^{18}F-FDG PET/CT value in the detection of seminoma and correlation with CT and tumor marker levels – up to 8 years of follow-up

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Abstract

Objective: Positron emission tomography/computed tomography using fluorine-18 fluorodeoxyglucose (^{18}F-FDG PET/CT) is not routinely used for diagnosis of testicular carcinoma. Unlike CT which cannot confirm with certainty the nature of the lesions, especially in post-therapy setting, ^{18}F-FDG PET/CT detects active disease by showing increased glucose metabolism within the lesions. **Aim:** Determination of ^{18}F-FDG PET/CT usefulness in detection of seminoma, therapy response evaluation and comparison to CT findings and tumor marker levels. **Materials and Methods:** Eighty-two men (age 39.8±10.1) after orchiectomy and histopathological confirmation of seminoma were included in this study. Indications for ^{18}F-FDG PET/CT were initial staging, restaging after chemo/radiotherapy with positive/uncertain CT, suspected recurrence on CT, elevated tumor markers. All patients had clinical follow-up of up to 8 years (median 33.5) after the first ^{18}F-FDG PET/CT examination. Degree of metabolic activity was analyzed visually and semi-quantitatively using maximum standardized uptake value (SUVmax). **Results:** Fluorine-18-FDG PET/CT was true positive in 36 patients (43.9%) with average SUVmax of 7.9±4.8. Recurrence was mostly found in retroperitoneal lymph nodes and distant metastases in lungs, bones, liver. Six findings were false positive and 3 false negative. Sensitivity, specificity, accuracy of ^{18}F-FDG PET/CT were 92.3%, 86.0%, 89.0% and of CT 60.8%, 66.6%, 63.4%. Pearson Chi-square test showed statistically significant difference between the results of ^{18}F-FDG PET/CT and CT (P=0.016). Significant correlation was found between positive ^{18}F-FDG PET/CT findings and levels of LDH (P=0.043), while non-significant between AFP, β-hCG (P>0.05). **Conclusion:** Fluorine-18-FDG PET/CT was superior to CT in evaluation of therapy response, active disease in residual tissue and normal size lymph nodes, as well as when CT was negative and tumor markers were elevated. Elevated lactate dehydrogenase (LDH) contributes to positive ^{18}F-FDG PET/CT findings.

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Introduction

Although rare in comparison to other neoplasias, testicular cancer has become one of the most common malignant tumor in young men of age 15 to 40. Around 95% are germ cell tumors which are classified into three main groups: pure seminoma (approximately 55% of all germ cell tumors), nonseminoma and spermatocytic seminoma [7, 18].

Seminoma is diagnosed based on patients' symptoms, tumor markers and radiological findings-mainly transscrotal ultrasonography. Initial manifestation is unilateral (bilateral in 3% of the patients) enlargement of the scrotum, usually discovered accidentally during self-examination, and it is painless in most cases. Also, disease can be presented with signs of metastatic spread: lower back pain in case of retroperitoneal spread, lower extremity swelling, cervical masses, bone pain and other [21, 27]. Furthermore, cases of primary extragonadal germ cell tumors, such as primary mediastinal seminoma, were also reported in the literature [15]. Tumor markers should always be measured before surgery (orchiectomy) and followed until their normalization. In pure seminoma α-fetoprotein (AFP) may be within normal limits and less than 20% of the patients have elevated human chorionic gonadotrophin (β-hCG). Although lactate dehydrogenase (LDH) is a less specific marker, it is increased in 80% of seminomas [2, 14, 21]. Radiological methods used in diagnosing primary testicular seminoma and metastases are ultrasonography, that reveals size and structural changes in the contralateral testis and computed tomography (CT) in initial estimation of the disease spread to regional and distant lymph nodes and other organs, as well as in restaging after radiation and chemotherapy [1, 2, 6, 14]. Radical inguinal orchiectomy is a treatment of choice for testicular cancer in order to achieve local control. Overall, prognosis for the patients with testicular seminoma is very good while these tumors are radio-and chemotherapy sensitive [16]. A survival rate of seminoma in early stage is 99%, in stage II around 94%-96% and stage III around 72%-

86% [13]. The risk of relapse is higher in patients with invasion of rete testis, primary tumor larger than 4cm, distant metastases, elevated serum β-hCG and LDH [6, 26, 32]. Rarely, late relapses may contain non-seminoma elements [23].

Positron emission tomography with computed tomography using fluorine-18 fluorodeoxyglucose (^{18}F-FDG PET/CT) is not routinely used for the detection of testicular tumor lesions. Unlike CT which cannot confirm with certainty the nature of the lesions, especially in post-therapy setting, ^{18}F-FDG PET/CT detects active disease by showing increased glucose metabolism within the lesions. Therefore, the aim of this study was to determine the role of ^{18}F-FDG PET/CT in: detection of seminoma rest/recurrence in 82 patients after orchiectomy, in evaluation of chemo/radiotherapy response and restaging. Also, the goal was to determine diagnostic accuracy of this method in comparison to CT and tumor marker levels.

