

ORIGINAL ARTICLE

Do we need ^{18}F -FDG PET/CT scan in staging and management of testicular tumors?



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KEYWORDS

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Abstract Objective: The aim of this study was to assess the role of positron emission tomography/computed tomography (PET/CT) scan in preoperative staging of testicular tumors and therefore determining the line of appropriate management.

Patients and methods: During two year duration we prospectively evaluated 34 patients with testicular tumors diagnosed by histopathology after biopsy or orchidectomy. All patients underwent PET/CT examinations following a preset protocol that included low dose non contrast study, whole body scanning post ^{18}F -FDG injection and post IV contrast CT scan. The images obtained were reconstructed using dedicated software and workstations. Results of PET/CT examinations were compared with histopathology and serum markers.

Results: Out of 34 cases all masses were malignant (germ cell tumors). 20 masses (58.8%) were diagnosed by histopathology as seminoma subtype while 14 masses (41.2%) were diagnosed as non seminomatous germ cell tumors (NSGCT) subtype.

There were 16 true positives, 14 true negatives, 2 false positive, and 2 false negative cases. Sensitivity, specificity, positive predictive value and negative predictive values were 88.9%, 87.5%, 88.9% and 87.5% respectively.

Conclusion: Positron emission tomography/computed tomography (PET/CT) has a major role in preoperative staging of testicular tumors and defines the need of post operative adjuvant therapy. © 2016 The Egyptian Society of Radiology and Nuclear Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Testicular tumors represent the most common non hematologic malignancy in men between 15 and 49 years old (1). Although the disease is relatively uncommon, the incidence has more than doubled over the past four decades (2,3). The

median ages of diagnosis and death are 33 and 41 years, respectively (4).

Testicular tumors are subdivided into two major categories: germ cell and stromal tumors. Germ cell tumors (GCTs) account for 90–95% of all testicular tumors and are the typical tumor tissue types considered when discussing testicular cancer. GCTs are further subdivided into seminoma and nonseminomatous GCT (NSGCT). This division plays a critical role in determining the approach to treatment.

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Table 1 Different pathologies encountered in the study.

Pathology	Post biopsy	Post orchidectomy	No. (Total)	%
Seminoma	0	20	20	58.8
NSGCT	4	10	14	41.2
All	4	30	34	100

Seminoma is an extremely radiosensitive tumor, whereas NSGCTs respond better to surgical and chemotherapeutic approaches (4).

Testicular malignancy has one of the most complete and thorough staging systems among genitourinary cancers. It combines clinical, pathologic, radiologic, and serum tumor marker components. Staging typically relies on surgical pathology of the orchidectomy specimen, tumor markers before and after orchidectomy (AFP, HCG, and LDH),

chest radiography or chest CT, and CT of the abdomen and pelvis (2).

Whereas surgical pathology determines the T category of the neoplasm, imaging plays a critical role in determining the N and M components of testicular tumor staging. N category is determined by the extent of retroperitoneal lymphadenopathy, and M category describes distant metastases. Roman numeral stage grouping divides testicular cancer into three major groups on the basis of TNMS characteristics: tumors limited to the testis are stage I, those with retroperitoneal nodal involvement are stage II, and those with distant disease are stage III (4).

With the advent of improved staging and treatment there has been a marked decrease in mortality over this time (5).

Recently, Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) has been used in combination with computed tomography (CT) to monitor patients for metastasis or recurrence. While CT is the standard modality for detection of lymphadenopathy or retroperitoneal

