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18F-FDG PET/CT in Staging Pediatric Rhabdomyosarcoma; Added benefits in comparison to conventional imaging.

El-kholy, E and Rezk M.

Radiation oncology & Nuclear Medicine Department, Radio diagnosis Department, NCI, Cairo University, Egypt.

ABSTRACT:

Purpose: The aim was to evaluate the added value of 18F-FDG PET/CT in initial staging of pediatric Rhabdomyosarcoma patients in comparison to other conventional images. **Materials and methods:** This is a retrospective study including total 112 patients with pathologically proven RMS (52 female, 60 males; mean age, 5.8 years, with predominant embryonal type), Results of PET/CT were compared with computed tomography and/or MRI. Max SUV of the primary lesion, lymph nodes and distant metastases were evaluated in an individual and lesion analysis. Clinical follow-up (mean 27 months), and histo-pathological data were served as the standard of reference. **Results:** Among 112 patients, 45 (40%) patients proved metastatic by PET/CT, and 5 was Indeterminate. For primary tumor site, both diagnostic CT and FDG PET/CT show comparable results. Extremities were the most common primary site in metastatic patients & Alveolar type was more prevalent pathology among metastatic patients. Initial PET/CT upstages 13 patients (11.6%). Additional 50 lesions were determinate by PET/CT (21 nodal, 16 osseous, 3 peritoneal, 5 soft tissue nodules, 5 bone marrow involvement).Unusual site of metastases were detected by both modalities, includes suprarenal, spermatic cord and IVC thrombosis in individual patients .The sensitivity and PPV for PET/CT were higher than CT for nodal, osseous, soft tissue & peritoneal metastases.

Conclusion: The current study showed that 18FDG-PET/CT is useful in initial staging of RMS patients as compared to CT regarding nodal, bone, bone marrow, soft tissue and peritoneal metastatic lesions, except for pulmonary deposits.

Key words: FDG PET/CT, Rhabdomyosarcoma, Metastases, Staging.

Corresponding Author: El-kholy, E. **E-mail**: esraa_kholy@yahoo.com.

INTRODUCTION:

Soft tissue sarcomas account for 6%– 10% of all childhood malignancies. Rhabdomyosarcoma (RMS) constitutes for over 50% of these in children and young adult [1, 2]. The presence of distant metastases is the strongest predictor factor for clinical outcomes in patients with RMS together with tumor size and invasiveness, primary site, age of the patient and different pathological differentiation [3]. The last 30 years shows increased event-free survival (EFS) and overall survival (OS) from 25% in 1970 to 70%, in patients with RMS, refereed to the improvement of risk stratification and multimodality therapy protocol. Despite this improvement, 5-year EFS for patients with distant metastasis are still 25% [4, 5]. So the assessment of metastatic disease at staging is very important. The usual diagnostic tools for staging soft tissue sarcomas includes clinical examination, magnetic resonance imaging (MRI), and computed tomography (CT), and bone scintigraphy.

The introduction of 18F-fluoro-2-deoxy-D-glucose (FDG) PET/CT as a functional imaging is proved to have potential improvement in staging accuracy and management strategies in many tumors as it can assess the biological activity and malignant capacity of the tumor. Beside its functional capability, this hybrid technique has an important advantage as it allow accurate tumor localization for more confident interpretation [6].

The aim of this study was to clarify the role of F18-FDG PET/CT in the initial staging of Rhabdomyosarcoma compared with other conventional imaging.

PATIENTS AND METHODS:

This study was conducted on 112 patients with histo-pathologically proven Rhabdomyosarcoma, referred for initial staging via FDG PET/CT scan from March. 2009 till April. 2016. Clinical information was extracted from the medical files, including age, sex, and detailed pathology & imaging findings.

18F-FDG PET/CT Imaging: All patients fasted for 4-6 hours before the exam. Blood glucose levels did not exceed 150 mg/dL. The procedure details are explained to both the patient and the parent. Scanning started 45-60 minutes after tracer injection of 4-5 MBq/kg. The number of bed positions was adjusted to cover the whole body with acquisition time, 2-3 min/bed position using a dedicated PET-CT scanner (Biograph, True-Point; Siemens), which integrates a PET scanner with a dual-section helical CT scanner (40 slice Emotion; Siemens). Intravenous contrast agent was administered in most patients except with those with certain contraindication. Most patients were examined in the supine position with elevated arms, and CT scanning was started from the skull and reached caudally to the feet (with 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5). PET over the same region was performed immediately after acquisition of the CT images (2-3min/bed position). Attenuation correction using the reconstructed CT-data with 5-mm slices reconstructed images was applied. Sedation was used according to guidelines before 18F-FDG PET/CT imaging in some cases to overcome unfavorable patient mobilization and ensure adequate image quality.

