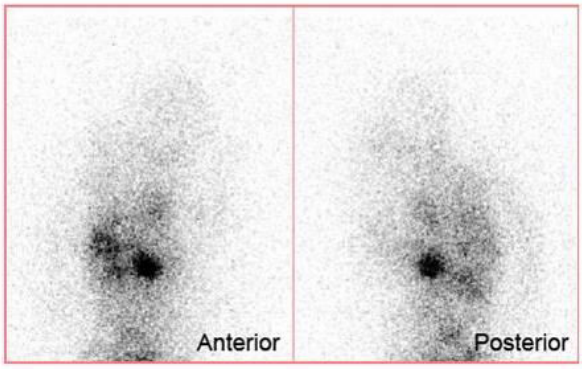


Fig. 3. **A 4-years old male child underweight MIBG scan to characterize abdominal mass. The scan shows intense MIBG uptake, these findings are consistent with Neuroblastoma**

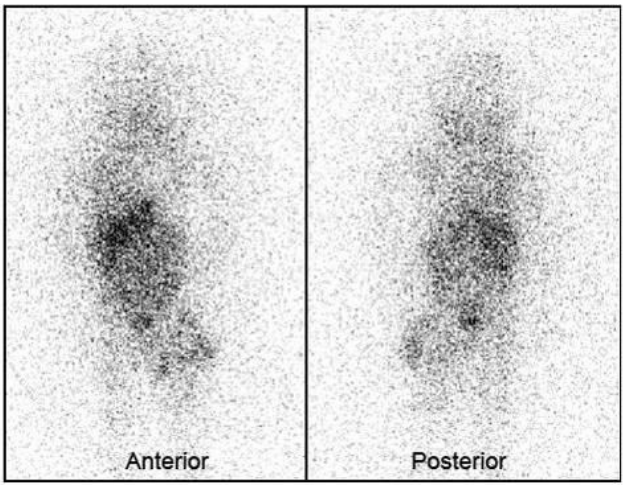


Fig. 4. **A 6 years old male diagnose case of neuroblastoma underwent MIBG scan to characterize right scalp swelling. Abnormal intense MIBG uptake was noted in the clinical palpable swelling suggestive of scalp metastasis**

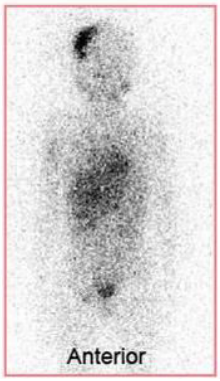
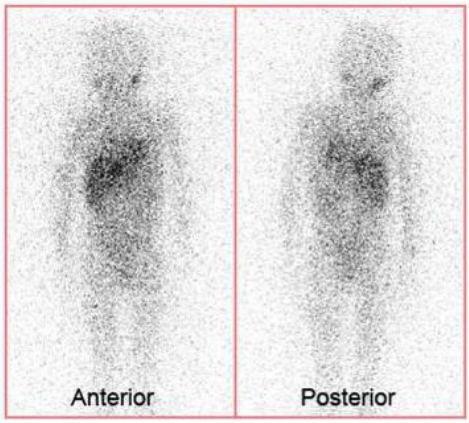


Fig. 5. **A 6 years old male child presented with hypertension. CT demonstrated Rt. Adr mass. MIBG scan revalued tran activity - s/o pheochromocytoma**



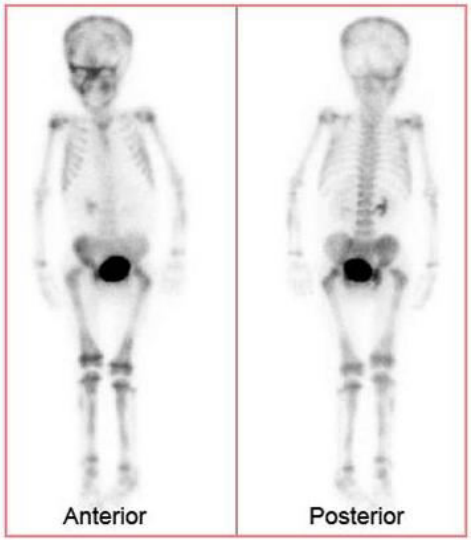
I-131 MIBG is injected intravenously in a dose of 0.5 to 1.0 mci and whole body images are acquired after 24, 48 and 72 hour, in a gamma camera set at a peak of 364 Kev which is photon energy peak of I-131. Physiological tracer concentration is noted in myocardium, liver and kidneys, bladder, gut and salivary glands. Consequent to observation that MIBG is rapidly cleared from the myocardium of pheochromocytoma patients, there exists an inverse relation between myocardial and tumor activity in these patients. 91.5% of neuroblastomas concentrate I-131 MIBG. So urine analysis of catecholamine metabolites and positive I-131 MIBG scan are most sensitive and highly specific indicators of neuroblastoma. MIBG is so specific that in a child of tumor of unknown origin it can establish the diagnosis of neuroblastoma non-invasively. The enhanced detection of metastasis upgrading the stage and detection of less number of metastasis with induction chemotherapy correlates well with response. In a post operative of post chemotherapy patient, biochemical investigations reflect global status of the disease and MIBG offers lesion by lesion evaluation **(Fig 5)**. Achievement of high lesion to background ratio in tumor, and long effective half life of I 131, also allows treatment of neuroblastomas by I 131 MIBG..