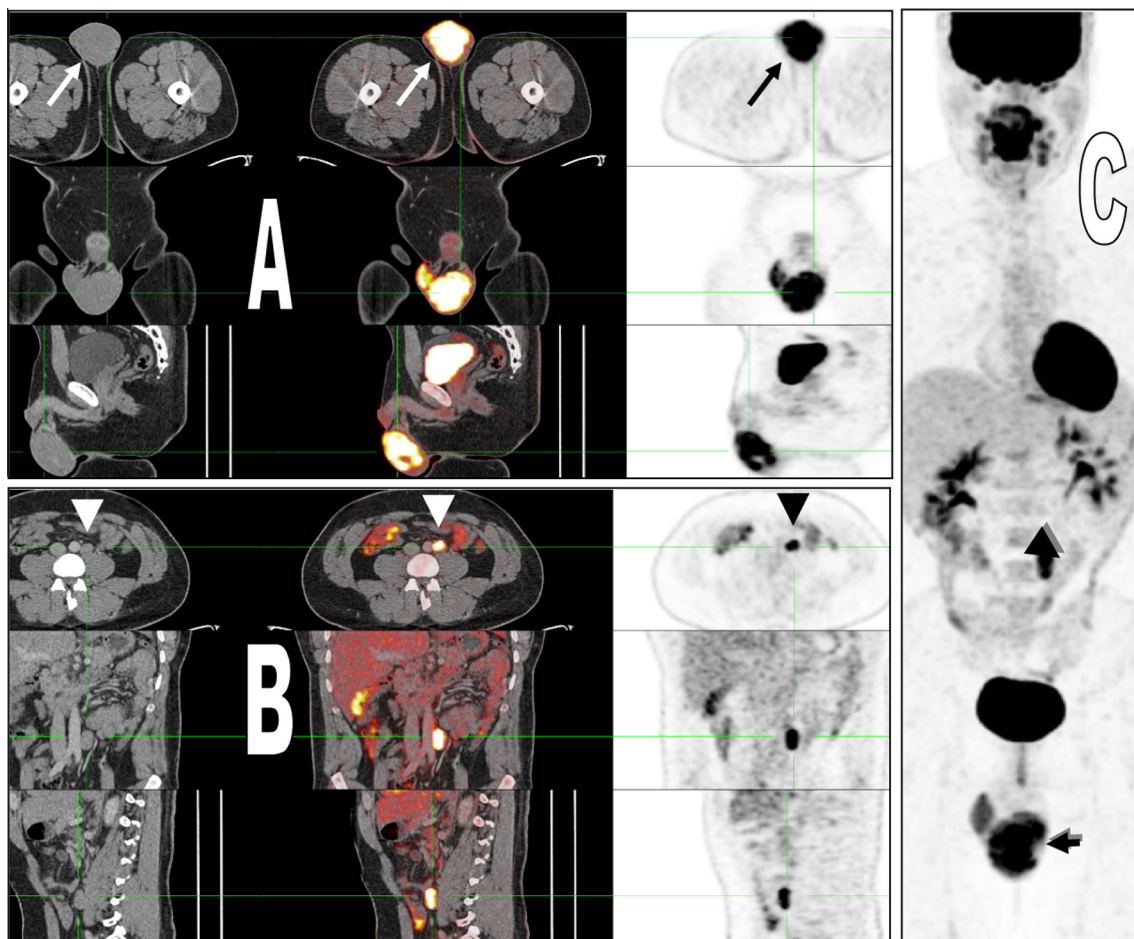


Fig. 1 35 years old male patient post biopsy of left testicular soft tissue mass proven by histopathology to be seminoma. The administered activity is 311 MBq ^{18}F -FDG, and blood glucose level (BGL) was 103 mg/dL. (A) Axial, coronal and sagittal post contrast CT images, fused PET/CT images and MIP PET images for the testicular lesion showing enlarged left testis with heterogeneously increased FDG uptake SUVmax 11.3 (arrows). (B) Axial, coronal and sagittal post contrast CT images, fused PET/CT images and MIP PET images showing FDG-avid few left para-aortic lymph nodes just at and above aortic bifurcation, largest and most active one measures about 2×3 cm in transverse and cranio-caudal diameters with SUVmax 8.7 (arrow heads). (C) Whole body coronal MIP PET image showing the active testicular lesion and left para aortic lymph node.