Contrast enhanced computed tomography scan: Whole body CT scan was done on 64 multi-detector CT scanner using nonionic iodinated contrast in a dose of (2.0 ml per kilogram body weight) that was automated injected with an overall injection time of 32s.

Imaging Interpretation: Images were interpreted at a workstation equipped with fusion software (Syngo; Siemens) which enables display of the PET images, CT images, and fused PET/CT images in any percentage relation. Side-by-side image interpretation was accomplished by 2 experienced nuclear medicine physicians.

Qualitative (Visual) assessment: For 18F-FDG PET/CT interpretation, any focal uptake , superior to background reference either in the primary site or other different metastatic locations (nodal, pulmonary, osseous, peritoneal or soft tissue) was interpreted as positive or abnormal FDG uptake.

Quantitative assessment: The maximum standardized uptake values were recorded for each lesion in each patient after manual application of the volumetric regions of interest on the trans-axial attenuation-corrected PET slices, around the areas demonstrating the greatest accumulation of 18F-FDG and away from any nearby overlapping activity.

Another sizable ROI was drawn over the normal liver where its max SUV was considered reference activity.

Data Analysis was performed depending on the following criteria:

True positive PET/CT results: 18F-FDG PET/CT and CT agreed, metabolically active FDG avid primary or metastatic lesion of SUV max higher than the reference hepatic activity or positive tissue pathology in unascertained lesions or bone marrow involvement in BMB.

True negative PET/CT results: CT and PET/CT results within one month agreed with clinical follow up (after 4-6 months from radiological investigations) were free i.e no newly developed relevant symptoms or signs.

False positive PET/CT results: Metabolically active FDG avid lesion proved to be benign using pathological analysis after excision or follow-up studies.

False negative PET/CT results: Mass of low metabolic activity of SUV max less than the reference hepatic activity that show significant increase in FDG uptake on the follow images, positive pathology or follow up CT revealed disease progression.

Statistical Analysis: The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of conventional imaging and PET/CT were calculated on the basis of the true-positive and true-negative findings as described in the same anatomic region with a lesion-based and a patient-based analysis. The McNemar test (x2 test) was used for comparison of the sensitivity, specificity and accuracy of diagnostic CT alone with those of fused PET/CT with a confidence level of 95% ($P<0.05$ was considered significant all through).

RESULTS:

136 patients with histologically proven RMS referred to perform PET/CT examination for initial staging in the period between April 2011 to April 2016 were retrospectively reviewed, 24 patients were excluded due to inability to retrieve their Diacom images because of a technical error.

They were (52 female & 60 male), the age of patients ranged from 4 mo-17 years with a mean of 5.8±4.5. Embryonal subtype was the most prevalent pathology in 63 patients (***Table 1)***. The majority of patients were classified as intermediate risk (n=76). All patients at initial staging had increased FDG uptake of the primary lesion ranged 0.9–12.3 with average maximal SUV ± SD: 5.1 ± 2.4.

Table (1): Patient demographics of 112 patients with Rhabdomyosarcoma.

Clinical Characteristics	Data Analysis
Age	
• Range	4 months-17 years
• Mean Age	5.8±4.5
Sex	
• Male	60
• Female	52
Site of primary	
• Favorable	20
• Unfavorable	92
Different sites	
• Head and Neck	45
• Para-meningeal	40
• Non para-meningeal	5
• Genitourinary	25
• Bladder/prostate	21
• Non Bladder/prostate	4
• Extremities	29
• Orbit	12
• Other	1
Risk stratification	
• High	31
• Intermediate	76
• Low	5
Pathological subtype	
• Alveolar	30
• Anaplastic	2
• Botryoid	9
• Embryonal	63
• Mixed Alveolar and Embryonal	3
• Spindle cell	5

Per-patient Analysis: Among 112 patients, 45 patients (40 %) had regional nodal and distant metastases. Extremities were the most common primary site in metastatic patients (17 out of 45 patient (37.7%) & alveolar pathological type were more prevalent among these patients (51%) and had the highest SUV max as well.

