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ORIGINAL ARTICLE

# Diagnostic and prognostic value of 18F-FDG PET/CT in recurrent germinal tumor carcinoma

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**Abstract**

*Aim* The aim of this bicentric retrospective study was to assess the diagnostic performance, the prognostic value, the incremental prognostic value and the impact on therapeutic management of $^{18}$F-FDG PET/CT in patients with suspected recurrent germinal cell testicular carcinoma (GCT).

*Materials and methods* From the databases of two centers including 31,500 $^{18}$F-FDG PET/CT oncological studies, 114 patients affected by GCT were evaluated in a retrospective study. All 114 patients underwent $^{18}$F-FDG PET/CT for suspected recurrent disease. Diagnostic performance of visually interpreted $^{18}$F-FDG PET/CT and potential impact on the treatment decision were assessed using histology (17 patients), other diagnostic imaging modalities (i.e., contrast enhanced CT in 89 patients and MRI in 15) and clinical follow-up (114 patients) as reference. Progression-free survival (PFS) and overall survival (OS) rates were computed by means of Kaplan-Meier survival analysis. The progression rate (Hazard Ratio-HR) was determined using univariate Cox regression analysis by considering various clinical variables.

*Results* Recurrent GCT was confirmed in 47 of 52 patients with pathological $^{18}$F-FDG PET/CT findings, by means of histology in 18 patients and by other diagnostic imaging modalities/follow-up in 29. Sensitivity, specificity, accuracy, positive and negative likelihood ratio (LR+ and LR-, respectively), pre-test Odds-ratio and post-test Odds-ratio of $^{18}$FDG PET/CT were 86.8%, 90.2%, 88.4%, 8.85, 0.14, 0.85, 8.85, respectively.$^{18}$F-FDG PET/CT impacted significantly on therapeutic management in 26/114 (23%) cases (from palliative to curative in 12 patients, from "wait and watch" to new chemotherapy in six patients and the "wait-and-watch" approach in eight patients with unremarkable findings). At 2 and 5-year follow-up, PFS was significantly longer in patients with a negative than a pathological $^{18}$F-FDG PET/CT scan (98% and 95% vs 48% and 38%, respectively; $p$ = 0.02). An unremarkable scan was associated also with a longer OS (98% after 2 years and 95% after 5 years, $p$ = 0.02). At univariate Cox regression analysis, a pathological $^{18}$F-FDG PET/CT scan was associated with an increased risk of disease progression (HR = 24.3, CI 95% 14.1-40.6; $p$ = 0.03) and lower OS (HR = 17.3 CI 95% 4,9-77; $p$ < 0.001). Its prognostic value was confirmed also if tested against advanced disease at diagnosis and rising Human Chorionic Gonadotropin Beta (HCGB) or Alpha-Fetoprotein (AFP) (HR = 7.3 for STAGE III-PET+, $p$ = 0.03; HR = 14.3 elevated HCGB-PET+, $p$ = 0.02; HR 10.7 elevated AFP-PET+, $p$ = 0.01) At multivariate analysis, only a pathological $^{18}$F-FDG PET/CT scan and advanced disease in terms of TNM staging were predictors of disease progression and OS. $^{18}$F-FDG PET/CT showed incremental value over other variables both in predicting PFS (chi-square from 24 to 40, $p$ < 0.001) and OS (chi-square from 32 to 38, $p$ = 0.003).

*Conclusion* $^{18}$F-FDG PET/CT has a very good diagnostic performance in patients with suspected recurrent GCT and has an

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important prognostic value in assessing the rate of PFS and OS. Furthermore, $^{18}$F-FDG PET/CT impacted the therapeutic regimen in 23% of patients, thus providing a significant impact in the restaging process.

**Keywords** Germinal cell testicular carcinoma · 18F-FDG-PET/CT · Restaging · Prognostic role · Therapeutic management

## Introduction

Testicular cancer is a relatively rare disease (1-5%), but it is the most common malignancy in men aged 20-35 years, with an incidence of 1/10,000 [1]. Three main pathological forms have been described: germinal cell tumors (GCT), accounting for 90 – 95% of all tumors, cord stromal tumors, and mixed germinal cell/sex cord stromal tumors [2]. At initial diagnosis, approximately 20% of patients may have metastatic disease. Lymphatic spread is common to all forms of GCT, although in the case of choriocarcinoma, vascular dissemination is a common clinical feature. GTC usually is represented as a limited disease in the testis, although retroperitoneal lymph node metastasis (20%) and extranodal metastasis (lung, liver, brain, bone; 5%) can be observed at the time of diagnosis [3].

Testicular tumors are usually diagnosed by means of ultrasonography (US) and commonly staged using computed tomography (CT) or magnetic resonance (MR) imaging [4].

Seminoma is the most common testicular tumor and has a more favorable outcome compared to non-seminomatous carcinomas. In fact, while the curative rate of seminoma approaches is 95% even in the presence of metastatic involvement at diagnosis, the outcome in patients with non-seminomatous cancer strongly depends on the initial staging. Early stages are generally associated with a cure rate approaching of 100%, while in advanced stages the rates vary from 90% to 50% depending on histological type and early diagnosis [5].