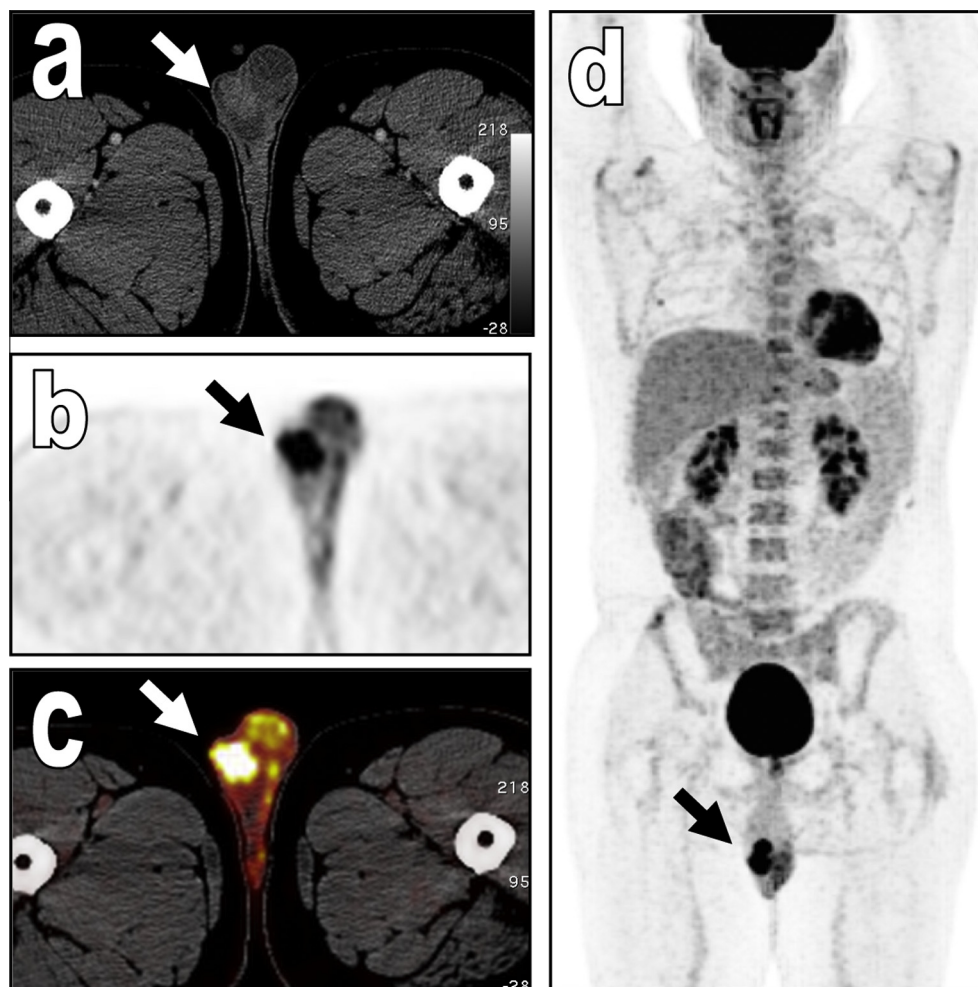


Fig. 2 37 years old male patient post biopsy of right testicular soft tissue mass proven by histopathology to be seminoma. The administered activity is 366 MBq ^{18}F -FDG, BGL was 97 mg/dL. (a) Axial post contrast CT image, (b) axial MIP PET image, (c) fused PET/CT image and (d) whole body coronal MIP PET image showing hypermetabolic right testicular mass, SUV max 8.1 (arrows). FDG avid right iliac bone small lytic lesion, SUV max 4.2 and focal FDG uptake of the central part of the prostate with related hypodensity and calcifications, and SUVmax 5.4 are also noted.

masses, its false negative rates have been reported to be as high as 30–59% (6,7).

PET/CT being able to identify regions of increased metabolic activity, has improved the detection of tumor at clinical staging (8,9). PET/CT scanners generate images that couple the metabolic sensitivity of PET with the precise anatomic detail of CT (10). FDG PET has the potential to improve clinical staging of testicular tumors (11). Since 60–70% of patients with stage I non-seminomatous germ cell tumors (NSGCT) and 80% of stage I seminoma patients do not have occult metastasis and do not require adjuvant therapy, PET/CT can reduce the morbidity of testicular tumors if it can identify which patients need adjuvant treatment (12,13).

PET scanning does not contribute in stage I of germ cell tumors, but is a possible option for stages II and III, in particular for defining treatment strategy (14).

The aim of this study was to assess the role of positron emission tomography/computed tomography (PET/CT) in preoperative staging of testicular tumors and therefore determining the line of appropriate management.