Materials and Methods

Study population

In a period from March 2010 to June 2018, all patients with diagnosis of seminoma, referred for ^{18}F-FDG PET/CT, in the National PET Center of University Clinical Center of Serbia, were enrolled in this retrospective study. Indications for ^{18}F-FDG PET/CT scan were: staging after orchiectomy, restaging after therapy with positive or uncertain CT results, follow-up, suspected recurrence based on CT or serum tumor marker levels. Criteria for inclusion were histopathological confirmation of seminoma during surgical intervention-orchiectomy, CT scans available prior to ^{18}F-FDG PET/CT, as well as measured tumor marker levels. Exclusion criteria were patients with mixed type of seminoma and other types of testicular cancer, presence of other neoplasias, glycaemia over 11mmol/L. Finally, eighty-two men (mean age 39.8±10.1, median 38) met the inclusion criteria for entering this study. Reference standards were clinical follow up, biopsy and surgery with histopathology. The results of ^{18}F-FDG PET/CT were compared to results of clinical follow-up (median 33.5 months). All the patients gave the informed consent for the investigation and the study was approved by Ethical Committee of Clinical Center of Serbia (668/6/2018).

Acquisition and interpretation of ^{18}F-FDG PET/CT findings

Fluorine-18-FDG PET/CT examination was performed in all patients on a 64-slice hybrid PET/CT scanner (Biograph, TruePoint 64, Siemens Medical Solutions, Inc. USA) at National PET Center, University Clinical Center of Serbia. 5.5MBq/kg of ^{18}F-FDG was administrated intravenously followed by an hour of resting. Whole body low-dose non-enhanced CT (120kV, 5mm slice thickness, pitch 1,5, rotation time 0.5s) and PET scans (3min per field, 6 fields of view) were then obtained. Corrected and uncorrected to attenuation low dose CT, PET and fused PET/CT scans were presented on a Syngo Multimodality workstation for interpretation. After excluding benign and regions of a physiological uptake, ^{18}F-FDG PET/CT findings were considered positive for seminoma in cases of greater accumulation of the tracer within an observed lesion than the accumulation in the great mediastinal blood vessels, surrounding tissue and liver, which were further analyzed visually and semi-quantitatively. Level of glucose metabolism within the lesion was assessed on reconstructed images using maximum standardized uptake value (SUVmax), which was calculated by tracer's uptake in the region of interest divided by an administrated radioactivity and patient's weight.

Statistical analyses

The results were showed as mean±standard deviation (SD) and percentage (%). The ^{18}F-FDG PET/CT and CT diagnostic output was evaluated by calculating specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy. Chi-square test was used for testing statistical difference of ^{18}F-FDG PET/CT and CT diagnostic value, as well as t- test for correlation of tumor marker levels and positive ^{18}F-FDG PET/CT findings.

Results

Characteristics of the patients

In this study 82 male patients were enrolled, mean age 39.8± 10.1, median 38. Radical inguinal orchiectomy with histopathological confirmation of seminoma was performed in all patients (41 had left side, 36 right side and 5 patients bilateral orchiectomy), followed by chemotherapy (69 patients) and/or radiation (9 patients). Restaging after therapy was mostly the indication for ^{18}F-FDG PET/CT (Table 1), in which cases imaging was scheduled at least a month after the last cycle of chemotherapy and at least 3 months after radiation treatment or surgical intervention.

^{18}F-FDG PET/CT results

Foci of an increased accumulation of radiopharmaceutical (SUVmax 7.9±4.8) were found in 36 (43.9%) patients and they were considered true positive (TP). Seminoma of the left testicle most frequently metastasized to the retroperitoneal left paraaortal, retrocaval and parailiac lymph nodes, while seminomas of the right testicle spread to the lungs, retroperitoneal aortocaval and paraaortal lymph nodes. Bilateral seminomas spread to retroperitoneal lymph nodes (Figure 1).

Two patients had recurrence of seminoma in a projection of surgically removed testicle and one patient in contralateral testicle (Figure 3). Metastases were shown in one localization in 23 patients (lymph nodes 15, lungs 5, bones 2 and liver 1), in two localizations in 6 patients (lymph nodes and lungs 2, lymph nodes and bones 4), in three localizations in 3 patients (lymph nodes, lungs and bones, lymph nodes. lungs and liver) and in one patient in lymph nodes, lungs, bones, liver and spleen (Figure 2 and 3).