Conventional radiologic imaging is commonly used for initial tumor assessment and plays an important role in the evaluation of the response to treatment and during follow-up. To date, computed tomography (CT) is the most widely used imaging technique. In this regard, the application of $^{18}$F-fluorodeoxyglucose positron emission tomography/CT ($^{18}$F-FDG PET/CT) has been emerging in recent years. Although $^{18}$F-FDG PET/CT is not routinely performed in patients with testicular cancer, its incremental diagnostic and prognostic value in the assessment of the primary tumor site, nodal and/or metastatic spread and early occult disease is well documented in many forms of malignant tumors [6–8] .

It may be hypothesized that a similar diagnostic performance also pertains to the detection of local and distant recurrences. In this regard, the incorporation of $^{18}$F-FDG- PET/CT into the management algorithm of patients with seminoma may allow better delineation of the presence of viable residual tumor and, thus, allow for a better risks stratification [9].

The aims of the present study were: 1) to assess the diagnostic performance of $^{18}$F-FDG PET/CT in patients with suspected recurrent GCT; 2) to evaluate the prognostic value of $^{18}$F-FDG- PET/CT in this clinical setting; 3) to evaluate the added prognostic value of $^{18}$F-FDG PET/CT findings associated with other clinical-laboratory parameters and 4) to assess the impact of $^{18}$F-FDG PET/CT on the therapeutic approach.

## Materials and methods

Patients were retrospectively evaluated from the $^{18}$FDG PET/CT databases of San Raffaele Hospital in Milan, Italy and Veneto Institute of Oncology in Padua, Italy. All subjects underwent $^{18}$F-FDG PET/CT for suspected recurrent GCT.

Inclusion criteria were as follows: (1) histologically proven GCT, (2) $^{18}$F-FDG PET/CT performed as a second-stage examination to detect recurrent lesions at the site of disease at staging treated with surgery or chemotherapy and/or new nodal or visceral metastatic involvement, suspected based on conventional imaging (residual tissue or nodes after surgery or chemotherapy, new undefined lymph nodes or lung nodules) and/or clinical data (rising serum tumor biomarkers, inguinal or abdominal swelling, acute pain in the lower abdomen or groin, breast tenderness or growth, lower back pain, shortness of breath, chest pain, and bloody sputum or phlegm); (3) $^{18}$F-FDG PET/CT performed within 3 months from conventional imaging and/or clinical data of suspicious recurrent disease, (4) pathological confirmation of $^{18}$F-FDG PET/CT findings and/or comparison to other imaging modalities (i.e., contrast enhanced CT [CE-CT], magnetic resonance imaging [MR]); and (5) clinical and instrumental follow-up data available (clinical case notes, multidisciplinary meeting reports coupled with evaluation of further available CE-CT, MR, $^{18}$F-FDG PET/CT, and bone scan). Minimum follow-up duration was set at 24 months after restaging $^{18}$F-FDG PET/CT (Fig. 1).

Follow-up information was used to assess the disease status in order to allow the assessment of disease progression rate, the overall survival (OS) and the impact of $^{18}$F-FDG PET/CT on the therapeutic approach (change in therapy or “wait and watch”). Plasma levels of Human Chorionic Gonadotropin Beta (HCGB) and Alpha-Fetoprotein (AFP) were also analyzed when available (HCGB normal levels less than 5 IU/L; AFP normal levels = <40 ng/mL) [10].

### FDG PET/CT acquisition

FDG PET/CT scans were performed in accordance with a standard whole-body oncological protocol in each Institution following the guidelines of the European Association of Nuclear Medicine (EANM) [11]. Studies were acquired on