2. Patients and methods

2.1. Patients

A prospective study of 34 male patients aged 22–56 years (with mean age of 33 years) presenting to a private specialized medical center with an initial diagnosis of testicular tumor coming for staging between January 2014 and December 2015 was performed. There were no set criteria for referral other than histopathologic evidence of primary testicular tumor after biopsy or orchidectomy. Patients had clinical evaluation including medical history. Information regarding serum markers levels, interventional procedures, open surgeries and histopathology was obtained from all cases.

2.2. Methods

PET/CT scan examination was obtained for each patient. Twenty-two patients were scanned using a dedicated PET

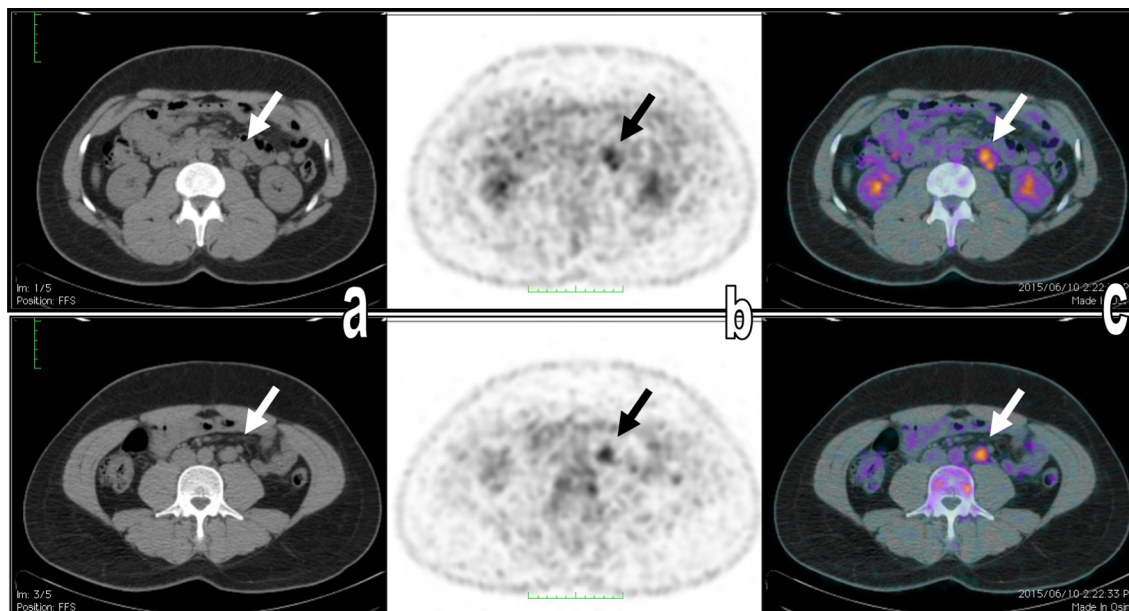


Fig. 3 29 years old male patient post excision of left testicular seminoma. The administered activity is 440 MBq ^{18}F -FDG, and BGL was 86 mg/dL. (a) Axial post contrast CT images, (b) axial MIP PET images and (c) axial fused PET/CT images showing hypermetabolic left para-aortic lymph nodes, largest one measures about 1.2 cm with SUVmax 6.5 (arrows).

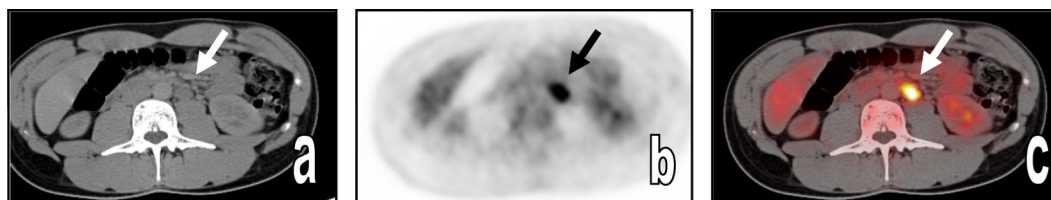


Fig. 4 22 years old male patient post excision of left testicular seminoma. The administered activity is 407 MBq ^{18}F -FDG, and BGL was 73 mg/dL. (a) Axial post contrast CT images, (b) axial MIP PET images and (c) axial fused PET/CT images showing hypermetabolic FDG-avid left para-aortic lymph node measuring about 1.5 cm with SUVmax 8.5 (arrows).