False positive (FP) findings were observed in 6 patients. Osteolytic lesion of sternum in 1 patient, with an increased LDH, was histopathological negative for seminoma but positive for sarcoma. In other 5 patients, moderate accumulation of ^{18}F-FDG was found in retroperitoneal lymph nodes after chemoradiotherapy (SUVmax up to 4.5) which were confirmed to be negative for seminoma on biopsy. False negative (FN) were 3 patients with nodular lung lesions and no uptake of radiophar-

Table 1. *Patients' characteristics.*

Characteristics	Value
Total number of patients (n)	82
Age (years)	
Mean age±SD	39.8±10.1
Median	38
Treatment, n (%)	
Surgery	82 (100%)
Chemotherapy	69 (84.1%)
Radiotherapy	9 (10.9%)
Surgery, n (%)	
Left side orchiectomy	41 (50%)
Right side orchiectomy	36 (43.9%)
Bilateral orchiectomy	5 (2.4%)
^{18}F-FDG PET/CT indication, n (%)	
Staging after orchiectomy	11 (13.4%)
Restaging after therapy with positive CT	40 (48.7%)
Restaging after therapy with uncertain CT	7 (8.5%)
Follow-up	8 (9.7%)
Suspected recurrence based on CT	10 (12.1%)
Suspected recurrence based on tumor markers	6 (7.3%)

^{18}F-FDG-fluorine-18 fluorodeoxyglucose; PET/CT-positron emission tomography/computed tomography

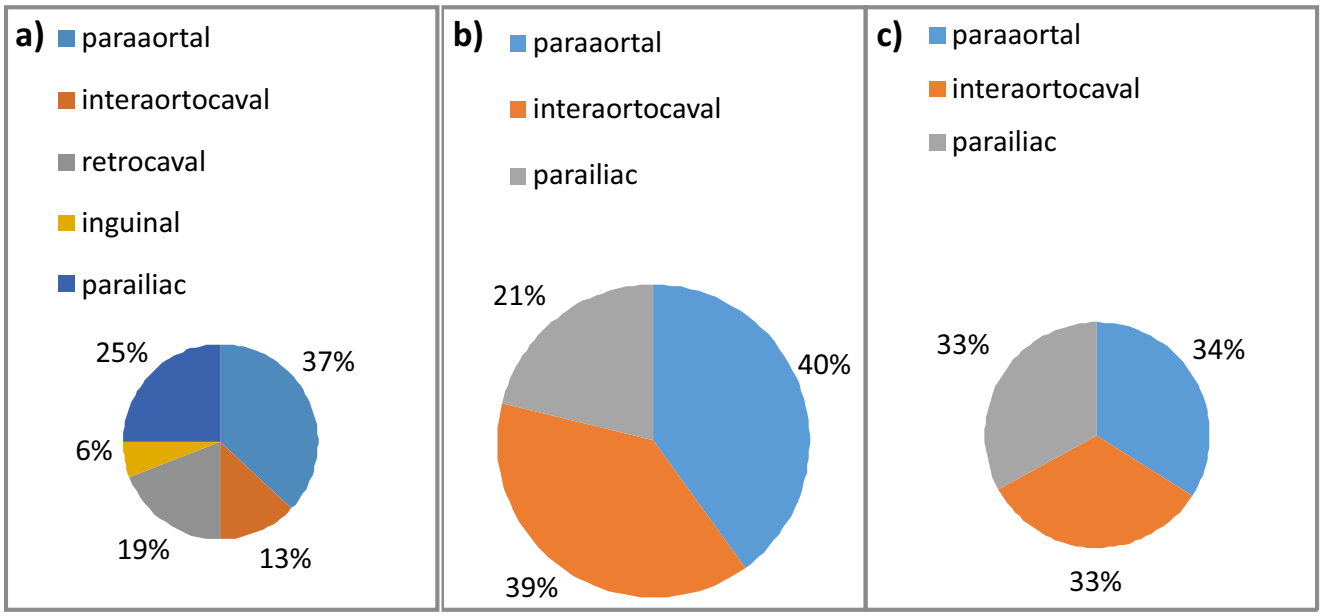

Figure 1. Lymph node metastases of: a) left testicle seminoma; b) right testicle seminoma; c) bilateral testicular seminoma.