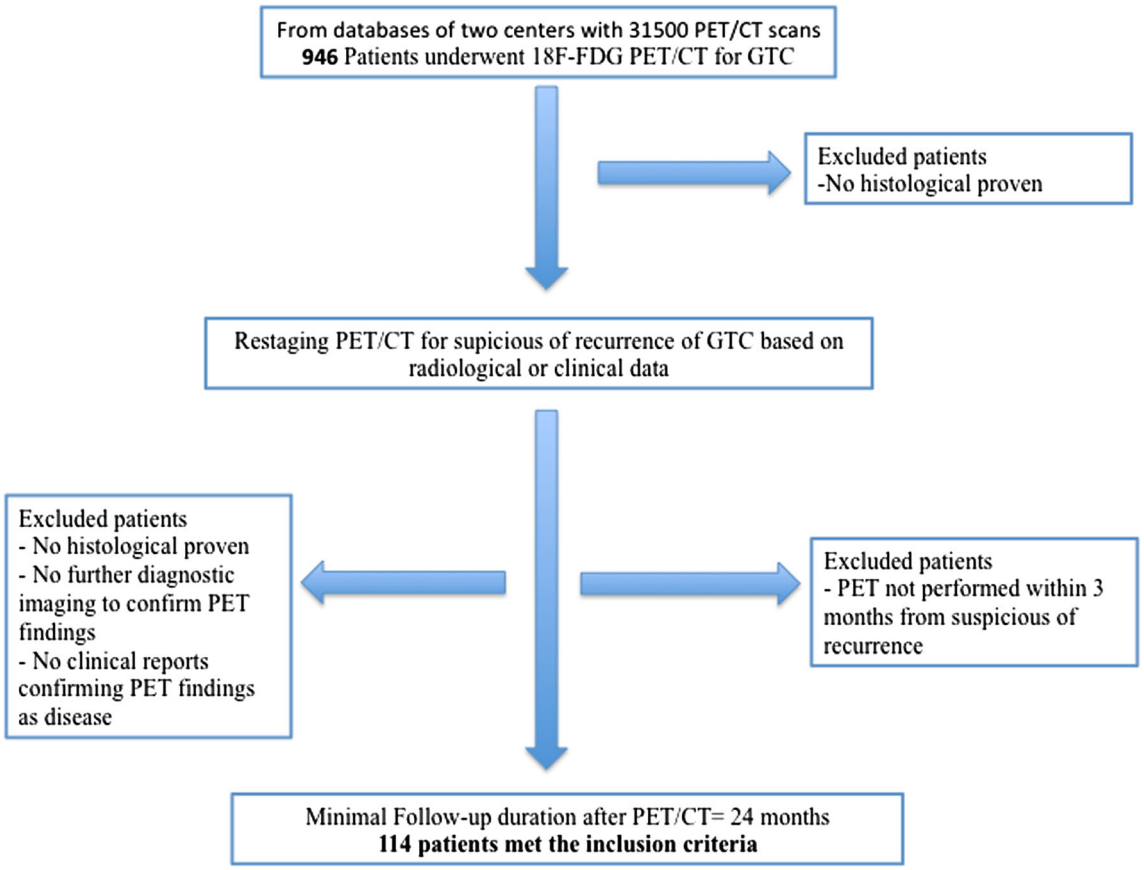


**Fig. 1** STARD flow diagram of patients' inclusion criteria

different tomographs: Siemens Biograph 16S (Siemens AG, Munich, Germany), GE Discovery ST, STE or 690 (GE Healthcare, Milwaukee, WI, USA). PET/CT scan was performed from the base of the skull to the mid-thigh, with inclusion of the upper extremities, and CT (90–120 mA, 140 kV, 0.8 s per tube rotation) was used to perform non-uniform attenuation correction.

### FDG PET analysis

FDG PET/CT images were qualitatively interpreted by two experienced (>5 years of clinical practice in FDG PET/ CT) nuclear medicine physicians, blind to clinical data. Image analysis was performed by two experienced nuclear medicine physicians at the Nuclear Medicine Department of IRCSS San Raffaele Scientific Institute (Milan, Italy) and the Nuclear Medicine and Molecular Imaging Unit of Veneto Institute of Oncology IOV – IRCCS (Padua, Italy). Maximum standardized uptake value (SUVmax) was calculated by using a three-dimensional volumetric region of interest (VOI) with a threshold of 40%. The threshold was determined experimentally on images obtained from an International Electrotechnical Commission (IEC) phantom of known volume, reconstructed identically to patient scans. In the presence of multiple TNM localizations with regard to local recurrences (T), pathological lymph nodes (N) and distant metastases (M), the analysis was performed on the lesion with highest tracer uptake. Written informed consent for $^{18}$F-FDG PET/CT and the anonymous publication of disease-related information was signed by each patient. The study was performed in compliance with the Declaration of Helsinki.

### Statistical analysis

Sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-, respectively), pre and post-test Odds ratios (OR) and diagnostic accuracy were calculated based on Bayesian law with 95% confidence intervals (CIs). The most accurate SUVmax cut-off to detect recurrent disease was computed using ROC curves. Progression free survival (PFS) and OS were calculated by means of Kaplan-Meier survival analysis. PFS was defined as the time interval between the date of the restaging PET and the onset of clinical and/or radiological progression, OS was defined as the time between the date of restaging PET and the date of all-cause death. Univariate and multivariate Cox proportional hazards models were fit in the whole sample and separately in different sub-groups (87 patients with TNM staging and 48 patients with serum biomarker available), to determine whether $^{18}$F-FDG PET/CT, TNM stage, HCGB and AFP levels, were significantly associated

with PFS and OS. Each Cox regression model was built using a stepwise selection procedure with the *p* value for a feature to enter or leave the model set to 0.05. The relationship between outcome and the variables included was summarized by hazard ratios (HR) and 95% confidence intervals (95%CI). Two separate models of Cox regression analyses were performed in order to: 1) evaluate the impact of $^{18}$F-FDG PET/CT findings on PFS and OS; 2) determine the additional prognostic value in regard to PFS and OS of $^{18}$F-FDG PET/CT results if associated with TNM staging data or serum biomarkers levels (HCGB and AFP) .

All statistical analyses were performed using the IBM SPSS Statistics software (version 20.0).

## Results

Between November 2006 and October 2014, at San Raffaele Hospital in Milan (Italy) and Veneto Institute of Oncology in Padua (Italy), 31,500 patients underwent whole-body $^{18}$F-FDG oncological PET/CT studies and 946 out of them were affected by GTC. Of them, 114/946 (12%) patients met the inclusion criteria. Figure 1 and Table 1 illustrate the characteristics of the study population. Eighty-five patients (75%) underwent surgery (radical orchiectomy) only as first-line therapy, whereas 17 (15%) underwent both chemotherapy and surgery (radical orchiectomy and/or lymphadenectomy) and 12 (11%) chemotherapy only. In 48 patients, data about HCGB and AFP levels were available. Of these, 11 (23%) had increased HCGB levels and 12 (25%) had high AFP levels.

