Original article

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^{18}F-Flourodeoxy glucose PET–computed tomography in testicular carcinoma: diagnostic and prognostic value

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Aim **This study aims to assess the diagnostic role of ^{18}F-FDG PET/computed tomography in primary staging and restaging of testicular cancer in comparison with contrast-enhanced diagnostic thoracic-abdominopelvic computed tomography.**

Material and method **Thirty-two consecutive male patients with testicular carcinoma (median age: 29, min–max: 17–65) who were referred to the nuclear medicine department for ^{18}F-FDG PET/computed tomography were retrospectively included in the study. Patients were evaluated based on the ^{18}F-FDG PET/computed tomography indications and germ cell tumor subtypes.**

Results **On patient-based analysis, overall sensitivity, specificity, PPV, NPV and accuracy of 18F-FDG PET/computed tomography were 71%, 100%, 100%, 30% and 75%. On lesion-based analysis, for evaluation of lymph node metastasis they were 76%, 100%, 100%, 57% and 81%, and for detection of distant metastasis 85%, 100%, 100%, 90% and 93%, respectively. Median SUVmax for seminomas were calculated as 14.2 and for nonseminomas 7.8 ($P = 0.62$) Mean time to progression and overall survival were calculated as 76.6 ± 10.7 and 111 ± 7.5 months, respectively. Mean overall survival and time to progression for PET-positive and negative groups was not found significant ($P = 0.69$ and $P = 0.81$). The only significant factor in predict overall survival was the presence of distant organ metastases in PET/computed tomography (124.6 ± 5.2 vs. 78.7 ± 14.0 months, $P = 0.02$).**

Conclusion **In this single-center experience with a limited number of patients, ^{18}F-FDG PET/computed tomography appears to have a value of staging and restaging for both seminomatous and non-seminomatous GCTs. *Nucl Med Commun* 40:1268–1274** **Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: ^{18}F-FDG PET/CT, restaging, staging, testicular carcinoma

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Introduction

Testicular cancer is the most common solid malignancy of young males. It frequently originates from germ cells, accounting for 95% of all cases [1]. Germ cell tumors (GCTs) are roughly classified as seminomatous GCTs (SGCTs) (60%) and non-seminomatous GCTs (NSGCTs) [2]. Although complete response rates of seminomas are about 95%, even in the presence of metastatic disease at the presentation, the clinical outcome of non-seminomatous GCTs is highly correlated with the disease stage at the diagnosis [3].

The most common presentation of GCTs is a dense, painless scrotal mass and usually diagnosed by ultrasonography. At the time of diagnosis, metastatic disease is seen in about 20% of patients [4]. Conventional imaging with abdominopelvic high resolution computed tomography (CT) is the method of choice in preoperative staging as testicular cancer first spreads to retroperitoneal lymph nodes. Distant metastases occur in lungs, brain or skeletal system [5]. Since ^{18}F-FDG PET/CT provides data about the metabolic state of the lesions described in conventional imaging modalities, it has now become a widely available imaging tool. Although ^{18}F-FDG PET/CT is recommended in staging, restaging and evaluation of therapy response in many solid tumors, it has not yet taken place in the diagnostic algorithm of GCTs. A seek for a new diagnostic tool to differentiate micrometastatic nodal disease at staging, localization and characterization of relapse or recurrent masses has lead clinicians to focus on the possible value of ^{18}F-FDG PET/CT in the metabolic evaluation of GCTs [6–8]. Whole-body imaging also provides scanning distant metastatic sites at a single step.

The aims of this single-center study were: (1) to assess the diagnostic role of ^{18}F-FDG PET/CT in primary staging and restaging of testicular cancer in comparison with contrast-enhanced diagnostic thoracic-abdominopelvic CT, (2) to evaluate if there is a difference between pathological subtypes in terms of ^{18}F-FDG uptake and prognosis and (3) to explore possible prognostic significance of PET positivity in the follow-up.

Material and method

Patients

Data of 55 patients who underwent ^{18}F-FDG PET/CT for the staging or restaging of testicular carcinoma in Ankara University Medical Faculty Nuclear Medicine

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Department from January 2010 to January 2019 were retrieved from the hospital database.