FDG PET CT based analysis showed that 42 were true positive metastatic patients, and 6 indeterminate, two of them had suspicious pulmonary lesions on CT and not associated with significant FDG uptake which progressed on follow up. Surgical resection & systemic chemotherapy were conducted. The other patient with iliac lymph node showed low grade uptake less than liver activity which proved metastatic in tissue biopsy, followed by surgical resection and received radiotherapy. The other three patients, one had FDG avid enlarged cervical LNs in head and neck primary, that pathology showed reactive changes and another patient with FDG avid tibia lesion which proved osteomyelitis on further investigations and biopsy. The last patient, presented with FDG avid pulmonary lesion with moderate metabolic activity, which subsided on follow up study after antibiotic therapy confirming its benign inflammatory nature.

Regarding CT interpretation, 32 true positive patients were detected, while 12 patients showed false negative results, most of them proved to have nodal and bone metastases. On a per-patient basis, sensitivity, specificity, positive and negative predictive values, diagnostic accuracy & other parameters using 2x2 table are illustrated in ***Tables (2)***.

PET/CT upstaged 13 (11.6%) patients as it succeeds to detect additional FDG avid nodal, osseous, peritoneal and soft tissue metastatic lesions. The most frequent cause was bone metastasis and bone marrow infiltration (n = 6), two patients had minimal osteoblastic change to be detected by CT ***(Figure 1)*** and the other 4 patient presented with bone marrow metastasis and spinal dissemination

Detection of additional nodal metastases in 4 patients changed their stage (para-pharyngeal lymph node in head and neck primary tumor, one Iliac and other Inguinal LNs in 2 patients with primary urinary bladder, and 1 popliteal node in patient with right leg primary lesion) regional node dissection with additional radiotherapy was done in the last 3 patients.

Other causes were peritoneal metastases (n = 2) and soft tissue metastasis (n = 1) the former were confirmed by progressive course in follow up and necessitate additional palliative chemotherapy. For the other patient, metastatic soft tissue lesion of the lower limb was resected.

Table (2): Comparison of overall different detection parameters of PET/CT & Diagnostic CT in 112 patients with Rhabdomyosarcoma.

Findings	PET/CT	Diagnostic CT	P value
True positive	42	32	0.51
True negative	64	55	0.49
False positive	3	12	0.21
False negative	3	13	0.2
SN%	93	71	0.03
SP %	95.5	82	0.3
PPV %	93	72.7	0.03
NPV %	95.5	80.8	0.04
Acc %	94.6	77.6	0.03
LR_+	20.6	3.9	0.05
LR-	0.07	0.35	0.2
DOR	14	2.5	0.05
Misclassification Rate	5.4	22.3	0.02
Younden's Index	0.88	0.53	0.3

P<0.05%. PPV: Positive predictive value, NPV: Negative predictive value, SN: Sensitivity, SP: Specificity, Acc: Accuracy, LR+: Likelihood ratio for positive, LR-: Likelihood ratio for negative test, DOR: Diagnostic odds ratio, PET/CT: Positron emission tomography/computed tomography, CT: computed tomography

Per-Lesion Analysis: Both PET/CT and conventional images shows comparable results for primary tumor site. Head and neck was the most common primary site (n = 45), followed by the extremities (n=29).For proper evaluation, per lesion analysis was also done for the metastatic lesions. A total of 188 lesions were detected where 71 nodal & 117 distant metastatic lesions were analyzed, as shown in ***Table (5)***. Eighty % of metastatic patients and 26.5% of total patient had pathological nodal involvement of different regions ***(Table 5)***. Cervical lymph nodes was predominant (n=17 lesion) as regard the high prevalence of head and neck as a primary tumor site.

Out of the 71 true positive nodal lesions, CT detected only 42 lesions, while 18 lesions were considered negative (false negative) based on CT criteria. However, PET/CT detected 58 lesions with only 1 false negative result. Consequently there is significant difference between the sensitivity, specificity PPV, NPV & accuracy of CT & PET/CT ***Table (3)***. Among 117 distant metastatic lesions, 57 metastatic osseous deposits were diagnosed in 12 patient and other 5 patients presented with diffuse bone marrow involvement confirmed by bone marrow biopsy. Soft tissue metastases distributed as pulmonary (n=30), soft tissue (n=17), 5 peritoneal lesions and other 3 unusual suprarenal, spermatic cord and IVC thrombosis.