**Table 1** Characteristics of patients

| *N* | *114* |
|---|---|
| Age, years (mean ± SD) | 42 ± 12 |
| Type of initial treatments | |
| - Surgery (radical orchifuniculectomy, n. (%) | 85 (75) |
| - Chemotherapy + surgery (radical orchiectomy and/or lymphoadenectomy), n. (%) | 17 (15) |
| - Chemotherapy, n. (%) | 12 (10) |
| Histology of primary tumor, n. (%) | |
| - Seminoma germ cell tumor | 68(60) |
| - Non-seminoma germ cell tumor | 46 (40) |
| *Non-seminoma germ cell tumor | 15 (13) |
| Misted Germ germ cell tumor | 21 (18) |
| Embryoinic testicular tumor | 10 (9) |
| TNM at initial staging, n. (%)** | |
| Stage I | 29 (33) |
| Stage II | 40 (46) |
| Stage III | 18 (21) |

*No other specification available

**Available in 87 patients

### PET/CT diagnostic performance

$^{18}$F-FDG PET/CT was rated positive in 52 (46%) and negative in 62 (54%) patients. Thirty-three patients had a pathological $^{18}$F-FDG accumulation in the abdominal or pelvis lymph nodes, eight in the supra-diaphragmatic lymph nodes, 13 in the lung, four in the bone and one in the liver. Specifically, pathological findings were detected in 7/29 (24%) patients on TNM stage I, 28/40 (70%) patients on TNM stage II and 9/18 (50%) patients on TNM stage III.

$^{18}$F-FDG PET/CT findings were pathologically verified in 17 subjects, and compared to clinical and/or other diagnostic imaging in the remaining 97 patients (ceCT in all subjects and MRI in 15).

Recurrent disease was confirmed in 46 of 52 patients with a pathological $^{18}$F-FDG PET/CT examination (88%; 16 pathologically, 30 by comparison to other imaging). Overall, $^{18}$F-FDG PET/CT showed 86.8% sensitivity and 90.2% specificity. LR+, LR-, pre-test and post-test OR were 8.85, 0.14, 0.85 and 8.85, respectively. Overall diagnostic accuracy was 88.4%. A SUVmax value of 8 was identified as the most accurate cut-off to diagnose recurrent disease (AUC = 0.72, $p = 0.03$).

Twenty-five patients with suspicious nodal relapse (mean size of lesion 14 mm) at the site of primary disease, 12 patients with suspicious metastatic lymph-nodal recurrence (mean size of lesion 11 mm) in other sites, six patients with suspicious lung nodules (mean size 9 mm) and 12 patients with clinical suspicious for recurrence were $^{18}$F-FDG PET/CT true negative (total patients PET true negative = 55). In 7/114 (6%) patients, $^{18}$F-FDG PET/CT failed to detect recurrent lesions, due to the small dimension of lymph-nodes (two patients with size less than 5 mm), lung nodules (three patients with size less than 5 mm) and to the histological subtype characterized by low glucose metabolism (two patients with nonseminomatous GTC). In six of 114 (5%) patients, $^{18}$F-FDG PET/CT showed false positive findings, later confirmed as concomitant inflammatory disease affecting lymph nodes (three patients), bowel (two patients) or lungs (one patient).

### PET/CT and outcome

After a median follow-up period of 36 months (mean 40.8 ± 22.2; range: 8-120), disease progression was reported in 29 patients (25.4%) among whom eight died (7% within all population). Among the 85 patients without disease progression, 41 had stable disease and 44 were disease-free.

A pathological $^{18}$F-FDG PET/CT was significantly associated with shorter PFS and OS compared to unremarkable scans, both at 2-year (PFS 48% vs 98% $p = 0.02$; OS 69% vs 98% $p < 0.001$) and at 5-year (PFS 38 vs 95% $p = 0.02$; OS 33% vs 95% $p < 0.001$ (Figs. 2 and 3). Furthermore, a

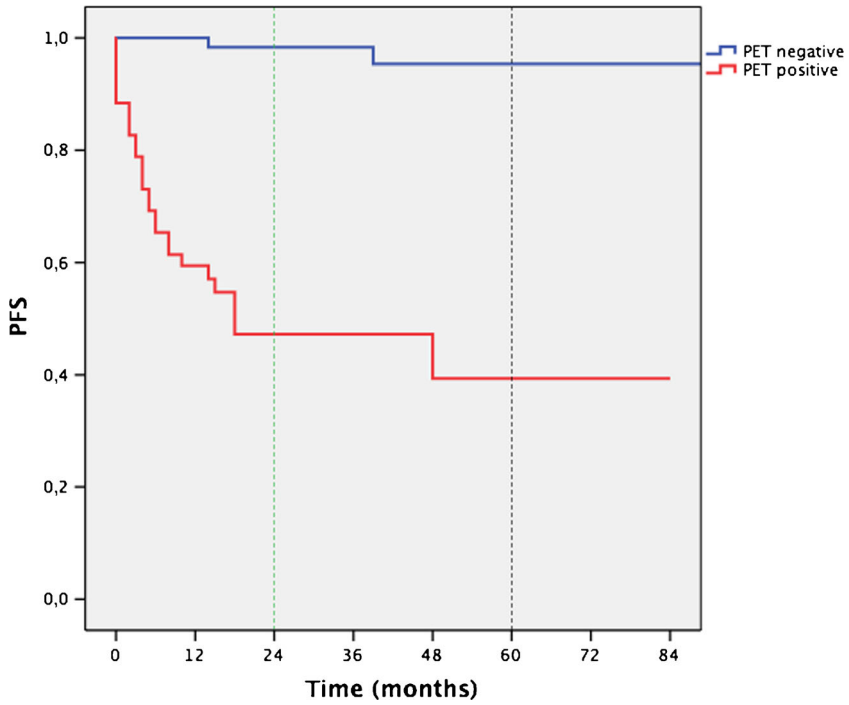


**Fig. 2** Kaplan Meier curves for progression free survival (PFS). Comparison between positive and negative PET/CT findings

SUVmax ≥8 was correlated with a significantly higher progression rate (Table 2).