MIBG was first labeled with I-131 and later with I-123.[7,8] I-123 MIBG gives higher-quality images as compared to I-131 MIBG.[9] The evolution of SPECT has also aided the I-123 MIBG diagnosis of neuroblastoma, improving anatomic localization.[10,11,12] Continued improvements are expected with the advent of SPECT/CT. I-123 has been used for nearly 15 years in the scintigraphic evaluation of neuroendocrine tumors, particularly pheocbromocytomas and neuroblastomas.[13,14,15] In patients with neuroblastoma, a sensitivity of 77% and 96% and a high specificity (approximately 100%) has been reported for both radiopharmaceuticals.[15,16] Due to its physical properties (159 keV photon energy, 13-hr half-life and paucity of particulate emission of 1-23) and the high activity that can be administered, MIBG labeled with 123I has superior imaging characteristics. These characteristics of I-123 MIBG, and its favorable dosimetry, even in higher administered doses, make its use preferable in children.[17,18] I-123-MIBG imaging is most commonly performed at 24 hr after tracer administration. Another theoretical advantage of I 123 MIBG is the feasibility of its use in high quality SPECT imaging. SPECT offers potential advantages in comparison to planar scanning: better anatomic localization of the lesions by three-dimensional re construction of tomographic images and better lesion definition by improved lesion contrast.

Bone Scintigraphy

The principal role of bone scintigraphy in these patients is to search for skeletal metastases. It can be used for initial staging, to evaluate response to treatment (provided we have baseline scan) and detection of recurrent bone metastasis. It has high sensitivity for detection of bone metastastasis, however, it has limited role if disease is involving bone marrow only **(Fig 6).** In such cases MIBG is better imaging modality than bone scintigraphy. As such, all these structural imaging modalities, MIBG scan and bone scan are complementary to each other for the management of patients with neuroblastoma.

Fig. 6 **A 7 years old male child presented with diffuse bone pain and pancytopenia and abdominal mass. Bone scan revalued diffuse skeletal involvement**



FDG PET/PET-CT

The role of F18-FDG PET in neuroblastoma and other pediatric malignancies continues to evolve with increasing use. F18-FDG is a positron-emitting glucose analog concentrated within cells using the glucose transporter. Because most tumor cells preferentially use glucose for energy, F18-FDG uptake is seen within most tumors. shulkin *et al*. demonstrated that most neuroblastomas will concentrate F18-FDG, although 18F-FDG uptake in nontumor sites (such as bone marrow, thymus, and bowel) can cause potential false-positive or false-negative results.[19]

Shulkin *et al*[19] reviewed 20 paired F18-FDG PET and MIBG scans in 17 patients with neuroblastoma. The authors demonstrated that most neuroblastomas concentrate F18-FDG. However, they found that F18-FDG PET imaging was inferior to MIBG scintigraphy in the evaluation of neuroblastoma because of its lower tumor to non-tumor uptake ratio especially after therapy. This was because physiological uptake of F18-FDG in non tumor sites such as bone marrow, thymus, and bowel, causing potential false positive results. The authors found F18-FDG most beneficial in tumors that failed to accumulate or weakly accumulated MIBG. Kushner *et al*[20] reviewed 92 F18-FDG PET scans obtained from 51 patients with neuroblastoma. F18-FDG PET was performed in conjunction with staging evaluations including MIBG scans, bone scans, CT (or MRI) scans, urine catecholamine, and bone marrow examinations. They found that F18-FDG PET and bone marrow sampling are sufficient to monitor for progressive disease in patients whose primary tumor has been resected and in whom cranial vault lesions are absent or resolved. Sharp *et al*[21] found that F18-FDG PET better depicted disease sites in stage 1 and 2 neuroblastoma. This was primarily because of more intense F18-FDG uptake relative to background and better depiction of disease extent. F18-FDG also better depicted disease sites in stage 3 and 4 patients when tumors weakly accumulated I123-MIBG **(Fig 7).** In addition, 18F-FDG was useful for delineating disease extent in the chest, abdomen, and pelvis and should be used when disease involvement on CT or MRI appears more extensive than demonstrated with I123-MIBG. There are some case reports[22,23] which demonstrated negative I123-MIBG scintigraphy in recurrent neuroblastoma while F18-FDG PET scan was positive. Therefore, emphasizing the importance of 18F-FDG PET when I123-MIBG reveals less disease than suggested by clinical symptoms or conventional imaging modalities. We found that F18-FDG PET is a useful modality in evaluating treatment response, especially in patients, who has positive FDG PET-CT baseline scan **(Fig 8).**