Inclusion criteria were (1) histopathologically confirmed GCT diagnosis, (2) ^{18}F-FDG PET/CT performed for staging or restaging of disease, (3) ^{18}F-FDG PET/CT and conventional imaging studies performed in 3 months period, (4) presence of pathological confirmation or comparison to other imaging modalities and (5) available clinical follow-up and survival data. Eventually, 32 male patients (median age: 29, min–max: 17–65) were included in the study.

Patients were evaluated based on the ^{18}F-FDG PET/CT indications (group 1, staging and group 2, restaging) and GCT subtypes. Plasma levels of human chorionic gonadotropin beta (HCGB) and alpha-fetoprotein (AFP) were evaluated.

^{18}F-FDG PET/CT protocol

After 6-hour fasting, 370 MBq ^{18}F-FDG was injected while the blood glucose level is <150 mg/dl. Whole-body PET/CT images were acquired with a GE Discovery PET/CT 710 series scanner 45–60 minutes after injection. Images from the vertex to the proximal femur were obtained while the patients were in the supine position. PET images were acquired for 2 minutes per bed position. Emission PET images were reconstructed with low dose non-contrast CT images. CT images were obtained with a standardized protocol of 140 kV, 70 mA, tube rotation time of 0.5 seconds per rotation, a pitch of six and a slice thickness of 5 mm. Patients were allowed to breathe normally during the procedure. Attenuation-corrected PET/CT fusion images were analysed in three planes (transaxial, coronal and sagittal) on Advance Workstation Volumeshare 5 (GE Medical Systems, Milwaukee, USA).

ceCT protocol

CT images were acquired using a 64-multidetector CT scanner (Toshiba Aquillion 64; Toshiba Medical Systems, Tokyo, Japan). Scanning parameters included a slice thickness of 5 mm, a reconstruction interval of 1 mm, automatic tube current modulation 120 KV and a tube rotation time of 0.5 seconds. The scanning range was from 1 cm superior to lung apices to middle thighs; the scan direction was craniocaudal. Patients fasted for 8 hours before the scanning. Patients received 2 ml/kg of nonionic iodinated contrast medium at 350 mg/ml iodine intravenously through a 22-gauge catheter into the antecubital vein at a rate of 2.5 ml/s by automatic power injector. All cases were acquired using a standardized CT protocol that did not change during the study. The timing of acquisition was established in all cases timed to be approximately 65 seconds after contrast agent administration.

Data and statistical analysis

Pathological findings on both ceCt and ^{18}F-FDG PET/CT were recorded based on lymph node and organ involvement. SUVmax for all the pathological lesions were calculated for semi-quantitative analysis. Clinical follow-up data and histopathological examination results were used for the confirmation of imaging findings. The patient-based and lesion-based analyses were performed.

The descriptive statistics of the variables were calculated as mean, median and 25%–75% range. Diagnostic performance for both methods was calculated. Pearson's Chi-square test was carried out for compatibility of diagnostic CT and ^{18}F-FDG PET/CT results, for the primary tumor, lymph node and distant metastasis, separately. Kappa value was calculated as a measure of agreement between two imaging modalities. Pearson's correlation analysis was carried out for biochemical parameters and SUVmax, and a correlation constant was calculated (P). Values of P less than 0.05 were considered significant. For the comparison of mean values of variables groups, the Student t-test was used. A Kaplan–Meier Curve was formed for evaluation of overall survival and time to progression (TTP). Possible parameters related to TTP were analysed with Cox regression. Statistical analysis was carried out using the SPSS 17.0 (Chicago, Illinois, USA).

Results

While 12 (37%) patients underwent ^{18}F-FDG PET/CT for staging of disease, 20 patients (63%) underwent ^{18}F-FDG PET/CT for investigation of possible etiology of tumor marker elevation or metabolic characterization of suspect lesions detected by conventional imaging modalities. Histopathologically, there were 11 seminomatous GCT (34%) and 21 non-seminomatous GCT patients (66%).