At univariate analysis, a positive $^{18}$F-FDG PET/CT scan was proven to identify patients at a higher rate of recurrence (HR24.3, $p = 0.03$) and lower OS (HR17.3, $p < 0.001$) if compared to a negative scan.

In patients with pathological $^{18}$F-FDG PET/CT findings, by adding PET-derived information to TNM staging and/or serum biomarkers there was allowed further stratification the risk of disease progression and survival. The risk for disease progression and worse survival was more frequent in case of advanced stage of disease (Stage III: PFS-HR = 6.5, $p = 0.04$ – OS-HR = 9, $p < 0.001$). Patients with both an advanced disease at diagnosis and a pathological PET examination had even higher risk of disease progression and lower survival (PFS-HR = 7.3, $p = 0.03$ – OS-HR = 11,$p = 0.04$, respectively).

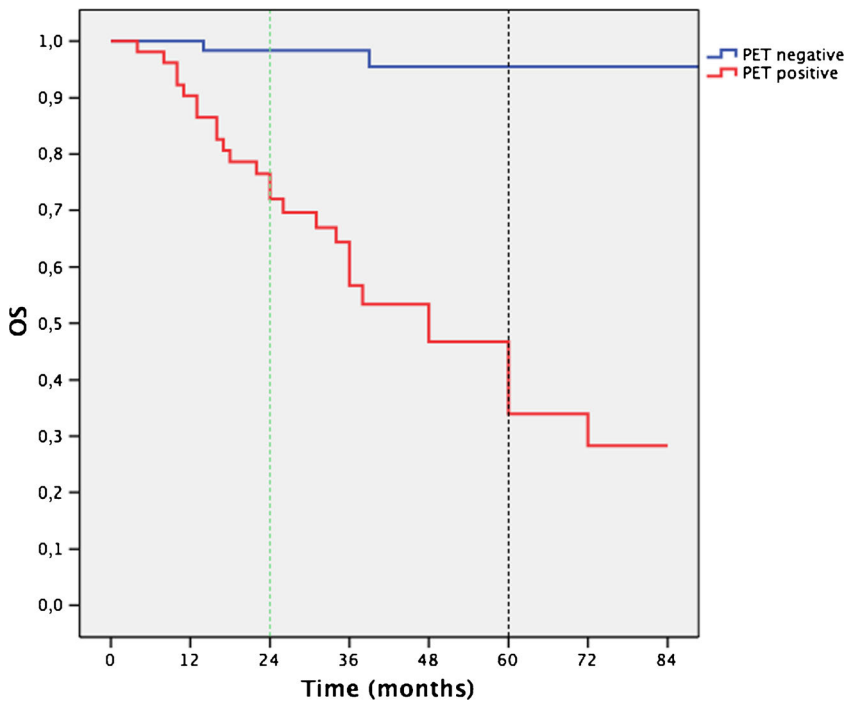


**Fig. 3** Kaplan Meier curves for overall survival (OS). Comparison between positive and negative PET/CT findings

**Table 2** Kaplan Meier analysis of 2- and 5-year Progression Free Survival (PFS) and Overall Survival (OS)

| | 2 year-PFS % | 5 year PFS % | *P* value | 2 year-OS % | 5 year OS % | *P* value |
|---|---|---|---|---|---|---|
| FDG PET/CT findings (*n* = 114 patients) | | | | | | |
| Positive | 48 | 38 | 0.02 | 69 | 33 | <0.001 |
| Negative | 98 | 95 | 0.02 | 98 | 95 | <0.001 |
| *FDG PET/CT SUVvalues | | | | | | |
| SUVmax > 8 | 37 | 34 | 0.007 | 61 | 41 | 0.002 |
| SUVmax < 8 | 66 | 53 | 0.007 | 90 | 52 | 0.002 |
| TNM staging (*n* = 87 patients) | | | | | | |
| Stage I (*n* = 29) | 92 | 92 | 0.04 | 96 | 91 | 0.08 |
| Stage II (*n* = 40) | 83 | 76 | 0.06 | 90 | 72 | 0.04 |
| Stage III (*N* = 18) | 61 | 33 | 0.02 | 58 | 34 | 0.07 |
| TNM and PET/CT (*n* = 87) | | | | | | |
| Positive PET/CT and stage I | 83 | 55 | 0.01 | 90 | 62 | 0.02 |
| Positive PET/CT and stage II | 65 | 42 | 0.02 | 83 | 51 | 0.01 |
| Positive PET/CT and stage III | 50 | 28 | 0.04 | 58 | 29 | 0.04 |
| Serum biomarkers (*n* = 48) | | | | | | |
| Rising HCGB | 71 | 71 | 0.04 | 87 | 70 | 0.05 |
| Rising AFP | 83 | 64 | 0.08 | 91 | 69 | 0.06 |
| Serum biomarkers and PET/CT (*n* = 48) | | | | | | |
| Positive PET/CT and rising HCGB | 64 | 64 | 0.05 | 85 | 68 | 0.07 |
| Positive PET/CT and rising AFP | 41 | 41 | 0.06 | 87 | 56 | 0.08 |

*Analysis among PET positive patients

The same added value holds true if $^{18}$F-FDG PET/CT findings are associated to AFP plasma levels. Increased levels of AFP identify patients with lower PFS (HR 7.0, $p = 0.02$) but fail to predict a difference in OS (HR 4.3, $p = 0.07$). Conversely, patients with both increased AFP plasma levels and a pathologic $^{18}$F-FDG PET/CT have a higher risk of disease progression (HR 10.7, $p = 0.01$) and a lower OS (HR 13.2, $p = 0.04$) (Table 3).