system (Siemens Syngo PET VG 50A Biograph 20 VA 44A, Berlin, Germany), covering an axial field-of-view (FOV) of 15.2 cm and a resolution of 4 mm axially and 3.8 mm transaxially at the center. Twelve patients were scanned using dedicated PET system (Philips 16 Release 3.5.2, the Netherlands), axial FOV of 16.2 cm and a resolution of 4 mm in axial and transaxial directions. After the patients had fasted for at least 8 h and were hydrated orally, blood glucose levels were assessed and found to be within normal range in all cases. First non contrast low dose CT images were obtained for fusion images. A 306–445 MBq (^{18}F -FDG) was injected and the patients rested for an uptake period of 50 min in relaxed position. After emptying the bladder, PET scans from the nose to the upper thighs were acquired.

Routine axial imaging, consisting of CT of the chest, abdomen and pelvis at 5 mm intervals after intravenous non ionic contrast administration was performed in all patients after they finished the PET/CT examination. Lymph nodes larger than 1 cm in diameter in short axes were considered pathologic.

2.3. Data analysis and interpretation

The raw data were reconstructed using special software and workstations. Images were reconstructed in coronal and sagittal multiplanar planes and read visually.

All PET/CT and CT imaging was performed and evaluated by one staff radiologist with expertise in genitourinary imaging accompanied by one staff nuclear medicine. SUV values were compared to background vasculature to determine positivity and all foci of unphysiologic FDG uptake were considered indicative of metastatic disease.

For the purposes of calculating sensitivity, specificity and predictive values, a true positive was confirmed by histopathology obtained after open surgery or biopsy ($n = 16$). True negatives ($n = 14$) were confirmed by normal levels of serum tumor markers using the three well established markers named α -fetoprotein (AFP), HCG and lactate dehydrogenase (LDH). False positives ($n = 2$) and negatives ($n = 2$) were also defined by histopathologic findings contrary to PET/CT results.