Diagnostic performance of ^{18}F-FDG PET/CT

In group 1, ceCT and ^{18}F-FDG PET/CT were both useful in the detection of lymph node metastasis. However, in 1 (8%) patient, ^{18}F-FDG PET/CT was able to detect metastasis in a millimetric lymph node which was not morphologically pathological. For evaluation of lung metastasis, pathological ^{18}F-FDG uptake was observed in corresponding lung nodules detected by CT in six patients. In another 1 (8%) patient; however, ^{18}F-FDG avidity could not be demonstrated due to the millimetric size of nodules; therefore, ^{18}F-FDG PET/CT was considered false-negative. Another 1 (8%) patient with ^{18}F-FDG negative lung nodules, nodules were accepted as benign, and they stayed stable in the follow-up. In another 1 (8%) patient skeletal metastasis was detected by ^{18}F-FDG PET/CT while there was no distinguishable metastatic lesion on CT.

In group 2, both modalities showed concordant results in the evaluation of lymph nodes except for 6 (33%) patients. Five out of six patients had pathological lymph nodes on ceCT, but ^{18}F-FDG PET/CT was negative. Lymphadenopathy was necrotic in three of them while

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lymph nodes were millimetric in other two patients. In one out of six patients, a pathological ^{18}F-FDG uptake was seen in a millimetric lymph node.

Results of ceCT and ^{18}F-FDG were not very much coherent for the detection of lung metastasis

Millimetric ^{18}F-FDG non-avid lung nodules were clinically accepted as benign in 5/20 patients. However, ^{18}F-FDG PET/CT missed lung metastasis in a patient with millimetric lung nodules detected by ceCT. Two examples of patients are represented in Figs. 1 and 2.

In the whole patient population, ^{18}F-FDG PET/CT changed management in 8 (25%) patients; by detecting millimetric lymph node metastasis in F-FDG two patients, skeletal metastasis in one patient, and excluding lung metastasis in five patients with lung nodules.

Overall sensitivity, specificity, PPV, NPV and accuracy of ^{18}F-FDG PET/CT were 71%, 100%, 100%, 30% and 75% on patient-based analysis; 76%, 100%, 100%, 57% and 81% for lymph node metastasis; and 85%, 100%, 100%, 90% and 93% for distant metastasis in regards to lesion-based analysis, respectively. For seminoma patients only, these parameters were calculated as 67%, 100%, 100%, 40% and 72% for lymph nodes and 67%, 100%, 100%, 89% and 91% for distant metastasis. In patients with non-seminomatous cancer, these values were 84%, 100%, 100%, 60% and 87% for lymph node detection and 87%, 100%, 100%, 90% and 94% for distant metastasis.

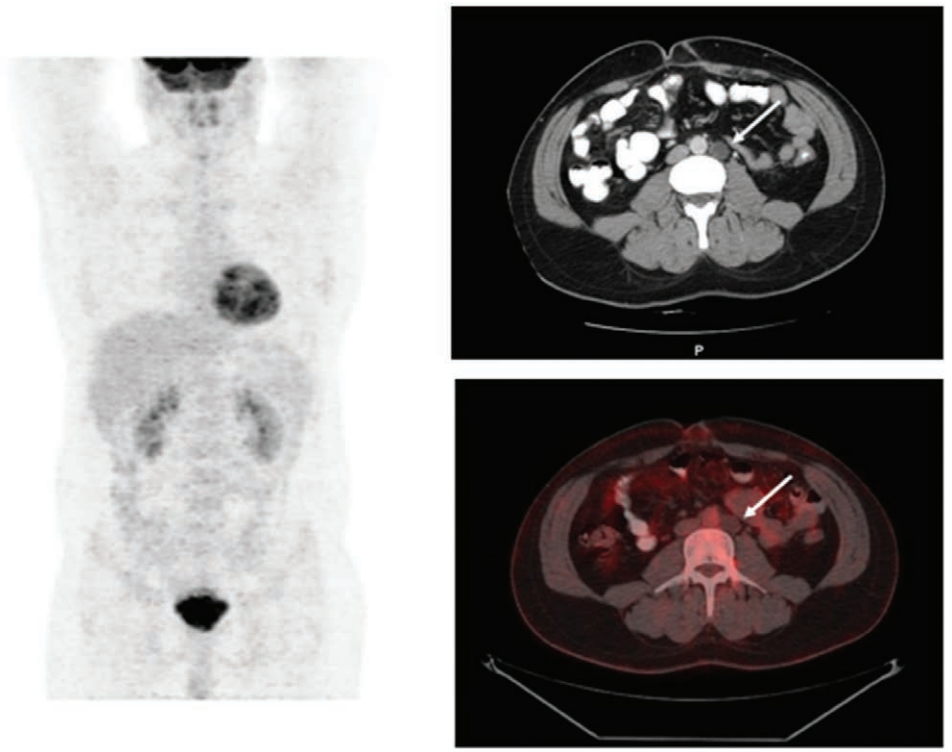
Demographic data and the findings of CT and PET/CT were summarized in Table 1.