$^{18}$F-FDG PET/CT yielded added value if associated with HCGB plasma levels only in regard to PFS. While rising HCGB identified patients at increased risk both of disease progression (HR 8.6, $p = 0.03$) and of reduced OS (HR 9.7 $p = 0.04$), the association between $^{18}$F-FDG PET/CT and rising HCGB levels identified a higher risk of disease progression (HR 14.3, $p = 0.02$) but was not significantly associated with increased risk of death (HR 10.4, $p = 0.60$).

At multivariate analysis, PFS and OS were significantly lower in patients with pathological $^{18}$F-FDG PET/CT findings (PFS-HR 21.5p = 0.005 – OS-HR 14.0, $p = 0.04$), and in patients with TNM stage III at staging (PFS-HR = 4.6, $p = 0{,}002$ - OS-HR = 5.7, $p = 0{,}01$) (Table 4).

Furthermore, at a step-wise multivariate Cox regression, a pathologic $^{18}$F-FDG PET/CT showed an incremental prognostic value over other variables in predicting PFS (chi-square from 24 to 40, $p < 0{,}001$) and OS (chi-square from 32 to 38, $p = 0{,}003$). However, SUVmax > 8 failed to yield incremental value.

### Impact of FDG PET/CT on therapeutic approach

$^{18}$F-FDG PET/CT findings changed the therapeutic management in 26 cases (22.8%). Specifically, in 12 patients the treatment was switched from palliative to curative, such as surgery (five patients) or radiotherapy (seven patients) with retroperitoneal or mediastinal lymph-nodal lesions. In six patients with advanced GCT, new chemotherapy was initiated (Fig. 4); in eight patients with unremarkable findings, a "wait-and-watch" approach was pursued.

## Discussion

The management of GCT has become relevant due to its increased incidence and mortality in the population worldwide [7]. While the diagnosis of testicular tumors is established with a carefully performed physical examination and scrotal ultrasonography, the identification of recurrent disease relies on tumor markers. Cross-sectional imaging studies (CT, MRI) are useful in determining the location of metastases. In this

**Table 3** Univariate Cox regression analysis for the prediction of progression disease and overall survival for all variables

| Variable | Univariate Cox Regression analysis | | | |
|---|---|---|---|---|
| | HR (95% IC) PFS | *P value* | HR (95% IC) OS | *P value* |
| FDG PET/CT findings | | | | |
| (*n* = 104 patients) | | | | |
| Positive | 24.3 (14.1-40.6) | *0.03* | 17.3 (4.9-77) | <0.001 |
| Negative | - | - | | |
| FDG PET/CT SUV values | | | | |
| SUVmax > 8 | 2.4 (0.9-5.2) | 0.04 | 3,8 (1.5-9.5) | 0.07 |
| SUVmax < 8 | - | - | | |
| TNM staging (*n* = 87 patients) | | | | |
| Stage I (*n* = 29) | 0.2 (0.04-0.8) | *0.03* | 0.3 (0.04-0.9) | 0.035 |
| Stage II (*n* = 40) | 0.6 (0.2-1.4) | *0.24* | 0.4 (0.18-1.2) | 0.13 |
| Stage III (*N* = 18) | 6.5 (2.6-16) | *0.04* | 9 (3.7-23) | <0.001 |
| TNM and PET/CT (*n* = 87) | | | | |
| Positive PET/CT and stage I | 1.7 (0.4-7.2) | *0.18* | 2,3 (0.5-10.4) | 0.23 |
| Positive PET/CT and stage II | 1.9 (0.6-4.2) | *0.07* | 1,46 (0.5-3.6) | 0.4 |
| Positive PET/CT and stage III | 7.3 (4.2-27.6) | *0.03* | 11 (4.5-28) | <0.001 |
| Serum biomarkers (*n* = 48) | | | | |
| Rising HCGB | 8.3 (1.3-26.3) | *0.03* | 9.7 (2.1-31.4) | 0.04 |
| Rising AFP | 7.01 (1.1-18.6) | *0.02* | 4,3 (0.8-16.9) | 0.07 |
| Serum biomarkers and PET/CT (*n* = 48) | | | | |
| Positive PET/CT and rising HCGB | 14.3 (1.5-41.3) | *0.02* | *10.4 (0.9-52)* | *0.6* |
| Positive PET/CT and rising AFP | 10.7 (1.9-59) | *0.01* | *13.2 (2.6-68)* | *0.04* |

regard, $^{18}$FDG PET/CT have slightly higher sensitivity than CT, although a large study did not draw any firm conclusions on its role in the staging process [8]. Similarly, the role of PET in the restaging process of GTC is still limited and the literature is scarce despite the incremental use in the clinical scenario.

