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ORIGINAL REPORT

# Questioning the Value of Fluorodeoxyglucose Positron Emission Tomography for Residual Lesions After Chemotherapy for Metastatic Seminoma: Results of an International Global Germ Cell Cancer Group Registry

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## ABSTRACT

### Purpose
Residual lesions after chemotherapy are frequent in metastatic seminoma. Watchful waiting is recommended for lesions < 3 cm as well as for fluorodeoxyglucose (FDG) positron emission tomography (PET)–negative lesions ≥ 3 cm. Information on the optimal management of PET-positive residual lesions ≥ 3 cm is lacking.

### Patients and Methods
We retrospectively identified 90 patients with metastatic seminoma with PET-positive residual lesions after chemotherapy. Patients with elevated α-fetoprotein or nonseminomatous histology were excluded. We analyzed the post-PET management and its impact on relapse and survival and calculated the positive predictive value (PPV) for PET.

### Results
Median follow-up time was 29 months (interquartile range [IQR], 10 to 62 months). Median diameter of the largest residual mass was 4.9 cm (range, 1.1 to 14 cm), with masses located in the retroperitoneum (77%), pelvis (16%), mediastinum (17%), and/or lung (3%). Median time from the last day of chemotherapy to PET was 6.9 weeks (IQR, 4.4 to 9.9 weeks). Post-PET management included repeated imaging in 51 patients (57%), resection in 26 patients (29%), biopsy in nine patients (10%) and radiotherapy in four patients (4%). Histology of the resected specimen was necrosis in 21 patients (81%) and vital seminoma in five patients (19%). No biopsy revealed vital seminoma. Relapse or progression occurred in 15 patients (17%) after a median of 3.7 months (IQR, 2.5 to 4.9 months) and was found in 11 (22%) of 51 patients on repeated imaging, in two (8%) of 26 patients after resection, and in two (22%) of nine patients after biopsy. All but one patient who experienced relapse were successfully treated with salvage therapy. The PPV for FDG-PET was 23%.

### Conclusion
FDG-PET has a low PPV for vital tumor in residual lesions after chemotherapy in patients with metastatic seminoma. This cautions against clinical decisions based on PET positivity alone.

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## INTRODUCTION

More than 50% of all germ cell tumors are seminomas, and the majority of patients present with localized stage I disease at diagnosis. However, 20% to 30% of patients with seminoma will develop metastatic disease[1,2] and be successfully treated with three to four cycles of cisplatin-based combination chemotherapy.[3,4] Residual masses after chemotherapy are frequent and can be found in up to 80% of men with advanced-stage disease.[5-7] There is an ongoing controversy regarding the optimal postchemotherapy management of residual masses > 3 cm in diameter. In contrast to nonseminomatous germ cell tumors (nonseminomas), postchemotherapy residual masses in seminomas almost exclusively contain necrosis, especially if they are smaller than 3 cm. Positron emission tomography (PET) scans are

ASSOCIATED CONTENT

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not recommended for these patients. In patients with residual masses of ≥ 3 cm, viable cancer is occasionally found[7-9] and may be identified by [$^{18}$F]fluorodeoxy-D-glucose (FDG) PET scanning. The first prospective study investigating the use of PET in this situation demonstrated a negative predictive value of up to 96% and a positive predictive value (PPV) of 100%, but subsequent studies showed that the PPV was only 42%.[10,11]

Currently, there is no undisputed strategy regarding how to manage patients with seminoma with PET-positive lesions after chemotherapy. Therefore, we decided to perform a retrospective data collection to analyze treatment patterns and outcomes of such patients.

## PATIENTS AND METHODS

Centers collaborating within the Global Germ Cell Cancer Group were contacted to share data of patients with metastatic seminoma and PET-positive residual lesions after chemotherapy. Detailed information was collected anonymously using structured questionnaires, and the planned data analysis was predefined in a priori written protocol (Data Supplement). Approval of the local ethical committees was obtained before data collection.