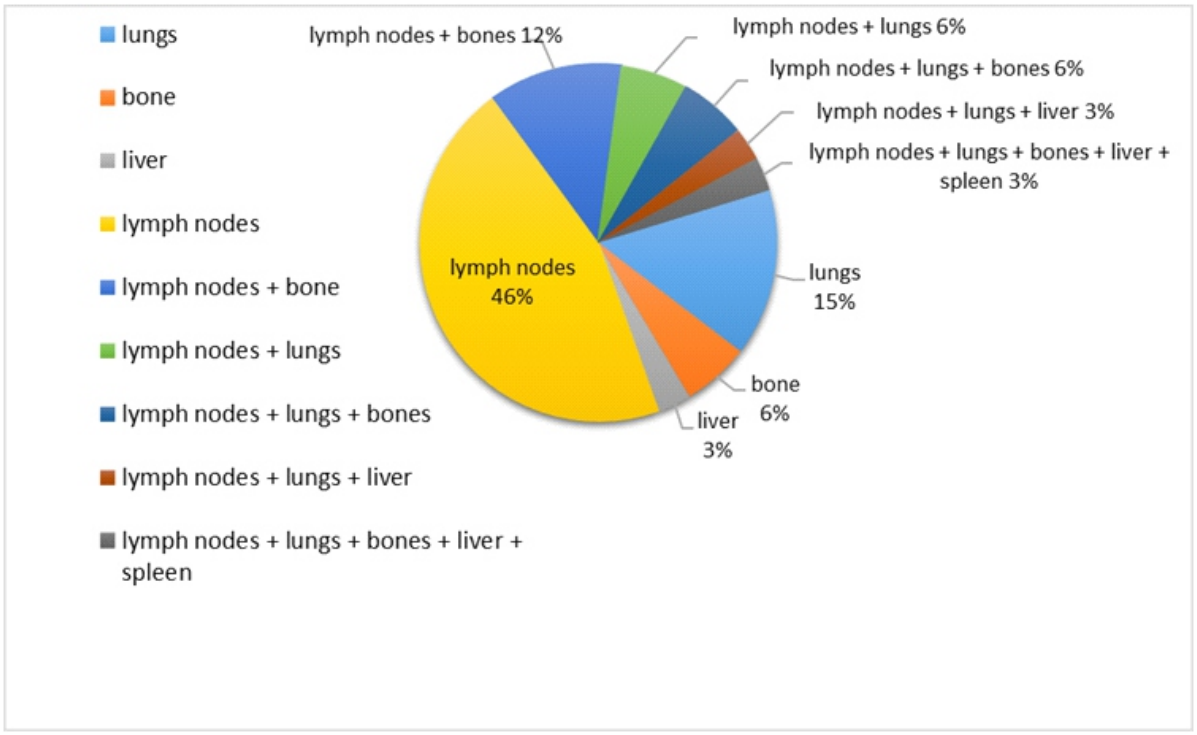

Figure 2. Overall localizations of metastases

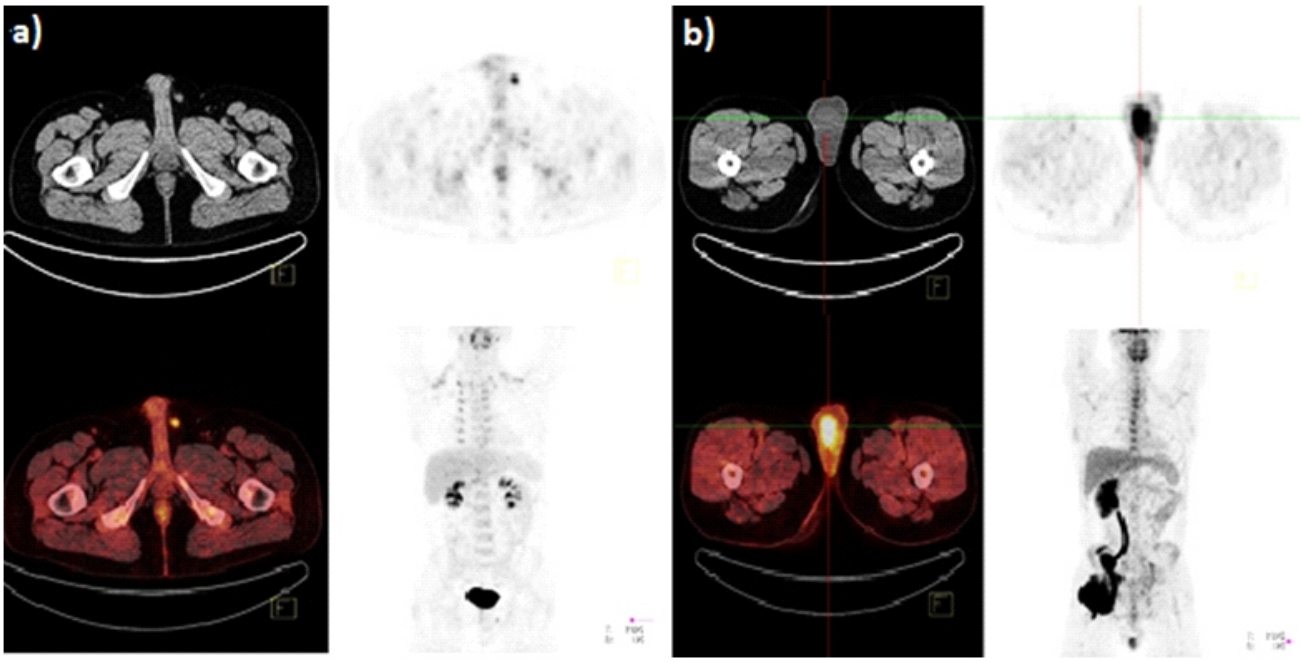

Figure 3. Axial CT, PET and PET/CT images and MIP (maximal intensity projection): Local recurrence of seminoma in: a) surgically removed left testicle (SUVmax 4.6); b) contralateral testicle (SUVmax 5.1).

maceutical, that showed growth in size and glucose metabolism on follow-up scan.

Patients with positive ^{18}F-FDG PET/CT had higher levels of serum tumor markers than the ones with negative ^{18}F-FDG PET/CT. Student t-test showed statistically significant correlation between the levels of LDH and positive ^{18}F-FDG PET/CT findings (P=0.043) (Table 2), while significant correlation between positive ^{18}F-FDG PET/CT findings and AFP and B-hCG was not found (P>0.05).