PET/CT correctly assessed 110 lesions as true positive metastatic sites compared to 82 by CT, with sensitivity, specify, PPV, NPV and accuracy as illustrated in ***Table (4) & Figure (1)***. Bone and bone marrow was the most common site, due to lacking sclerotic changes. 27 proved true positive lung lesions, all were detected by CT with a sensitivity of 100% compared to PET which detect 25 of these lesions (92.5% sensitivity). PET failed to detect 2 small sized pulmonary lesions (~ 5 mm) seen on CT and proved to be progressed on the follow up. On the other hand, the 3 true negative lung lesions [illustrated by CT only with no corresponding FDG activity] were stationary on the follow-up CT, confirming their benign nature ***(Table 5 & Figure 2)***.

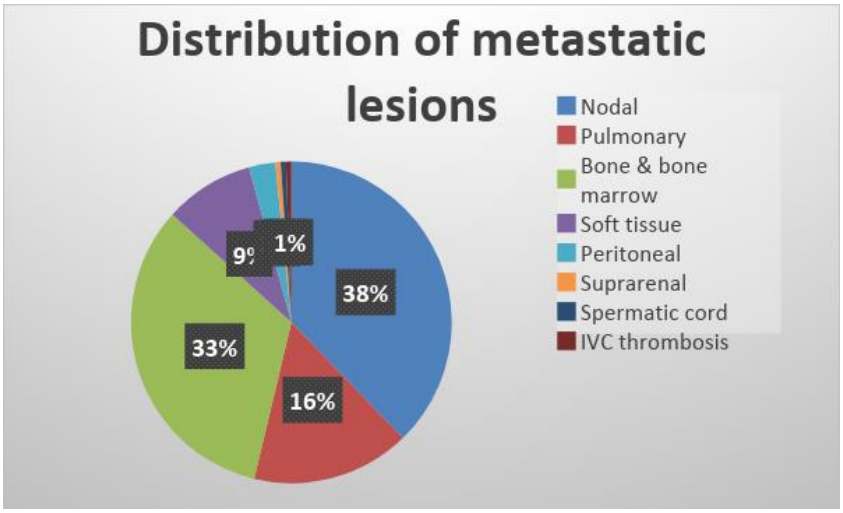

Fig (1): Distribution of different sites of metastatic lesions [*n.* 188].

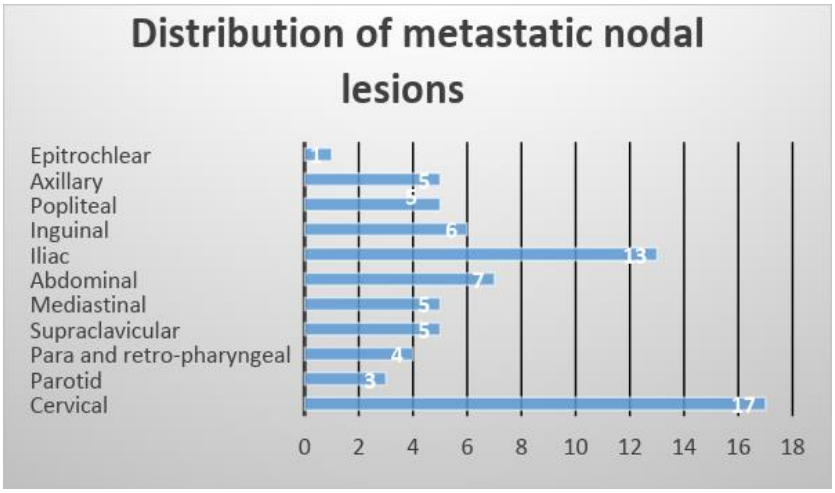

Fig (2): Distribution of metastatic nodal lesions [n. 71].

Table (4): Comparison between overall detection parameters of PET/CT & Diagnostic CT on both nodal & distant metastases.

		Sensitivity	Specificity	PPV	NPV	Accuracy
Nodal Metastases (n.71)	**PET/CT**	100	85	96.7	100	95.5
	Diagnostic CT	71	93	88	86.7	87.5
Distant Metastases (n.117)	**PET/CT**	98	86.5	96.5	93	95.7
	Diagnostic CT	75.5	60	94	11	75

Table (5): Comparison between overall detection parameters of PET/CT & Diagnostic CT in different distant metastatic sites.