The following items were included: patient characteristics at the time of starting chemotherapy for metastatic disease; chemotherapy regimen as well as any additional treatment modalities and the best response to it; time from last day of chemotherapy to first PET scan; detailed PET results as determined by the local investigator, including standardized uptake value (SUV) and visual interpretation of equivocal versus definite positivity; post-PET management decisions (repeated imaging *v* resection *v* biopsy *v* radiotherapy); outcome according to the post-PET management decisions (relapse, histology of resected specimen, or biopsy); and treatment of relapse and outcome. Relapse was defined as a significant increase in human chorionic gonadotropin (hCG) tumor marker or unequivocal progression in size of residual lesions or appearance of new lesions. Data were anonymized locally, transferred, and entered into a joint database hosted by the Swiss Working Group for Clinical Cancer Research in Bern, Switzerland.

### *Patients*

The following inclusion criteria were applied: male sex, age 18 years or older, histologically confirmed pure seminoma, serum α-fetoprotein < 2× the upper limit of normal at any time; curative-intent chemotherapy for stage IIB, IIC, or III disease; and residual masses with increased FDG uptake on PET imaging (according to local investigator) after completion of chemotherapy.

Patients were excluded if they had nonseminomatous histology or any other histology apart from seminoma, progressive disease at the time of first PET assessment (increasing hCG or unequivocal progression on imaging), or other malignant diseases. Patients with responses (partial response with ≥ 30% size reduction and hCG negative) or with stable disease (tumor reduction < 30%, no growth ≥ 20%, and hCG negative) as best response after chemotherapy were eligible. Patients with a response but persistently elevated lactate dehydrogenase were classified as having marker-positive partial remissions. Disease stage was reported according to the International Union Against Cancer classification.[12] For allocation into risk categories, the prognostic classification of the International Germ Cell Cancer Consensus Group was used.[13]

### *Statistical Analysis*

The primary objectives were the management and outcomes (relapse or histologic finding of vital seminoma) of patients with a positive PET scan and the association between outcome and potential prognostic factors. Secondary objectives were the time from the end of chemotherapy to the first PET scan, the histologies of resection specimens and biopsies, the treatment and outcomes of patients with relapses, and the calculation of the PPV of PET.

Follow-up was calculated from the day of the first PET to the date of last contact. Positive PET scans were rated as true positive if either viable tumor was detected histologically or relapse was diagnosed clinically during follow-up as defined by significantly increasing hCG tumor marker level or unequivocal progression on imaging; all other positive PET scans were rated as false positive. Continuous data were summarized using medians and ranges, categorical data were summarized using frequency counts and percentages, and time-to-event end points were determined using the Kaplan-Meier method using median and interquartile range (IQR). Fisher's exact test was used to check univariable associations between variables.

## RESULTS

Data from 95 patients with metastatic seminoma and PET-positive postchemotherapy residual masses detected between March 2003 and September 2016 in 18 different centers or groups from nine different countries were identified. Five patients were excluded as a result of ineligibility, including PET negativity in three patients and clinically progressive disease at date of first PET in two patients. Therefore, 90 patients with a median follow-up time of 29 months (IQR, 10 to 62 months) were considered eligible according to protocol and included in the analysis (Fig 1).

### *Patient Characteristics*

Detailed patient characteristics are listed in Table 1. The median size of the largest PET-positive residual mass was 4.9 cm (range, 1.1 to 14 cm). Only eight patients (9%) had a residual mass of < 3 cm. The clinical setting before PET was first-line treatment in 87 (97%) of 90 patients, including 80 patients with primary metastatic disease, three patients with relapses after adjuvant carboplatin, two patients with relapses on active surveillance, and one patient each with disease progression after adjuvant radiotherapy or after radiotherapy for stage IIB disease. In three patients (3%), the clinical setting was salvage treatment after prior chemotherapy of metastatic disease (one patient each with stage IIB, IIC, and III disease). Chemotherapy consisted of standard bleomycin, etoposide, and cisplatin (BEP) for three courses in 44 patients (49%); more intensive treatment with BEP for four courses in 21 patients (23%); BEP for three courses plus one course of etoposide and cisplatin in five patients (6%); standard etoposide and cisplatin for four courses in eight patients (9%); and other miscellaneous platinum-based combination regimens in 12 patients (13%).