Tumor markers and ^{18}F-FDG PET/CT

Median AFP and HCGB levels for seminoma patients were calculated as 3.2 (range: 42.1) ng/ml and 0.1 (range 2.8) mIU/ml and for non-seminoma groups 3.8 (range: 2909) ng/ml and 0.5 (range: 1550) mIU/ml, respectively. There was no significant difference between the median serum AFP or HCGB levels of seminoma and non-seminoma patients (P = 0.1 and P = 0.2). In ^{18}F-FDG PET/CT positive patients, no correlation was found between SUVmax and serum AFP or HCGB levels (P = 0.41 and P = 0.26, respectively). Pathological uptake was seen in abdominal-pelvic lymph nodes in 19 and distant organs in 11 (lung in 10 and bone in one) patients. Median SUVmax for seminomas were calculated as 14.2 (range: 20) and for nonseminomas 7.8 (range: 24) (P = 0.62).

In patients with a negative and a positive ^{18}F-FDG PET/CT, median serum AFP levels were 2.8 (range: 612) and

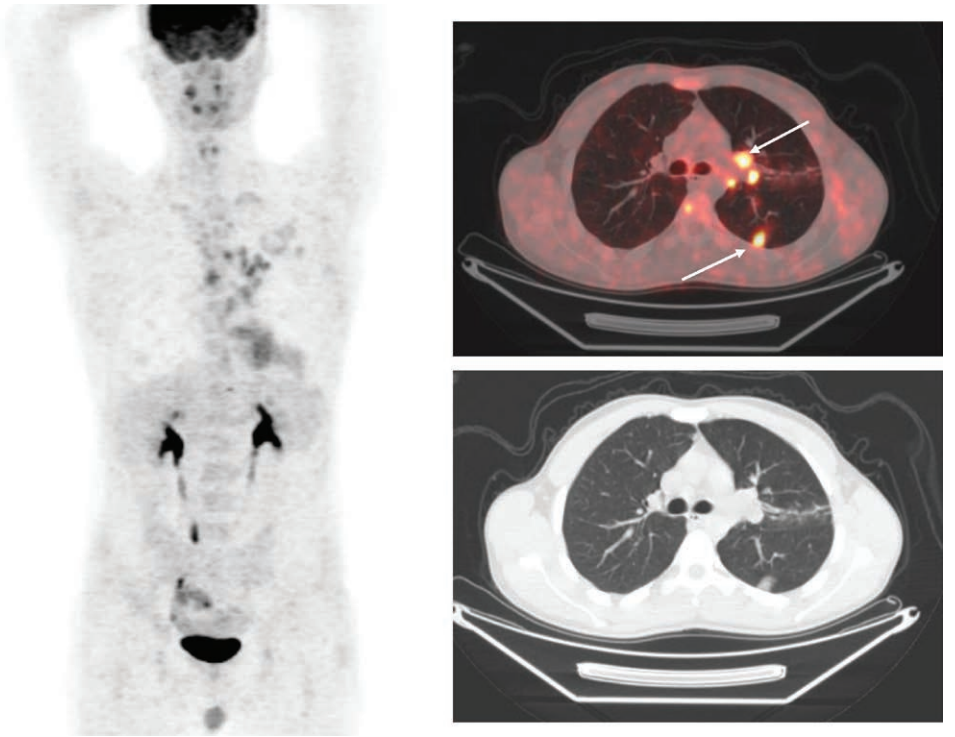
Fig. 1



Maximum intensity projection PET, transaxial CT and fused images of 21-year-old patient with NCGCT. He underwent PET/CT for the restaging of disease for a paraaortic lymph node detected by CT. There is no ^{18}F-FDG uptake in the lymph node (arrows). Histopathological examination of lymph node was resulted in metastasis with large necrotic component. CT, computed tomography; NSGCT, non-seminomatous germ cell tumors.