	PET/CT			Conventional		
	Sensitivity	**PPV**	**Accuracy**	**Sensitivity**	**PPV**	**Accuracy**
Pulmonary	92.5	96.3	90	100	93	93
Osseous	100	98	98	73	97	72
Peritoneal	100	100	100	50	67	60
Soft Tissue	100	100	100	70	95	70

Additional 50 lesions were detected by PET/CT (21 nodal, 16 osseous, 3 peritoneal, 5 ST nodules and 5 bone marrow involvement, that were missed on CT. The enumerated bony lesions were demonstrated only by the increased FDG activity on PET scan without any sclerotic/lytic CT changes distributed as demonstrated in ***Table (5) and Figure (3&4)***.

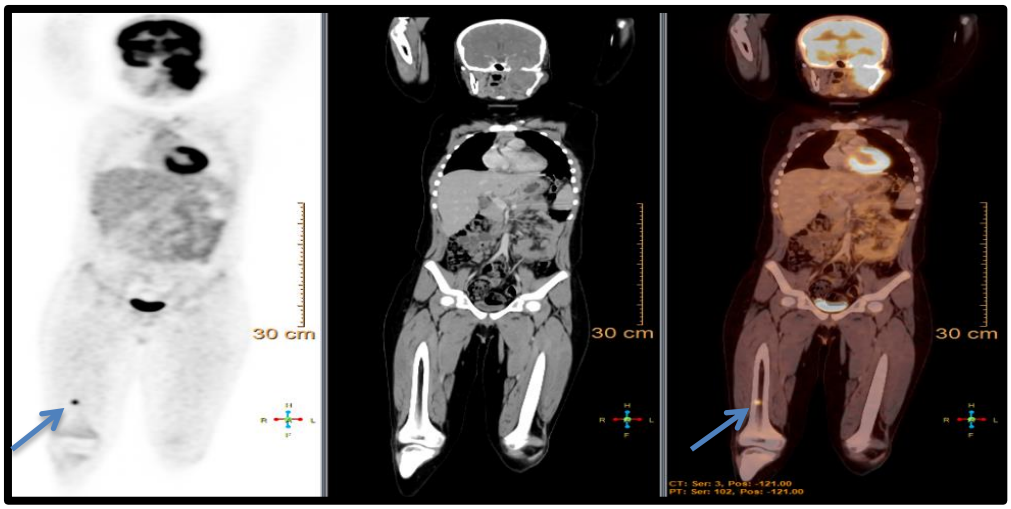

Fig (3): 6 years old girl with left infra-temporal primary alveolar Rhabdomyosarcoma. Initial PET/CT upstage the patient by detecting solitary FDG avid distal right femoral osseous lesion lacking sclerotic changes on CT.

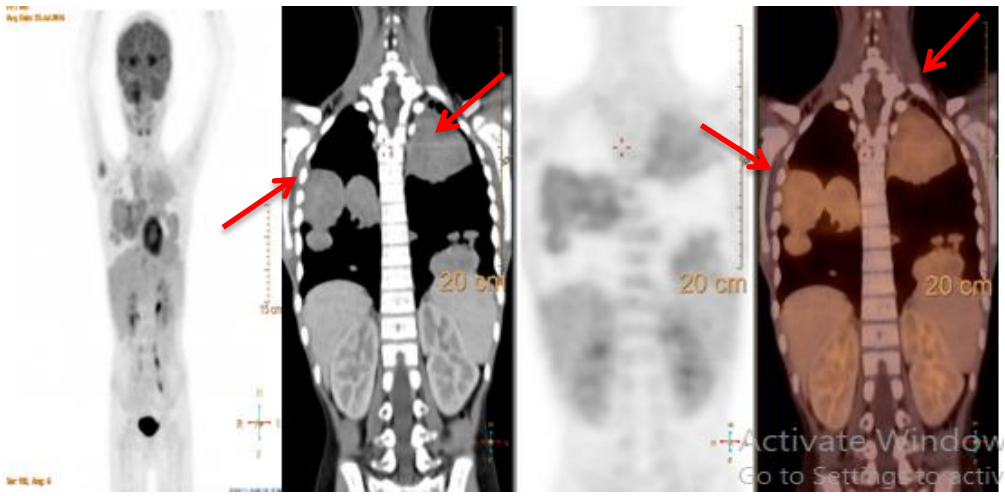

Fig (4): 8 years old boy with right para-meningeal Rhabdomyosarcoma. Initial PET/CT shows multiple metastatic pleuro-pulmonary, nodal and osseous deposits.

Table (6): Analysis of additional distant metastatic lesions detected by PET/CT (n. 50).