The cumulative radiation dose of paired studies should also be considered, particularly in low-stage-disease patients who may be treated by surgery without radiotherapy or chemotherapy, given concerns about long-term radiation effects in pediatric patients.[24,25] Sharp *et al*[21] found I123-MIBG to be overall superior in the evaluation of stage 4 neuroblastoma, primarily because of the better detection of bone or marrow metastases. Detection of bone or marrow metastases with F18-FDG was frequently difficult, with uptake patterns that could be considered either normal or physiologic.

Other positron-emitting tracers have been studied for neuroblastoma imaging with potential advantages over I123-MIBG including improved resolution of PET, compared with SPECT; ability to accurately quantify uptake; and potential for imaging within minutes of injection. 11Chydroxyephedrine and 11C-epinephrine have

been studied in neuroblastoma.[26,27,28,29] However, the short half-life of C11 requires on-site cyclotron synthesis and limits the practical use of these radiopharmaceuticals. Compounds labeled with F18, such as fluoronorepinephrine, fluorometaraminol, fluorodopamine, and 4-18F-fluoro-3-iodobenzylguanidine, have the potential for imaging neuroendocrine tumors.[30,31,32,33,34,35,36] PET using 124I-MIBG has also been described.[37] I 124 labelled MIBG and 3F8 monoclonal antibodies have been used for PET for dosimetric purpose in relation to therapy. Many neuroendocrine tumors including neuroblatoma demonstrates somatostatin receptors. Recently, Somatostatin (SSR) analog DOTA-D-Phe1-Tyr3-octreotide (DOTA-TOC) has been developed which can be labeled with positron emitter Gallium-68 (Ga68). Ga68-DOTA-TOC has advantage of PET imaging and increased spatial resolution. In our experience Ga68-DOTA-TOC PET-CT can play an important role in diagnosis, staging, treatment response evaluation and detection of recurrent disease in these patients **(Fig 9).**

Fig. 7 **F18-FDG PET-CT in neuroblastoma: Coronal sections of CT, PET and PET-CT scan showing increased FDG uptake in right suprarenal mass**

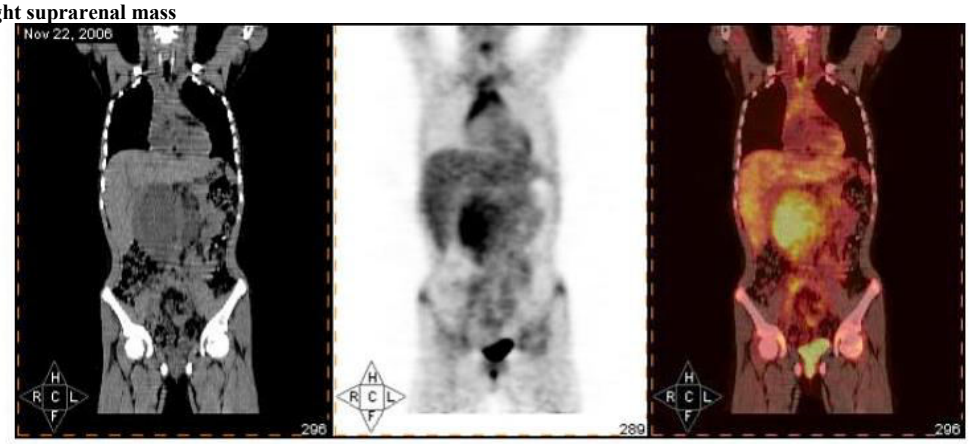
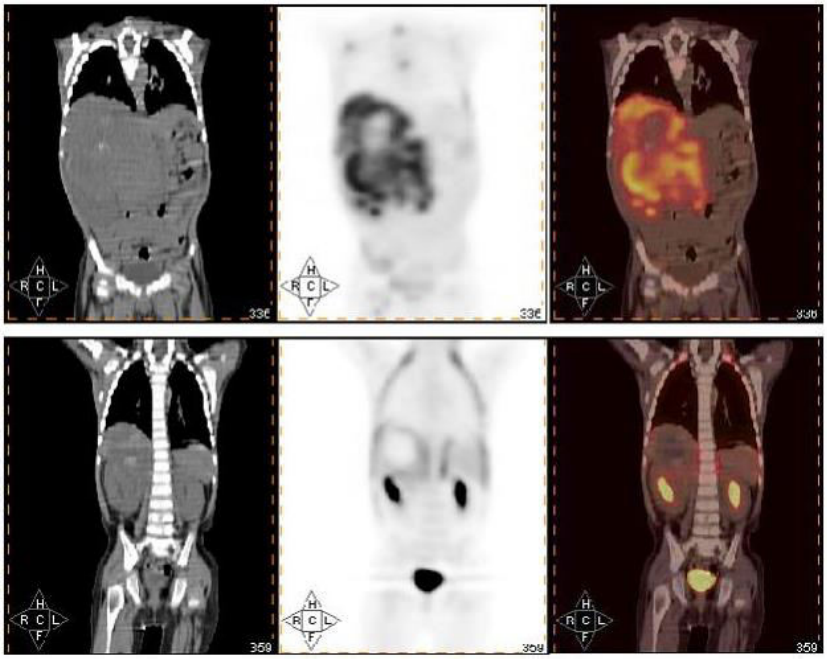