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Fig. 2



Maximum intensity projection PET, transaxial CT and fused images of 18-year-old patient with NCGCT. He underwent PET/CT for restaging of disease. Lung metastases and mediastinal lymph node metastases were revealed with PET/CT (arrows). CT, computed tomography; NSGCT, non-seminomatous germ cell tumors.

3.6 (range: 1504) (P = 0.34), median serum HCGB levels were 0.5 (range:1550) and 0.59 (range: 1550) (P = 0. 88), respectively. There was no statistically significant difference between the two groups in the comparison of mean serum tumor marker levels.

PET/CT and survival

During the mean 124 ± 9.8 months' follow-up, disease progression was seen in 14 (44%) patients and mean TTP was calculated as 76.6 ± 10.7 months. Deaths occurred in five patients (15%) and mean OS was 111 ± 7.5 months. In the seminomatous GCT group, none of the patients died during the follow-up. Disease progression and death happened in 8 (40%) and 5 (25%) in PET-positive patients, respectively. None of the PET-negative patients died during follow-up. Mean OS and TTP was insignificant for PET-positive and -negative groups (P = 0.69 and P = 0.81). The presence of distant organ metastases in PET/CT was a significant factor to predict OS {124.6 ± 5.2 [95% confidence interval (CI), 114.3–134.9 months] vs. 78.7 ± 14.0 (95% CI, 51.1–106.4) months, P = 0.02} (Fig. 3). Additionally, a cutoff value of eight for SUVmax was a significant factor in the univariate analysis [124.3 ± 5.5 (95% CI, 113.6–135.1 months) vs. 79.9 ± 13.7 (95% CI, 52.9–106.9) months, P = 0.03] (Fig. 4).

Discussion

Diagnosis of testicular carcinoma is made with physical examination and scrotal ultrasonography. In the initial staging of testicular tumors, lymph node pathways should be screened and the presence of distant metastases should be assessed. Testicular carcinomas most commonly spread to the retroperitoneal lymph nodes. Although right-sided testicular cancers spread to inter-aortocaval lymph nodes, left-sided cancers spread to para-aortic lymph nodes [9–12]. Staging and treatment strategy choice depends on the lymph node involvement, and the size of the metastatic lymph nodes [13]. In the absence of lymph node involvement, disease is defined as early-stage (less than stage II) and active surveillance can be an option. In case of lymph node involvement, disease stage elevates to II. Size of the positive retroperitoneal node divides stage II patients into stage IIA, IIB and IIIC. Investigation of the presence of retroperitoneal lymph node metastases is crucial for patient management, and CT is the most common imaging modality for this purpose. However, for evaluation of retroperitoneal lymph node involvement, as high as 44% rates of false negativeness have been reported [14]. The most probable reason proposed for false-negative results is the micrometastatic disease. Additionally, radiologists miss the right-sided lymph nodes more than

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Table 1 Demographic data and findings of computed tomography and PET/computed tomography of patients