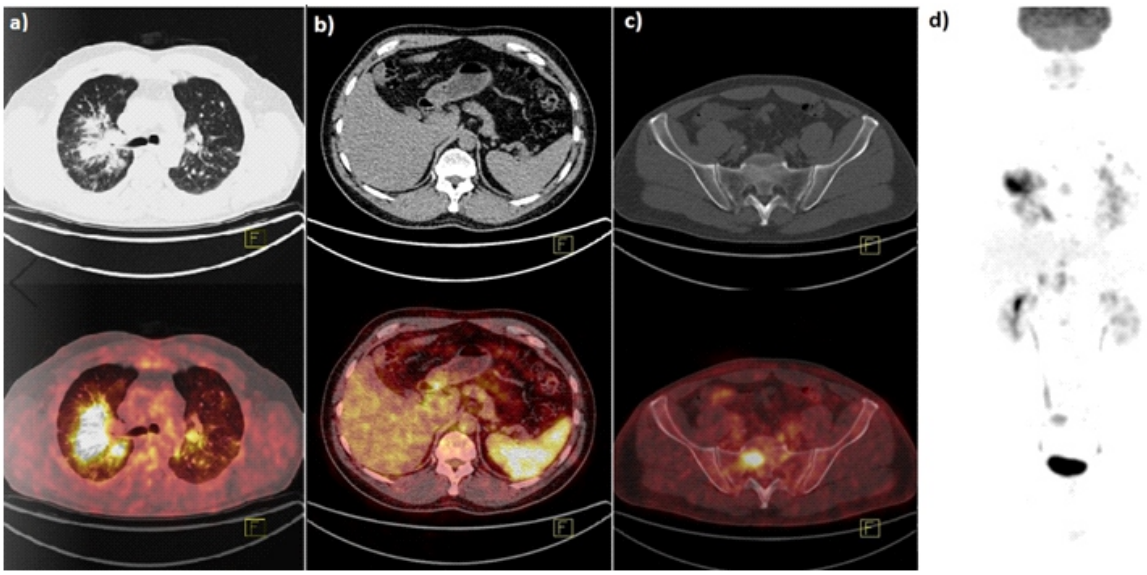

Figure 4. Hematogenic spread of seminoma in a 36 year-old after right side orchiectomy. Axial CT and PET/CT images: a) massive lung metastases b) spleen metastases; c) sacral bone metastasis; d) MIP (maximal intensity projection) (SUVmax=20.4) of the same patient.

Table 2. *Mean levels of tumor markers and respective p-values in positive ^{18}F-FDG PET/CT findings.*

Tumor marker	Mean	SD	^{18}F-FDG PET/CT positive findings
LDH	658.8	489.6	P= 0.043
AFP	5.7	13.2	P> 0.05
B-hCG	93.2	285.5	P> 0.05

LDH- Lactate dehydrogenase, AFP- α-fetoprotein, B- hCG- human chorionic gonadotrophin, SD- standard deviation, ^{18}F-FDG-fluorine-18 fluorodeoxyglucose, PET/CT-positron emission tomography/computed tomography

Table 3. *Diagnostic performance of ^{18}F-FDG PET/CT and CT.*

	TP (n)	TN (n)	FP (n)	FN (n)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
^{18}F-FDG PET/CT	36	37	6	3	92.3	86.0	85.7	92.5	89.0
CT	28	24	12	18	60.8	66.6	70.0	57.1	63.4

^{18}F-FDG-fluorine-18 fluorodeoxyglucose;, PET/CT-positron emission tomography/computed tomography; TP-true positive; TN-true negative; FP-false positive; FN-false negative, Sens- sensitivity, Spec- specificity, PPV- positive predictive value, NPV- negative predictive value, Acc- accuracy

All patients had clinical follow-up of up to 8 years (median 33.5 months) after the first ^{18}F-FDG PET/CT examination. Seventeen (20.7%) patients had a second ^{18}F-FDG PET/CT done 9.9±6.6 months after the first examination in order to evaluate therapy response or suspected lesions seen on CT with/out elevated tumor markers. Out of 17, 5 patients had progression, 4 partial metabolic regressions, and 8 had negative ^{18}F-FDG PET/CT finding (Figure 5). Altogether, PET/CT led to a change in management of 22/82 patients.

Overall sensitivity of ^{18}F-FDG PET/CT is 92.3%, specificity 86.0%, PPV 85.7%, NPV 92.5% and accuracy 89.0%. Calculated sensitivity and specificity of CT were much lower, 60.8% and 66.6%, as well as accuracy 63.4% (Table 3). Pearson Chi-square test showed statistically significant difference between the results of ^{18}F-FDG PET/CT and CT (P=0.016).