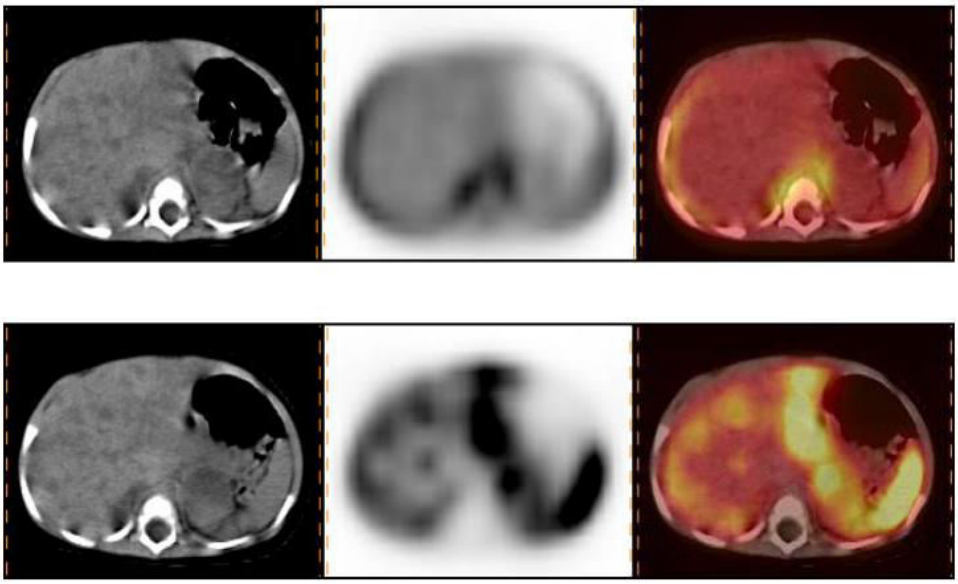
Fig. 8 **F18-FDG PET-CT for response evaluation in neuroblastoma: Coronal sections of CT, PET and PET-CT scan showing increased FDG uptake in right suprarenal mass (primary) with liver lesion and right paraaortic lymph nodes metastasis (upper row). Follow-up PET-CT scan after 6 cycles of chemotherapy, demonstrated resolution of primary and metastases suggestive of good response (lower row)**



MIBG Therapy

Although survival for children with advanced disease has improved with the use of intensive multimodality therapy, including autologous bone marrow transplantation, more than half of these children continue to relapse after therapy.[38] I131-MIBG provides a means of specific tumor localization for radionuclide delivery to neuroblastoma.[39,40] This agent has a well-established role in detection of primary and metastatic tumor[41] and in eliciting responses in both newly diagnosed[42] and refractory disease.[43,44,45,46] In phase I and other pilot studies, little toxicity other than myelosuppression has been seen, which can be obviated with autologous hematopoietic stem cell support.[45,47,48]

Fig. 9 **F18-FDG PET-CT and Ga68-DOTA-TOC PET-CT in neuroblastoma: Axial sections of CT, PET and PET-CT scan showing left suprarenal mass with no FDG uptake. There are multiple hypodense lesions in liver on CT which do not show any increased FDG uptake (upper row). Ga68-DOTA-TOC PET-CT scan shows increased DOTA-TOC uptake in primary as well as in liver metastases (lower row)**