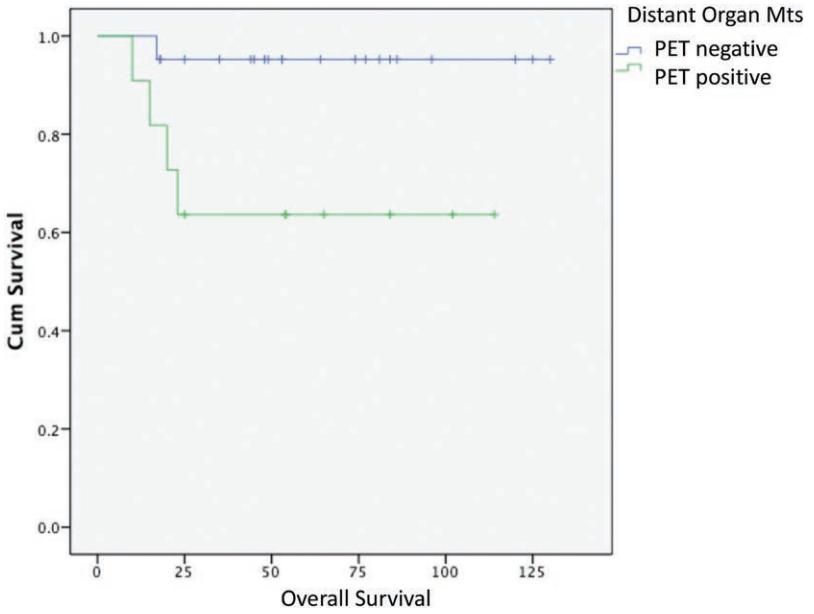
Patient No	Age	Histological subtype	Indication of PET	Primary site	Lymph nodes	The largest size of the lymph nodes (mm)	Structure of the lymph node	Location	Distant (m)	Primary site	Lymph nodes	Distant (m)
1	19	NSGCT	Restaging	neg	pos	42	Cystic	Left paraaotic	lung	neg	pos	neg
2	21	NSGCT	Restaging	neg	neg	NA	NA	NA	lung	neg	pos	lung
3	20	NSGCT	Restaging	pos	neg	NA	NA	NA	lung	pos	neg	lung
4	22	NSGCT	Restaging	neg	pos	38	Necrotic	Paraaortic	neg	neg	pos	neg
5	54	SGCT	Restaging	neg	pos	35	NA	Left paraaotic	neg	neg	pos	neg
6	57	NSGCT	Staging	neg	pos	45	NA	Paraaortic, retrocrural, paracaval	lung	neg	pos	lung
7	26	SGCT	Restaging	neg	pos	16	Necrotic	Paraaortic	neg	neg	pos	neg
8	17	NSGCT	Restaging	neg	neg	NA	NA	NA	lung	neg	neg	lung
9	36	SGCT	Staging	neg	neg	NA	NA	NA	lung	neg	neg	neg
10	33	SGCT	Restaging	neg	neg	NA	NA	NA	lung	neg	neg	neg
11	41	NSGCT	Restaging	neg	neg	NA	NA	NA	neg	neg	neg	neg
12	21	NSGCT	Restaging	neg	pos	14	Necrotic	Left paraaortic	lung	neg	neg	neg
13	32	NSGCT	Restaging	neg	neg	NA	NA	NA	lung	neg	neg	neg
14	25	NSGCT	Restaging	neg	pos	20	NA	Interaortocaval, paraaortic	neg	neg	pos	neg
15	25	NSGCT	Restaging	neg	neg	NA	NA	NA	neg	neg	neg	neg
16	32	SGCT	Restaging	neg	pos	15	hipodens	Interaortocaval	neg	neg	neg	neg
17	29	SGCT	Restaging	neg	pos	7		Left paraaortic	neg	neg	neg	neg
18	18	NSGCT	Restaging	neg	pos	35	Necrotic	Gastric, celiac, portal, paraaortic, interaortocaval	lung	neg	neg	neg
19	23	NSGCT	Staging	neg	pos	34	NA	All stations in the abdomen, left supraclavicular, axillary and mediastinal multiple	lung	neg	pos	lung
20	35	SGCT	Staging	neg	pos	60	NA	Left paraaortic	lung	neg	pos	lung
21	27	NSGCT	Restaging	neg	neg	NA	NA	NA	lung	neg	neg	neg
22	65	SGCT	Staging	neg	pos	95	Cystic-necrotic	Paraaortic, interaortocaval, paracaval	neg	neg	pos	neg
23	29	NSGCT	Staging	neg	pos	30	Hypodense	Interaortocaval	neg	neg	pos	neg
24	48	SGCT	Staging	neg	pos	30	NA	Paraaortic, interaortocaval, paracaval, parailiac, retrocrural, retroperitoneal	lung	neg	pos	lung
25	22	NSGCT	Restaging	neg	pos	24	Hypodense	Paracaval, paraaortic, right obturator	neg	neg	pos	lung
26	43	NSGCT	Staging	neg	neg	NA	NA	NA	neg	neg	pos	neg
27	19	NSGCT	Staging	neg	pos	15	NA	Paraaortic	neg	neg	pos	bone
28	57	NSGCT	Staging	neg	pos	45	NA	Paraaortic, interaortocaval, paracaval, retrocrural, mesenteric	lung	neg	pos	lung
29	34	SGCT	Restaging	neg	pos	20	Necrotic	Paraaortic, interaortocaval	neg	neg	pos	neg
30	40	NSGCT	Staging	neg	pos	75	Necrotic	Paraaortic, interaortocaval, retrocrural	lung	pos	pos	lung
31	25	SGCT	Restaging	neg	pos	8	NA	Paraaortic, interaortocaval	neg	neg	neg	neg
32	54	NSGCT	Staging	neg	pos	39	NA	Paraaortic, retrocrural	lung	neg	pos	neg