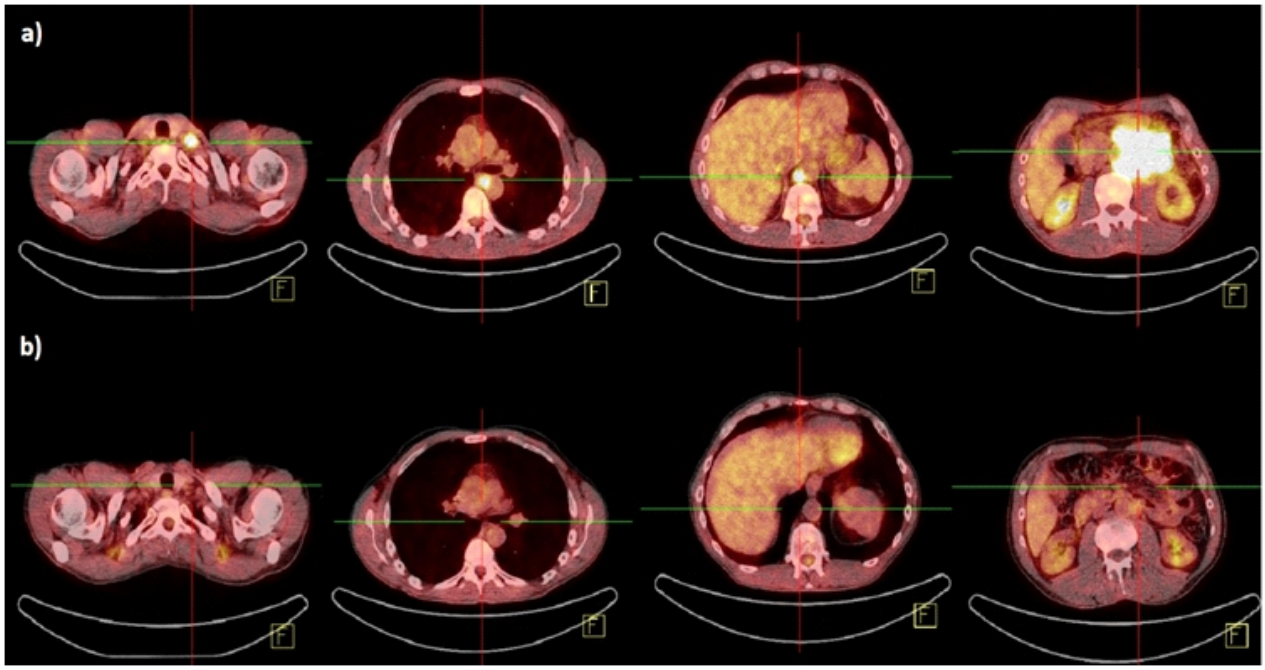

Figure 5. Transversal plane of ^{18}F-FDG PET/CT: a) Initial ^{18}F-FDG PET/CT shows disseminated disease in supraclavicular, mediastinal, retrocrural lymph nodes and left hemiabdomen (SUVmax up to 13.4); b) Evaluation of therapy response on a control ^{18}F-FDG PET/CT showing regression.

Discussion

Detection of disease recurrence and metastases in early stage is crucial in planning the optimal treatment. Computed tomography is a routinely used diagnostic method in staging, early detection of recurrence and therapy response evaluation, however, it relies only on morphological criteria. The probability of false negative and false positive findings is higher due to its inability to distinguish still active disease to normal size lymph nodes or viable tumor cells in residual tissue after therapy [29, 37]. Advantage of ^{18}F-FDG PET/CT is a whole-body imaging that allows evaluation of all tissues and organs, as well as detection of metabolically active lesions and the presence of viable tumor cells [11].

Most relapses occur within 2 years after orchiectomy. Based on EAU guidelines, ^{18}F-FDG PET/CT is currently recommended for detection of residual seminomatous masses after surgery, especially for masses over 3cm in size [30]. Our results showed two local recurrences of seminoma in a projection of surgically removed testicle and one in contralateral testicle. Also, retroperitoneal lymph nodes were the most common metastatic sites. Seminoma of the left testicle most frequently metastasized to the left paraaortic, while seminomas of the right testicle spread to the interaortocaval lymph nodes [19]. Three patients with the right testicular seminoma had cross-drainage to the left side lymph nodes, while drainage from left to right side was not reported [31]. Inguinal and parailiac lymph node metastases were showed in 14 patients, usually when the disease has already spread to the retroperitoneal and other distant lymph nodes, while 2 patients had inguinal lymph node metastases only, which happens in up to 10% of the patients with testicular tumors [32]. Hematogenous spread in testicular cancer is predominantly to the lungs as in our study, while bone metastases are reported less frequently. A study of 2550 patients with testicular tumor detected bone metastases only in 3 patients with seminoma (0.12%) [12], whereas we had 7 out of 82 (8.53%) patients with the bone involvement, which is probably a result of a larger number of patients in stage IV.

Serum tumor markers are used routinely in preoperative diagnostics, staging and monitoring relapse in patients with advanced seminoma [17]. In pure seminoma AFP may remain within physiological range values and less than 20% of the patients have elevated β-HCG, while less specific LDH can be the only tumor marker positive but with limited positive predictive value in follow-up, as it was the case in our study. Lactate dehydrogenase is a useful indicator of relapse, but needs to be interpreted with caution [20, 21, 28, 33]. In our study correlation between levels of LDH and positive PET/CT findings was proved statistically significant, while this was not the case with AFP and B-hCG [25, 10].