### *Primary Management and Outcome*

The management of PET-positive patients is shown in Figure 1. The majority of patients (51 of 90 patients; 57%) were observed with repeated imaging (including PET, computed tomography [CT], or ultrasound), and 11 (22%) of these 51 patients experienced a relapse. In 26 (29%) of 90 patients, the management consisted of surgical resection; two (8%) of these 26 patients experienced a relapse. Nine (10%) of 90 patients had a biopsy, and two (22%) of these nine patients experienced a relapse.

  

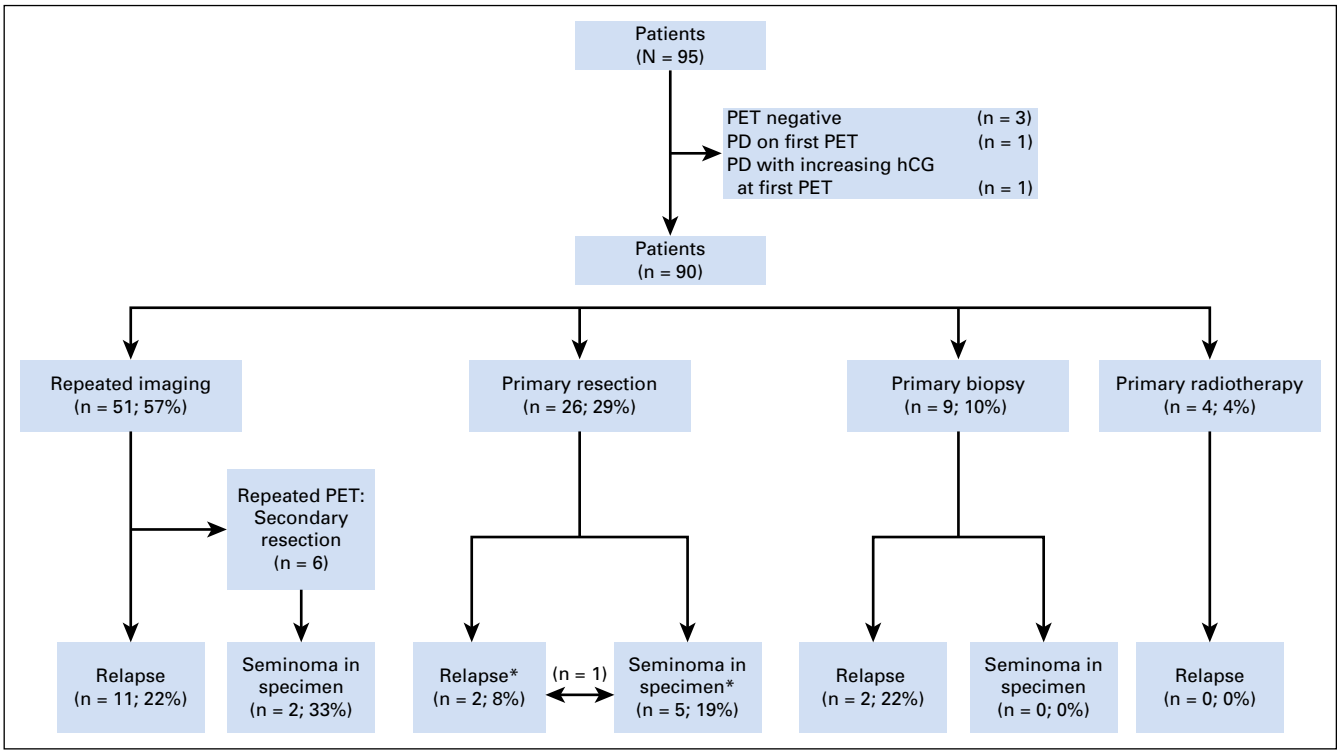


**Fig 1.** Overview of patients. (*) One patient with seminoma in the resected specimen had a later relapse and is included in both boxes. hCG, human chorionic gonadotropin; PD, progressive disease; PET, positron emission tomography.

Radiotherapy was performed in four (4%) of 90 patients, in whom no relapses occurred.