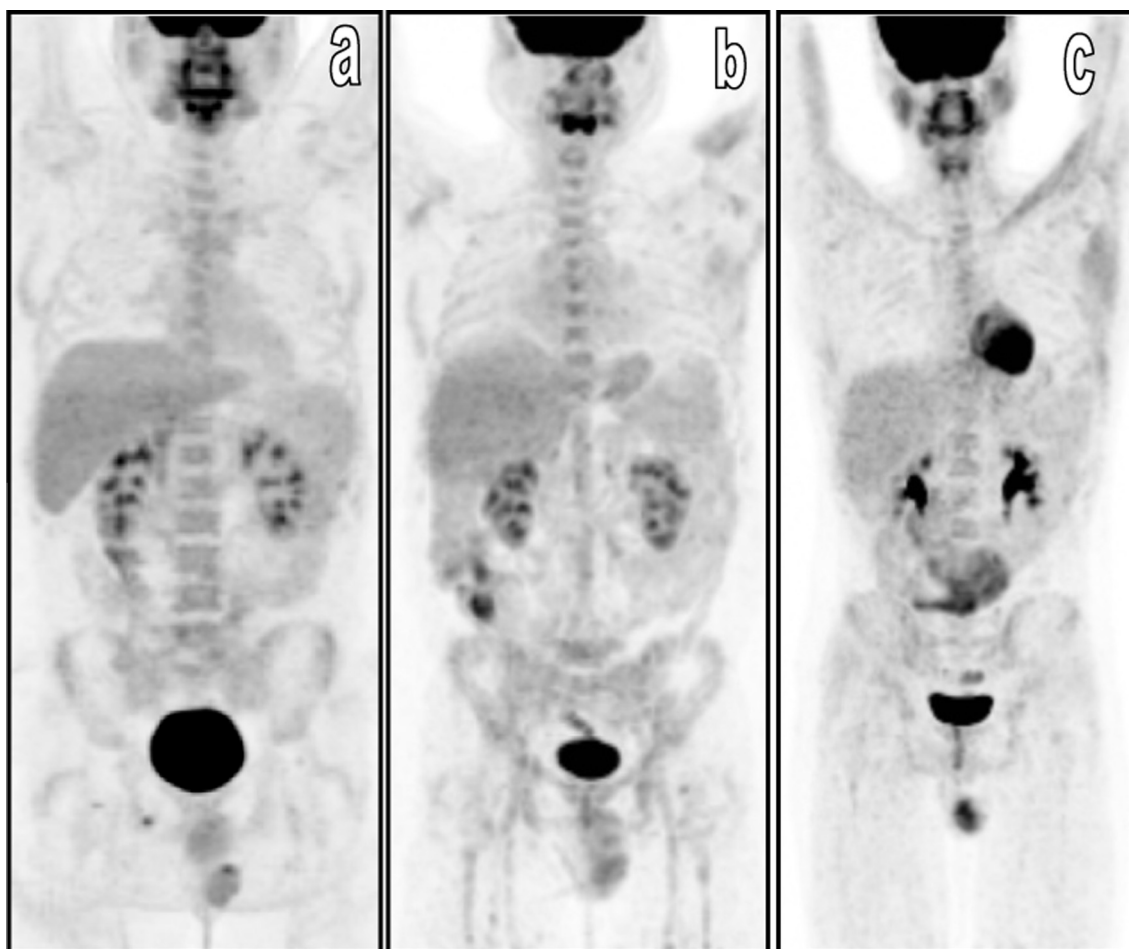


Fig. 5 (a–c) Whole body coronal MIP PET images for three different patients showing no current evidence of metabolically active local or metastatic disease.

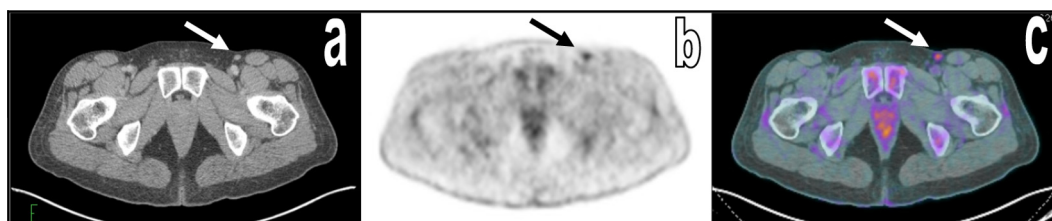


Fig. 6 28 years old male patient post excision of left testicular NSGCT. The administered activity is 370 MBq ^{18}F -FDG, and BGL was 91 mg/dL. (a) Axial post contrast CT image, (b) axial MIP PET image and (c) axial fused PET/CT image showing mild metabolic activity in two small subcentimeter left inguinal lymph nodes measuring about 1.0 cm in diameter with SUVmax 3.0 (arrows).

3. Results

From January 2014 to December 2015, 34 patients were entered in the study aged on average 33 years (range, 22–56 years).

Out of 34 cases all masses were malignant (germ cell tumors). 20 masses (58.8%) were diagnosed by histopathology post orchidectomy as seminoma subtype while 14 masses (41.2%) were diagnosed post orchidectomy or biopsy as non seminomatous germ cell tumors (NSGCTs) subtype as listed in Table 1.

There were 16 true positives, 14 true negatives, 2 false positive, and 2 false negative cases. Sensitivity, specificity, positive predictive value and negative predictive values were 88.9%, 87.5%, 88.9% and 87.5% respectively. CT and PET/CT findings matched in 30 of 34 patients and differed in 4 patients.