Rhabdomyosarcomam

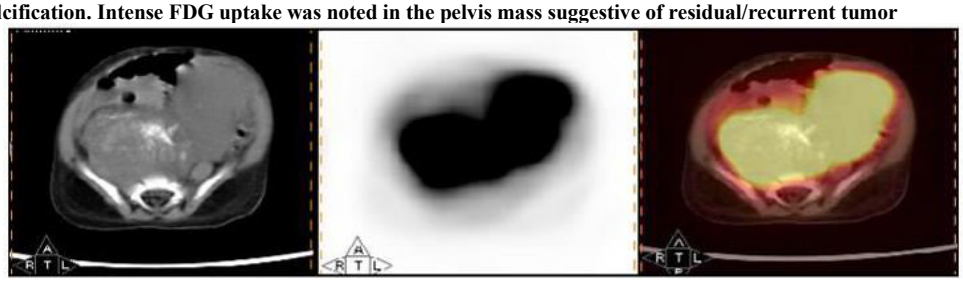
Rhabdomyosarcoma (RMS) originating from primitive mesenchymal cells accounts for more than half of all soft tissue sarcomas in children. RMS can arise in any part of the body containing striated muscle, and its clinical manifestations depend on the primary site and tumor extent.[49] Many studies show a slight male predominance, with two age pea peaks: 2-6 years and 15-19 years.[49,50] Infants less than one year old and adolescents showed advanced tumor staging, unfavorable histopathology, and a poorer outcome than children aged 1-9.[51] The survival of children with RMS was closely associated with initial stage at diagnosis and initial response to treatment, indicating that treatment modulation should incorporate initial response and risk factor data, and that new treatment strategies are needed for high-risk patients.[52] MRI and CT are important for initail staging of disease. Skeletal scintigraphy is useful for detection of osseous metastasis. MRI and FDG PET/CT can detect bone marrow metastasis.

Klem *et al* included 24 patients with rhabdomyosarcoma and performed PET scans for initial evaluation and before or within 13 days of initiation of therapy.[53] PET findings then were compared with CT, MRI, BS and pathology. SUV ranged from 2.4 to 12.7 (mean 6.4). A negative PET helped to exclude disease in 21 of 23 patients where CT or MRI was equivocal for the detection of regional or distant spread. Sensitivity and specificity of PET reported is 77% and 95%, respectively.

There are two other studies, which evaluated the role of PET in seeing the treatment response and evaluation of the recurrence. Peng *et al*, performed a retrospective study on four patients with RMSA who underwent both pre-treatment and post-treatment FDG-PET studies.[54] A dramatic decrease in FDG uptake by the tumor was correlated with a favorable response to the therapy and prolonged remission of the disease. In contrast,

persistent abnormal FDG uptake in one patient was associated with early relapse of the RMSA **(Fig 10).** Arush *et al*, evaluated 19 children with sarcoma (9 Ewing sarcoma, 3 osteogenic sarcoma, 7 rhabdomyosarcoma) by FDG-PET/CT for suspected local relapse or distant metastases.[55] They found that FDG-PET detected local relapse in all seven patients and distant metastases in 10/13 (77%). FDG-PET/CT and CT/MRI/BS results were discordant in eight patients. FDG-PET/CT was the only modality that detected distant metastases in two patients. PET/CT was true negative and excluded disease in three patients with abnormal CT/BSs and was false negative in three patients with distant metastases.

Fig. 10 F18-FDG PET-CT in rhabdomyosarcoma: Axial sections of CT, PET and PET-CT scan showing pelvic mass with calcification. Intense FDG uptake was noted in the pelvis mass suggestive of residual/recurrent tumor



Conclusion

As of now, there is no single imaging modality which can provide all information like early diagnosis, correct initial staging, treatment response evaluation and detection of recurrent disease. Most of these investigations are complementary to each other. Various nuclear medicine investigations play important role in the management of urinary malignancies in children as these provide functional and metabolic status of tumors. Recent introduction of PET-CT has revolutionized non-invasive imaging as it provides structural and functional details in one setting. PET and PET/CT has been found to be useful in urinary system malignancies in children. PET/CT has limited role in early diagnosis, however, it plays an important role in initial staging, treatment response evaluation and detection of metastatic disease in these cancers. At present, there are few radiotracers in PET imaging under active research like 11C-methionine, 11C-choline, 11C-acetate etc, which characterize tumor biology other than glucose metabolism.

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