### *Repeated Imaging*

Among the 51 patients with repeated imaging, overall 39 patients (76%) had a subsequent PET. The median time to next PET scan was 2.9 months. In six (15%) of 39 patients, the PET scan became negative, and no relapses occurred in those six patients. Overall, 33 (85%) of 39 patients had a positive PET scan on repeated imaging. Resections were performed in six (18%) of these 33 patients, among whom two patients had seminoma in the resected specimens and no further relapses were observed. The remaining 27 patients (82%) were observed with repeated imaging, and seven of these patients (26%) experienced relapse. Therefore, even in the case of repeated positive PET scans, no relapse or vital seminoma was

**Table 1.** Patient Characteristics

| Characteristic | All Patients (N = 90) | Patients Who Underwent Observation (n = 51) | Patients Who Underwent Resection (n = 26) |
|---|---|---|---|
| Median age, years (range) | 41 (19-69) | 40 (19-69) | 43 (25-53) |
| Primary tumor, No. (%) | | | |
| Gonadal | 67 (75) | 36 (71) | 20 (77) |
| Retroperitoneal | 10 (11) | 8 (16) | 5 (19) |
| Mediastinal | 12 (13) | 7 (14) | 1 (4) |
| IGCCCG risk group, No. (%) | | | |
| Good | 80 (91) | 46 (94) | 23 (88) |
| Intermediate | 8 (9) | 3 (6) | 3 (12) |
| Elevated LDH at diagnosis, No. (%) | 64 (71) | 37 (73) | 21 (81) |
| Elevated hCG at diagnosis, No. (%) | 54 (60) | 33 (65) | 14 (54) |
| Median size of largest residual mass, cm (range) | 4.9 (1.1-14) | 4.6 (1.1-13.1) | 5.0 (2.3-14) |
| Site of residual mass, No. (%) | | | |
| Retroperitoneum | 69 (77) | 36 (71) | 24 (92) |
| Pelvis | 14 (16) | 6 (12) | 7 (27) |
| Mediastinum | 15 (17) | 11 (22) | 1 (4) |
| Lung | 3 (3) | 2 (4) | 0 |
| Median time from last day of chemotherapy to first PET scan, weeks (IQR) | 6.9 (4.4-9.9) | 7.3 (5.0-10.6) | 6.0 (3.9-8.4) |

Abbreviations: hCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; IQR, interquartile range; LDH, lactate dehydrogenase; PET, positron emission tomography.

found in 24 (73%) of 33 patients. Another 12 (24%) of 51 patients had CT scans, of whom four patients (33%) experienced progression.

### Surgical Resection

In total, 32 (36%) of 90 patients underwent resection of a PET-positive residual lesion; 26 (81%) of 32 patients underwent immediate resection after the first positive PET, and six (19%) of 32 patients underwent resection after a subsequent PET that demonstrated continued positivity. The majority of resections (29 of 32 resections; 91%) were performed in patients with masses in the retroperitoneum and/or pelvis, and only three resections were for masses in the mediastinum. Vital seminoma was found in five (19%) of 26 patients with immediate resection of PET-positive lesions and in two (33%) of six patients with a second positive PET scan. In 25 (78%) of 32 patients who underwent resection, only necrosis was found. One of the resected patients received two cycles of adjuvant cisplatin and etoposide chemotherapy, and two patients were treated with postoperative adjuvant radiotherapy to the resection site. Viable seminoma was found in the retroperitoneum or pelvis but not in the mediastinum. Two patients suffered a relapse at the resection site after immediate surgery of PET-positive lesions despite reported complete resections (one after resection of necrosis and one after resection of vital seminoma). Local investigators reported serious postoperative complications in six (19%) of 32 patients, including chylous ascites, pulmonary embolism, bilateral jugular deep vein thrombosis, retroperitoneal hematoma, adhesion with intestinal pseudo-obstruction, and retrograde ejaculation.

### Biopsy

Biopsies for histologic assessment were obtained using core needle biopsies or open techniques (eg, mediastinoscopy). None of the nine biopsies from PET-positive residual masses revealed seminoma on histologic work-up. The following histologic results were found: sarcoidosis (n = 2), necrosis (n = 2), fibrosis (n = 1), abscess (n = 1), reactive lymphoid tissue (n = 1), desmoid tumor (n = 1), and schwannoma (n = 1). Two relapses occurred at biopsy sites. One relapse was identified after 67 days in a patient in whom the initial postchemotherapy biopsy had shown necrosis. The other relapse occurred in a PET-negative retroperitoneal residual mass 28 days after a biopsy had shown schwannoma at a PET-positive presacral lesion.