The true positives patients showed active testicular soft tissue masses in 4 patients who performed the examination post biopsy and histopathology (Figs. 1 and 2), active residual tissues at the operative bed detected in 2 patients post orchidectomy, active para aortic lymph nodes in 8 patients (Figs. 3 and 4), active inguinal lymph nodes in 4 patients and active hilar lymph nodes in 2 patients. It was noted that

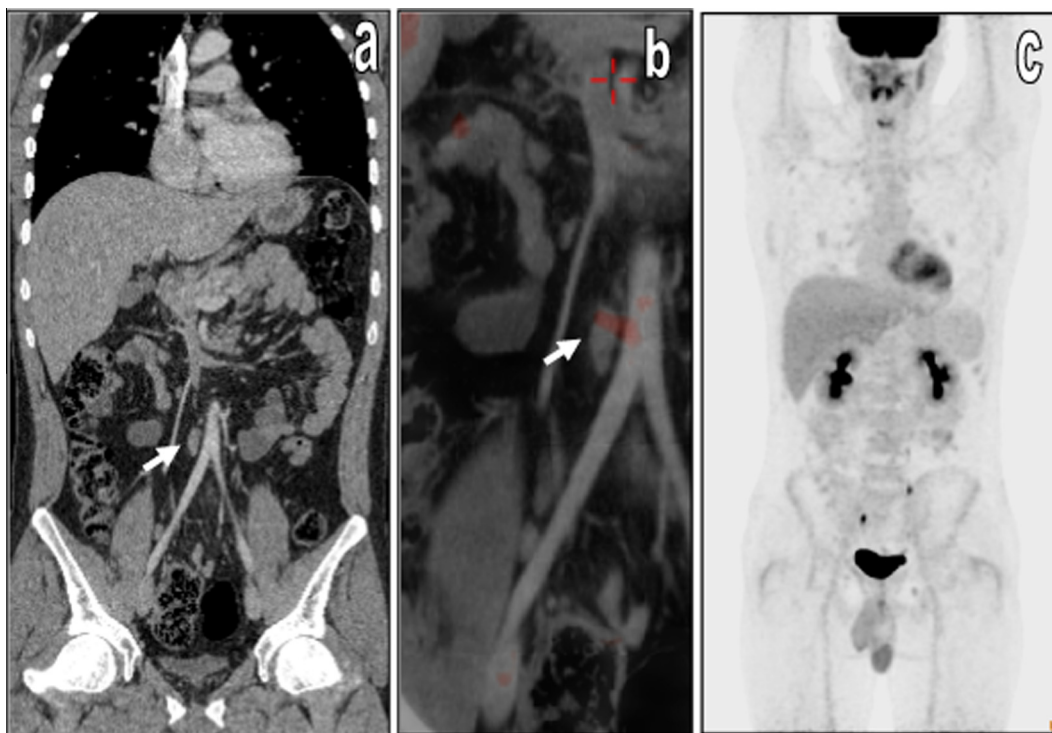


Fig. 7 33 years old male patient post right orchidectomy for NSGCT. The administered activity is 340 MBq ^{18}F -FDG, and BGL was 84 mg/dL. (a and b) Coronal post contrast CT image showing enlarged para-aortic lymph node measuring about 1 cm in short axis with no significant FDG uptake (arrows), (c) whole body coronal MIP PET image.

Table 2 Lymph nodes involvement in all cases, n (%).

Pathology	Lymph Nodes			No LNs
	Para Aortic	Inguinal	Hilar	
Seminoma (20 patients)	6 (30%)	2 (10%)	2 (10%)	10 (50%)
NSGCT (14 patients)	4 (28.5%)	4 (28.5%)	–	6 (43%)
Total (34 patients)	10 (29.4%)	6 (17.6%)	2 (5.9%)	16 (47%)

10 patients out of 16 true positive cases were diagnosed as seminomas.

The true negative patients had no evidence of residual active operative bed masses or active distant lymph nodes and had within normal serum tumor markers levels (Fig. 5).

The false positive cases occurred in 2 patients who had enlarged inguinal lymph node(s) turned out to be non specific in histopathologic examination after biopsy and no malignant cells were detected (Fig. 6).

The false negative cases occurred in 2 patients who had multiple para aortic lymph nodes not exceeding 1 cm in diameter in short axis who had open surgery despite negative PET/CT scans. Histopathology revealed at least one lymph node containing embryonal carcinoma, confirming a false negative for PET/CT (Fig. 7).