The aim of our study was to retrospectively evaluate whether PET/CT could provide valuable clinical and prognostic data for patients affected by GTC after primary treatment with suspicion of recurrent disease. Overall, our data confirmed the good diagnostic accuracy of PET/CT in the detection of GTC lesions. 18F-FDG PET/CT showed good overall sensitivity, specificity and accuracy in GTC (86.8%, 90.2% and 88.4%, respectively). In our series, PET/CT allowed the exclusion of an active disease in 55 of 114 patients. Conversely, PET/CT could confirm the recurrent disease in 46 patients. As extensively known, PET provides metabolic information on morphologically defined lesions, allowing differentiation between scar tissue/fibrosis and viable residual tumor cells. However, data on the usefulness of PET/CT in GTC for the assessment of recurrent disease after first line therapy is still under evaluation.

A recent communication of the American College of Radiology (ACR) also indicated that $^{18}$F-FDG PET/CT may play a role in the follow-up of higher stage seminoma after chemotherapy [8]. Specifically, $^{18}$F-FDG PET/CT may effectively distinguish between residual tumor and fibrosis/necrosis, while CT and MRI show suboptimal prediction of the

**Table 4** Multivariate Cox regression analysis for the prediction of progression disease and overall survival for variable wih *P* value <0.05 at univariate analysis in a sub-group of 87 patients

| Variable | Multivariate Cox regression analysis | | | |
|---|---|---|---|---|
| | HR (95% IC) PFS | *P value* | HR (95% IC) OS | *P value* |
| FDG PET/CT positive | 21,5 (2.5-185) | 0.005 | 14 (1.3-168) | 0.04 |
| SUVmax > 8 | 1.175 (0.4-3.2) | 0.7 | 2.4 (0.6-4.8) | 0.9 |
| STAGE I | 0,9 (0.4-0.9) | 0.9 | 0.6 (0.03-3.3) | 0.7 |
| STAGE III | 4.6 (1.7-12) | 0.002 | 5.7 (2.1-18) | 0.01 |

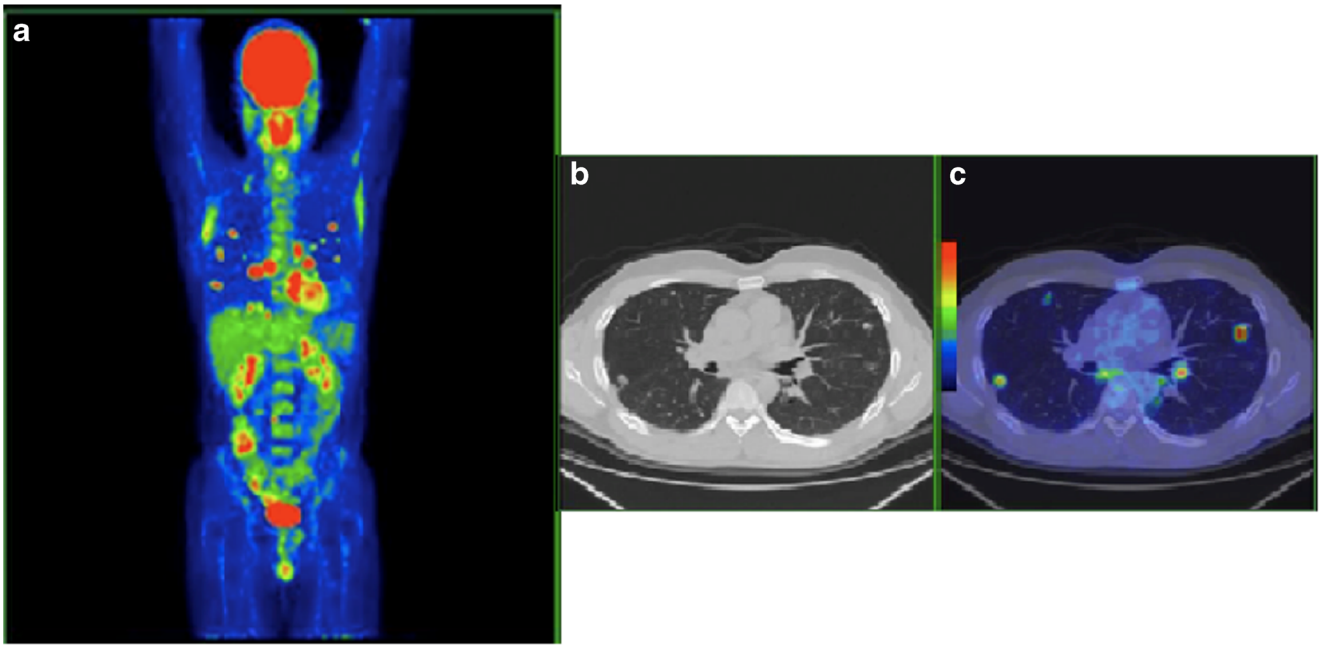


**Fig. 4** A 41-years-old patient affected by widespread metastic seminomatous GCT. After primary surgery and chemotherapy, CT was unclear for residual fibrotic mediastinal lymph-node and pulmonary nodule after chemotherapy vs. residual disease. Restaging PET (1 months from last treatment) showed persistence of mediastinal and hilar lymph-node and pulmonary metastatic disease with SUVmax = 9.2 on left lung nodule. New chemotherapy treatment was initiated. PFS was 7 months and OS was 24 months. A = Maximum Intensity Projection (MIP); B = axial image of CT scan; C = axial image of fused PET/TC