mm, millimeter; NA, not available; neg, negative; NSGCT, non-seminomatous germ cell tumors; pos, positive; SGCT, seminomatous germ cell tumors.

the left [15]. It has been shown that about 20%–25% of stage I patients who did not undergo retroperitoneal lymph node dissection (RPLND) have presented lymph node relapse [16,17]. Another reason can be the cutoff value chosen for the length of the short axis of the lymph nodes reported on CT. A 15 mm cutoff seems to be insufficient to catch all metastatic nodes, whereas 5 mm may be oversensitive, resulting in unnecessary RPLND [18]. MRI provides very little additional information over CT in the loco-regional evaluation and is mostly indicated in case of brain metastasis [19]. ^{18}F-FDG PET/CT has been reported to have higher sensitivity than CT in the evaluation of retroperitoneal lymph node metastases and distant organ metastases [8]. ^{18}F-FDG PET/CT has been reported to have a diagnostic value in early determination of metabolically active lymph nodes before they grow to pathological sizes [20]. In our series, there were two similar cases with increased metabolic activity in morphologically nonmalignant, small lymph nodes. In group 1, ceCT and ^{18}F-FDG PET/CT were highly concordant for lymph node evaluation, but it was not the same in group 2 since ^{18}F-FDG PET/CT failed to confirm metastasis in five patients. The reasons for false-negative results in these patients were; the small size of the lymph node or necrotic structure of the enlarged lymph node. Evaluation of the metabolic activity of small lesions is a diagnostic challenge in PET imaging due to the partial volume effect [21]. Necrosis is another possible reason to false-negative results by causing failure to transport of the radiopharmaceutical to the lymph nodes despite their enlarged dimensions. Increased uptake in physiological sites may cause misinterpretation, as brown fat uptake was the obstacle in our cases. Overall sensitivity and accuracy (76% and 81%) of this study were not found as high as the previously reported studies, because of these false-negative cases [20–22]. Another well-documented reason for false negativity is the relatively lower metabolic rate of non-seminomatous tumors with teratoma component [23–25]. The role of ^{18}F-FDG PET/CT in the decision of the need of lymph node dissection