Nodal metastatic spread was found in 18 patients (53%) while 16 patients (47%) had negative PET scan for nodal involvement. Out of 20 cases diagnosed as seminoma, 6 patients (30%) had para aortic active lymph nodes, 2 patients (10%) had active inguinal lymph nodes, 2 patients (10%) had active hilar lymph nodes and 10 patients (50%) had

negative PET scans. Out of 14 cases diagnosed as NSGCT, 4 patients (28.5%) had para aortic active lymph nodes, 4 patients (28.5%) had active inguinal lymph nodes and 6 patients (43%) had negative PET scans as listed in Table 2.

4. Discussion

Imaging plays major role in the clinical staging of testicular germ cell tumors. While CT and CXR have served as the standards for these evaluations, recent studies have demonstrated the utility of PET/CT (8). It provides additive information that may positively impact decision-making (15).

Primary staging of germ cell tumors is important to implement the plan of treatment and to reduce the potential for morbidity from this treatment. Unnecessary radiotherapy/chemotherapy or surgery can be avoided especially in early stages.

All staging procedures have their limitations. The rising serum markers after removal of the primary may indicate disease presence but cannot locate its site. Anatomical staging techniques particularly CT have severe limitations in the

identification of disease, with reported false-negative rates of 30–59% (7).

When planning for this study the decision was taken to perform the examination before chemotherapy taking into consideration the findings of Cremerius et al. (11), who described a high rate of false negative PET scans within 2 weeks following chemotherapy, a finding that was confirmed by Hain and colleagues (9).

The results of current study suggested that PET/CT identified the sites of disease in both seminomas and NSGCT during primary staging and has high specificity and positive predictive accuracy. This agrees with study done by Sterbis and colleagues (15).

PET/CT has been shown to identify viable tumor in residual masses for both NSGCT and seminomas (16,17). In current analysis 2 residual malignant masses were detected post orchidectomy proven by histopathology to be NSGCT. Cremerius et al. (11) found a high accuracy for FDG-PET/CT in masses containing seminomas and this goes with current study as 10 patients out of 16 true positive cases were confirmed by histopathology as seminomas.

The majority of patients with early stage seminoma and NSGCT do not require adjuvant treatment post operatively. Therefore 14 true negative cases diagnosed in this analysis took a significant potential benefit.

Hain et al. (9) reported 10 true positive cases and 16 true negative cases out of 31 patients and this matches with current study including 16 true positive cases and 14 true negative cases out of 34 patients.

There were 2 cases recorded as false negative, and they had malignant para aortic lymph nodes that could have been treated with radiotherapy if detected by PET/CT. Fortunately, these patients chose to go for open surgery. This was a bit disappointing since ideally PET/CT should be capable of limiting unnecessary operations. Sterbis et al. (15) reported 1 false negative case out of 49 patients in 6 year duration while current study included 2 out of 34 patients despite shorter period of time.

In addition only 2 patients with false positive PET/CT scans had moderately active inguinal lymph nodes and borderline high normal serum markers pushing the diagnosis toward metastatic nodal involvement. This was proven to be false after histopathology revealing reactive changes and absence of malignant cells. Sugawara and colleagues (18) were concerned about the capability of PET/CT to identify metastatic lesions smaller than 1 cm. The current analysis combining PET and CT taking benefit of metabolic sensitivity of PET as well as anatomic accuracy of CT was able to detect small subcentimetric lesions to the extent that two of them turned to be non malignant reactive nodes.

PET/CT has limitations as registration may be influenced by artifacts induced by motion or by metallic implants. SUV levels obtained manually may be subjected to potential measurement errors. Areas with high physiologic activity such as the liver may obscure small lesions. It is important to recognize that fusion imaging with PET/CT is not accurate for small sized nodes. A minimum 2 week waiting period between the completion of chemotherapy if any and performance of PET/CT should be accomplished.

The current small study confirms the findings of previous few studies using ¹⁸F-FDG for primary staging; however,

further investigations with a larger patient cohort are needed to further define its role.

In conclusion PET/CT provides valuable data about the extent of testicular tumor, its local spread, regional as well as distant lymph nodal involvement and can detect distant metastasis. It can provide higher level of detection compared to CT due to anatomical/functional image registration. Therefore it has a major role in preoperative staging of testicular tumors and selection of appropriate post operative adjuvant therapy.

Conflict of interest

The authors declare that there are no conflict of interests.

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