	Site	n
Nodal (n=21)	Cervical	4
	Para pharyngeal	1
	Mediastinal	2
	Abdominal	4
	Iliac	4
	Inguinal	2
	Popliteal	2
	Axillary	1
	Epitrochlear	1
Osseous (n=16)	Pelvis	5
	Femur	2
	Tibia	2
	Scapula	2
	Spine	1
	Humorous	1
	Ulna	1
	Ribs	1
	Sternum	1
Peritoneal (n=3)		3
Soft tissue (n=5)		5
Bone Marrow		5
Total		**50**

DISCUSSION:

The diagnosis, initial staging, risk stratification, therapy planning, and reevaluation of soft-tissue sarcoma are the corner stone to achieve disease remission and good prognosis. The presence of metastatic disease is considered the strongest predictor of clinical outcomes in patients with RMS, as it dramatically decrease the expected 5-year EFS from ~70% in non-metastatic to ~25% in metastatic patients [7, 8]. So accurate diagnosis and staging are essential to select the most appropriate therapeutic strategy and major determinants of patient prognosis and survival.

The important aspect of this study was the evaluation of the impact of PET/CT in therapy strategy. PET/CT upstaged 13 (11.6%) patients as it succeeds to detect additional FDG avid nodal, osseous, peritoneal and soft tissue metastatic lesions.

In current study, PET/CT proved to have higher sensitivity, specificity, and accuracy than conventional images, sensitivity of 100% and specificity of 95.5% at the patient level. This is compared to sensitivity of 71% and 82% specificity for conventional imaging. This is agreed with other previous studies [9].

PET/CT was better than conventional imaging in identifying patients with lymph node involvement and was obviously more sensitive to individual nodes. ***Tateishi, et al.*** showed that PET/CT had higher sensitivity, specificity and accuracy than conventional images in N staging [10].

Regarding distant metastases, in agreement with ***Rich and colleagues***, extremities was the most common primary site in metastatic RMS patients represented in 17 patient (42.5%) in our study, and Alveolar subtype was more prevalent pathological type (51%) and showed the highest max SUV as well [11].

The present image analysis support the previous studied findings reported that PET/CT improve sensitivity in identification of distant metastases not otherwise detected by conventional images [12, 13], as PET/CT had a sensitivity of 98%, specificity of 87 and accuracy 96% in detection of distant metastases as compared to 75%, 60% and 75% respectively for conventional imaging in our current findings.

In reviewing some previous studies, determination of metastatic disease in different sites was limited and investigated at the level of individual patients only [12, 13]. However in our study, additional 50 lesions were detected by PET/CT that was not appreciated on CT. In agreement with other few studies, PET/CT was superior to CT for the identification of bone lesions, either in detection of additional lesion or in changing patient's stage [12, 13].

PET/CT may also have potential to identify marrow involvement.

The advantage of conducting a whole body scan is highlighting the limitations of relying on histopathology obtained from a single site [5, 6].

The enumerated bony lesions were demonstrated only by the increased FDG activity on PET scan without any sclerotic/lytic CT changes.

There were indications that PET/CT may perform better than conventional imaging in detecting soft-tissue lesions in non-pulmonary locations [9, 10]. These results accord with reviews of PET-CT in staging of osteosarcoma and PET in general diagnosis of pulmonary nodules [14, 15].

In spite of the favored sensitivity for PET/CT in M staging, 98%, its sensitivity for lung metastases was ~92%. This agrees with the findings of previously reported studies showing that FDG PET is not able to adequately assess lung metastases smaller than ~ 6 mm.

It could be generated from respiratory motion artifacts or from the low metabolic activity of the small sized lung metastases not detected by the limited spatial resolution of PET.

It is well known that CT has a better accuracy for the detection of lung metastases, especially in children, due to the lower probability of unspecific nodules in children than in adults [(16)].

The limitation of this study, was its retrospective nature so, was not adequately designed as a comparative imaging study, for example MRI was the 1st choice for the primary tumor, CT for the detection of distant metastases, yet, bone scan was not done in all patients.

Second, lymph node biopsy was not feasible in all patients so was assessed by increase in number and/or an apparent progression in size on follow up examinations.

CONCLUSION:

FDG PET-CT is helpful in initial staging of Rhabdomyosarcoma patients as compared to Diagnostic CT regarding nodal, bone, bone marrow, peritoneum, and soft tissue metastatic lesions, except for pulmonary deposits.

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