Our study showed that ^{18}F-FDG PET/CT has higher sensitivity and specificity than CT (92.3% and 86.0% vs 60.8% and 66.6%) in the detection of active disease in patients with seminoma. Results acquired in the study of Bechere et al. (2005), also show that PET is superior to CT, with sensitivity and specificity for CT of 73%, as well as 80% and 100% for PET [24]. Sharma et al. (2014) report in their study a sensitivity of 94.2% and a specificity of 75% of ^{18}F-FDG PET/CT in the assessment of disease recurrence and therapy response evaluation of 92 patients with seminoma [9]. In the study of Cremerius et al. (1998),^{18}F-FDG PET/CT was useful in the evaluation of postchemotherapy seminoma relapses, with higher uptake in seminoma versus non seminomatous testicular cancer [34].

In this study false positive findings were mostly a result of a recent chemoradiotherapy, as reported in a study of Bilen et al. (2014) who raise awareness to unnecessary post surgical complications in a patient with resected viable mass, that was false positive on ^{18}F-FDG PET/CT, proved to be persistent inflammation even 9 months after radiotherapy and 11 months after chemotherapy [8]. Inflammation after radiotherapy could sometimes be impossible to distinguish from still active disease, so it is recommended to schedule ^{18}F-FDG PET/CT at least 3 months after the end of radiation, and in case of a positive finding to obtain biopsy [35]. Eventhough suggested by Decoene et al. (2015), there is not sufficient evidence to support the hypothesis of chemotherapy induced inflammation potentially interfering with ^{18}F-FDG uptake [5].

Three false negative findings were related to nodular lesions in lungs, size up to 6mm, that could not be evaluated with certainty. Lesions smaller than 1cm might not show high ^{18}F-FDG uptake in the lungs or mediastinum and may add to false negativity due to partial volume effect [22].

Fluorine-18-FDG PET/CT is useful when initial staging findings of CT are equivocal and not enough sensitive to foresee a relapse in high-risk patients with negative CT [36]. Also, ^{18}F-FDG PET/CT was helpful in our study in determination of recurrence in the majority of patients with negative CT and elevated serum tumor markers [4].

In conclusion, although ^{18}F-FDG PET/CT is not routinely performed in patients with seminoma, it has high diagnostic value and it is superior to CT in therapy response evaluation and detection of still active disease after chemotherapy in normal size lymph nodes and viable tumor cells of the residual tissue, due to its anatomical and functional assessment. Also, ^{18}F-FDG PET/CT can lead to a change of clinical management of the patients, in particular when serum tumor markers are positive and results of other imaging methods are uncertain. The possibility of false positive findings exists especially in cases of post-therapy inflammation, when histological verification is advised and a follow-up ^{18}F-FDG PET/CT. Elevated LDH is a useful indicator of relapse and it contributes to positive ^{18}F-FDG PET/CT findings.

The authors declare that they have no conflicts of interest.