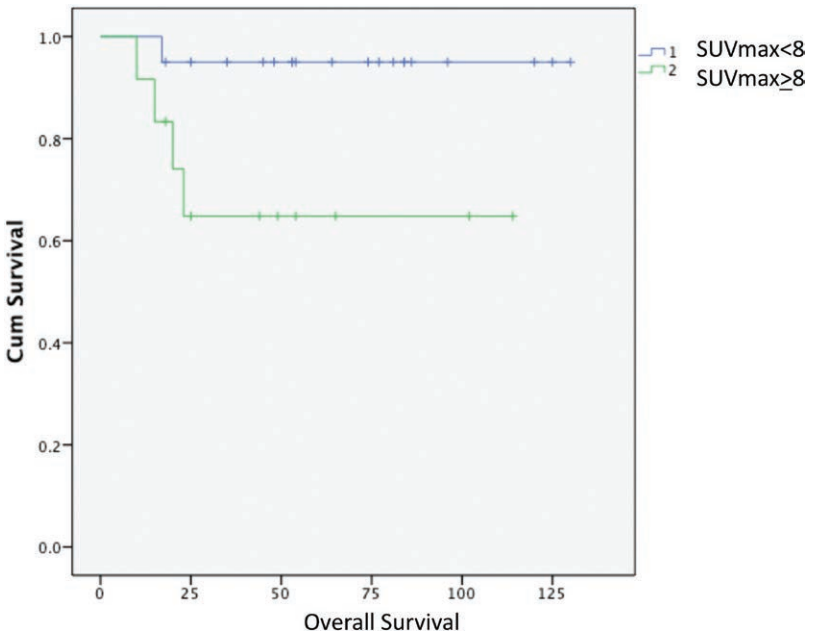
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Fig. 3



Kaplan–Meier curves for patients with and without distant organ metastases on PET/CT. CT, computed tomography.

Fig. 4



Kaplan–Meier curves for patients with SUVmax equal-higher and lower than eight on PET/CT. CT, computed tomography.

is not clear. In case of lymph node involvement, a chest CT is recommended to look for distant metastases [26]. Evaluation of distant metastasis was much more successfully done by ^{18}F-FDG PET/CT, compared to ceCT. Whole-body examination provides an advantage over ceCT, a well-known superiority of ^{18}F-FDG PET/CT over conventional imaging methods in many malignancies [23]. In our series, unexpected skeletal metastasis was detected by ^{18}F-FDG PET/CT in one and lung metastasis in one patient. ^{18}F-FDG PET/CT excluded lung metastasis in five patients. Only two patients with millimetric metastatic nodules were misdiagnosed by

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^{18}F-FDG PET/CT. For this reason, close follow-up with ceCT of the thorax can be recommended for patients with suspected lung nodules.

Although for seminomas, a good sensitivity and specificity have been demonstrated for ^{18}F-FDG PET/CT, for non-seminomas, lower sensitivity and specificity could be found [23,27]. Contrarily to these results, in subgroup analysis, we found that detection rates were lower in seminoma patients compared to the patients with pure non-seminomatous tumors. One reason for this result can be the limited number of patients in the seminoma group. The sensitivity of PET/CT might increase in the higher number of patients. Similar to our results, Sharma *et al*. [22] found higher sensitivity in the NSGCT group compared to seminomatous group (96.8% vs. 90%) in their large patient population. These results support the potential usage of ^{18}F-FDG PET/CT in NSGCT patients.

In our study, clinical management of 9 (28%) patients has been changed based on ^{18}F-FDG PET/CT. Similar to our data, Alongi *et al*. [21] demonstrated clinical management change in 23% of the patients who underwent ^{18}F-FDG PET/CT for recurrent testicular tumor. ^{18}F-FDG PET/CT might be a routine imaging tool for these patients if large prospective studies can support data of these studies. Alongi *et al*., additionally, for the first time in the literature, investigated the prognostic role of ^{18}F-FDG PET/CT in the recurrent testicular carcinoma patients. They found that ^{18}F-FDG positiveness and SUVmax value higher than eight were indicative of survival. In our group, PET positivity was not found a significant factor to predict PFS or OS. However, similar to previous study, eight as a cutoff value for SUVmax was a significant factor to predict OS. Discordant findings might be related to the limited number of patients and the heterogeneous population of our group. Since late recurrence can be observed in these patients and almost lifetime follow-up is needed, detection of new prognostic factors might be useful to select high-risk patients. Similar studies in this topic would make clear the prognostic role of ^{18}F-FDG PET/CT in testicular carcinoma patients.

Conclusion

In this single-center experience with a limited number of patients, ^{18}F-FDG PET/CT seems to have a value in staging and restaging for both seminomatous and non-seminomatous GTCs. Higher SUVmax values and presence of PET-positive distant organ metastases might have a prognostic role.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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