histology of residual masses [12]. A recent meta-analysis by Treglia et al. showed that $^{18}$F-FDG PET/CT, as performed in the post-chemotherapy management of patients with seminoma, has 78% sensitivity, 86% specificity and 84% accuracy [13]. Similar results were reported by Bachner et al., who demonstrated 82% sensitivity and 90% specificity for $^{18}$F-FDG PET/CT if performed at least 6 weeks after completion of chemotherapy [14]. The European Association of Urology (EAU) suggests the use of PET in the restaging process, confirming that this diagnostic method has a high negative predictive value in patients with residual masses after treatment of seminoma. False-positive results are less frequent when scans are scheduled >2 months after chemotherapy [15]. Our results confirmed a high negative predictive value and demonstrated a limited false positive and negative rate for PET/CT. False negative findings were due to small lesions ($n$ = 5 patients) or to lesions with a low glucose metabolism ($n$ = 2 patients), as it frequently happens in low-stage nonseminomatous tumors [16]. Similarly to other cancers, false positive findings occur in concomitant inflammatory disease affecting lymph nodes (three patients), bowel (two patients) or lungs (one patient).

Furthermore, our study showed relevant results regarding the clinical management of GTC patients. In 23% of patients, $^{18}$F-FDG PET/CT guided clinicians to change therapy management, thus demonstrating the added value of this imaging modality in a recurrent GCT setting. PET/CT led to chemotherapy or radiotherapy being started/continued, to surgery of secondary lesions and to clinical surveillance. This may provide robust evidence that decisions regarding therapeutic approach can effectively rely on $^{18}$F-FDG PET/CT findings.

It has been shown that late relapse of testis cancer is relatively common and may occur more than 2 years after completion of treatment [9]. As such, patients treated for testicular GCT need annual follow-up evaluations throughout their life due to the possibility of late relapse. It is, therefore, intuitive that prognostic factors able to impact the clinical follow-up of these patients are highly warranted. While the detection rate of $^{18}$F-FDG PET/CT in patients with suspected recurrent testicular GCT has been extensively investigated, it still remains unclear whether $^{18}$F-FDG PET/CT may also play an important role in the prognostic assessment of patients affected by testicular GCT. To date, the long-term prognostic value of $^{18}$F-FDG PET/CT as performed during the restaging process has not been investigated. The present study could demonstrate that both advanced disease and pathological $^{18}$F-FDG PET/CT findings are independent predictors of a higher rate of disease progression and a lower survival rate. Conversely, a negative scan allows for predicting a more favorable outcome. Of note, adding PET information to other recognized important variables such as TNM staging and/or serum biomarkers allows for further stratification of the risk of disease progression. In particular, at univariate Cox regression analysis,

patients with advanced disease (stage III) and a positive PET have a higher risk of progressing and dying, respectively, 7.3 and 11 times more, than patients with a negative PET scan and also not advanced disease. At Kaplan Meier analysis, PET was demonstrated to be able to classify patients with a worse survival rate. These results are important for distinguishing patients with a favorable outcome, by considering clinical stage and PET results. In all patients the risk of progression was doubled when PET resulted in positive findings, demonstrating its potential role for risk stratification of GTC patients. To the best of our knowledge, this is the first paper investigating the prognostic role of $^{18}$F-FDG PET/CT in restaging patients affected by testicular GCT. This may lead to a broader applicability of this technique in selected centers.

Rather, a paper investigated the early prediction of the efficacy of high dose chemotherapy in patients with recurrent testicular GCT by means of $^{18}$F-FDG PET/CT [17]. The authors demonstrated that $^{18}$F-FDG PET/CT can help identify patients most likely to achieve a favorable response to subsequent high-dose chemotherapy. However, no other data about the prediction of progression-free survival and overall survival have been reported. In other two studies investigating the prognostic role of $^{18}$F-FDG PET/CT in restaging patients affected by other types of cancer, our group reported a pivotal role played by $^{18}$FDG PET/CT in assessing long-term outcome [6, 18].

From the results of our study, we may support the clinical and prognostic role of $^{18}$F-FDG PET/CT in the management of patients with testicular GCT. Clinical trials with a prospective design and a large cohort of patients are needed to expand the use of PET/CT in the restaging process of GTC.

Our study has some limitations. Due to the retrospective nature of the present study and missing clinical data of patients treated or transferred in other hospitals, data concerning TNM staging and serum tumor biomarkers levels were not available for all the patients. As the number of patients with all data available is relatively low, the study was underpowered for a subgroup analysis based on tumor histology or type of primary treatment; as such, we cannot rule out that the different conditions at staging may have affected our results. The relative shorter follow-up (median 36 months) was not adequate to evaluate overall survival and real risk of death in a long period. However, the patient sample is the most comprehensive to date and was sufficient to perform an adequate pooled statistic.

## Conclusion

$^{18}$F-FDG PET/CT has a high diagnostic performance in patients with suspicion of recurrent GCT and provided a change in treatment decision in about 23% of cases. Moreover, $^{18}$F-FDG PET/CT has an important prognostic value in assessing the rate of PFS and OS and to estimate risk of disease progression and survival rate in this setting of patients. $^{18}$F-FDG PET/CT results in combination with TNM staging and serum biomarkers allowed incremental risk stratification. While larger prospective trials are warranted, these results suggest that $^{18}$F-FDG PET/CT may provide valuable information in the management of testicular cancer and in planning adequate effective therapy.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Financial support** The authors have no disclosure of any personal or financial support for this multicenter study.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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