Bibliography

1. Marko J, Wolfman D, Aubin A, Sesterhenn I. Testicular Seminoma and Its Mimics: From the Radiologic Pathology Archives. *Radiographics* 2017; 37: 1085-98.
2. Saba L. The primitive extratesticular seminoma: diagnosis of a rare pathology. *Acta Biomed* 2017; 88: 82-5.
3. Norton BC, Robertson I, Fan H et al. Massive seminoma presenting with inguinal lymph node metastases only. *J Surg Case Rep 20*16; 2016: rjw177.
4. Cook G, Sohaib A, Huddart R et al. The role of ^{18}F-FDG PET/CT in the management of testicular cancers. *Nucl Med Commun* 2015; 36: 702-8.
5. Decoene J, Winter C, Albers P. False-positive fluorodeoxyglucose positron emission tomography results after chemotherapy in patients with metastatic seminoma. *Urol Oncol* 2015; 33: 23.e15-23.e21.
6. Moreno CC, Small WC, Camacho JC et al. Testicular Tumors: What Radiologists Need to Know-Differential Diagnosis, Staging, and Management. *Radio Graphics* 2015; 35: 400-15.
7. Moch H, Cubilla AL, Humphrey PA et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol* 2016; 70(1): 93-105.
8. Bilen MA, Hariri H, Leon C et al. Positive ^{18}F-FDG PET/CT Scans of a Residual Seminoma after Chemotherapy and Radiotherapy: Case Report and Review of the Literature. *Clin Genitour Cancer* 2014; 12(4): e147-e150.
9. Sharma P, Jain TK, Parida GK et al. Diagnostic accuracy of integrated ^{18}F-FDG PET/CT for restaging patients with malignant germ cell tumours. *Br J Radiol* 2014; 87: 20140263.
10. Bilen MA, Hariri H, Leon C et al. Positive ^{18}F-FDG PET/CT Scans of a Residual Seminoma after Chemotherapy and Radiotherapy: Case Report and Review of the Literature. *Clin Genitour Cancer* 2014; 12: e147-e50.
11. Ambrosini V, Zucchini G, Nicolini S et al. ^{18}F-FDG PET/CT impact on testicular tumours clinical management. *Eur J Nucl Med Mol Imaging* 2014; 41: 668-73.
12. Jamal Hanjani M, Karpathakis A, Kwan A et al. Bone metastases in germ cell tumours. *BJU Int* 2013; 112: 176-81.
13. Rodriguez Vida A, Chowdhury S. Diagnosis and management of testicular cancers. *Trends Urology Men's Health* 2013; 4: 25-30.
14. Oldenburg J, Fossa SD, Nuver J. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; 6: vi125-32.
15. Nachankar A, Krishnatry R, Joshi A et al. Primary mediastinal seminoma; resistance and relapse: An aggressive entity. *Indian J Med Paediatr Oncol* 2013; 34: 309-12.
16. Boujelbene N, Cosinschi A, Boujelbene N et al. Pure seminoma: A review and update. *Radiat Oncol* 2011; 6: 90.
17. Gilligan D, Seidenfeld J, Basch E et al. American Society of Clinical Oncology Clinical Practice Guideline on Uses of Serum Tumor Markers in Adult Males With Germ Cell Tumors. *J Clin Oncol* 2010; 28: 388-404.
18. Chia V, Quraishi S, Devesa S. International trends in the incidence of testicular cancer, 1973-2002. *Cancer Epidemiol Biomarkers Prev* 2010; 19(5): 1151-9.
19. Krohmer SJ, Mcnulty NJ, Schned AR. Testicular Seminoma with Lymph Node Metastases. *Radio Graphics* 2009; 29: 2177-83.
20. Venkitaraman R, Johnson B, Huddart A et al. The utility of lactate dehydrogenase in the follow-up of testicular germ cell tumours. *BJU Int* 2007; 100: 30-2.
21. Khan O, Protheroe A. Testis cancer. *Postgrad Med J* 2007; 83(984): 624-32.
22. Chang JM, Lee HJ, Goo JM et al. False Positive and False Negative ^{18}F-FDG PET Scans in Various Thoracic Diseases. *Korean J Radiol* 2006; 7: 57-69.
23. Oldenburg J, Alfsen GC, Waehre H, Fossa SD. Late recurrences of germ cell malignancies: a population-based experience over three decades. *Br J Cancer* 2006; 94: 820-7.
24. Becherer A, De Santis M, Karanikas G et al. ^{18}F-FDG PET is superior to CT in the prediction of viable tumour in post-chemotherapy seminoma residuals. *Eur J Radiol* 2005; 54: 284-8.
25. Bruns F, Raub M, Schaefer U, Micke O. No predictive value of beta-hCG in patients with stage I seminoma-results of a long-term follow-up study after adjuvant radiotherapy. *Anticancer Res* 2005; 25: 1543-6.
26. Warde P, Specht L, HorwichA et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *J Clin Oncol* 2002; 20: 4448-52.
27. Heidenreich A, Weissbach L, Höltl W et al. German Testicular Cancer Study Group. Organ sparing surgery for malignant germ cell tumor of the testis. *J Urol* 2001; 166: 2161-5.
28. Fujikawa K, Matsui Y, Oka H et al. Prognosis of Primary Testicular Seminoma: A Report on 57 New Cases. *Cancer Res* 2000; 60: 2152-4.
29. Sanchez-martin FM. Surgery of retroperitoneal residual mass. *Arch Esp Urol* 2000; 53: 535-46.
30. Albers P, Albrecht W, Algaba F et al. EAU Guidelines on Testicular Cancer: 2015 Update. *Eur Urol* 2015; 68: 1054-68.
31. Sheinfeld J. Nonseminomatous germ cell tumors of the testis: current concepts and controversies. *Urology* 1994; 44: 2-14.
32. Mencel PJ, Motzer RJ, Mazumdar M et al. Advanced seminoma: treatment results, survival, and prognostic factors in 142 patients. *J Clin Oncol* 1994; 12: 120-6.
33. Fossa A, Fossa SD.Serum lactate dehydrogenase and human choriogonadotrophin in seminoma. *Br J Urol* 1989; 63: 408-15.
34. Cremerius U, Effert PJ, Adam G et al. ^{18}F-FDG PET for detection and therapy control of metastatic germ cell tumor. *J Nucl Med* 1998; 39: 815-22.
35. Safaie E, Matthews R, Bergamaschi R. PET scan findings can be false positive. *Tech Coloproctol* 2015; 19: 329-30.
36. Dotzauer R, Thomas C, Jäger W. The use of ^{18}F-FDG PET/CT in testicular cancer. *Transl Androl Urol* 2018; 7: 875-8.
37. Calabrò D, Telo S, Ambrosini V. PET imaging in testicular tumours. *Curr Opin Urol* 2020; 30: 665-71.