### Radiotherapy

Only four patients had immediate radiotherapy of a residual PET-positive lesion without further diagnostic procedures. One patient had received high-dose chemotherapy and autologous stem-cell transplantation for relapsed seminoma and demonstrated a PET-positive residual lesion in the right iliac/inguinal area. The other three patients had retroperitoneal disease after BEP, including two patients with marker-negative PET-positive partial remissions and one patient with marker-negative PET-positive stable disease. None of the irradiated patients experienced a relapse.

### Risk Factors for Relapse or Presence of Vital Seminoma and Outcome of Relapse

The risk of relapse or presence of vital seminoma in the resection specimen according to different clinical variables was investigated in univariable analyses (Data Supplement), but no factor achieved statistical significance. Visual interpretation of FDG activity and response to prior chemotherapy revealed a trend ($P$ = .06). To further elucidate the impact of visual PET interpretation, we analyzed the relapse rate for each primary management according to visual PET interpretation demonstrating no major imbalance between the groups (Data Supplement). Actual SUV results were available for 73 (81%) of 90 patients; patients with relapse had higher SUV values than patients without relapse (median SUV, 4.2 *v* 3.6, respectively; $P$ = .02), but no cutoff value with an improved PPV could be defined.

Table 2 provides a summary of all 15 patients who experienced relapse. Relapses occurred within a maximum of 129 days after initial PET or resection or biopsy. Two of five patients with marker-positive partial remissions and four of eight patients with stable disease experienced a relapse or had vital seminoma in the resected specimen. Of note, relapses occurred at the site of residual masses in all patients; in three patients, additional metastatic sites were found. One patient died during salvage treatment from progressive disease, but all other patients were successfully treated with salvage therapy using conventional-dose chemotherapy in two patients and high-dose chemotherapy followed by autologous stem-cell transplantation in 12 (80%) of 15 patients.

At the time of last follow-up, 56 (62%) of 90 patients were reported to be in complete remission, 32 (36%) of 90 patients had residual but inactive disease, one patient was lost to follow-up, and one patient had died of progressive disease.

### PPV of PET

The PPV of PET was calculated for all patients as well as for the following subgroups: equivocal or definite PET positivity on visual interpretation; PET performed within 6 weeks after last day of chemotherapy or later; SUV cutoff value of 4; and size of residual lesion cutoff of 3 cm. The results are listed in Table 3. The PPV for the entire patient population is low at 23%. None of the subgroups revealed meaningful improvement of PPV, with values of 29% for patients with definite PET positivity, 19% if PET was performed later than 6 weeks after the end of chemotherapy, 32% in case of SUV of $\geq$ 4, and 22% if the residual lesion was $\geq$ 3 cm.

## DISCUSSION

This report summarizes the results of the analysis of the largest cohort of patients with metastatic seminoma with PET-positive residual masses after chemotherapy. In contrast to previous smaller series with only a few PET-positive patients included (ranging from eight to 33 patients), our data could not confirm a favorable PPV of PET in this setting.[10,11,14,15] We calculated a PPV of only 23% for a group of patients that consisted mainly of the target population with residual masses $>$ 3 cm. Subgroup analyses using more stringent additional criteria, including unequivocal PET positivity, elevated SUV of $\geq$ 4, PET scanning later than 6 weeks after the end of chemotherapy, and residual mass size of $\geq$ 3 cm, did not substantially improve the PPV; these analyses resulted in PPVs of only 29%, 32%, 19%, and 22%, respectively.

  

**Table 2.** Overview of All Patients Who Experienced Relapse

| UPN | Immediate Postchemotherapy Management | Overall Best Response to First-Line Treatment | Size and Location of Residual Disease | Maximum SUV | Time to Relapse (weeks) | Method Diagnosis of relapse | Location of Relapse | Management and Outcome | FU Since End of Salvage Treatment (months) |
|---|---|---|---|---|---|---|---|---|---|
| 775 | Resection (necrosis) | SD | 14 cm, retroperit | 2.9 | 17, after resection | CT | Retroperit and new distant site | TIP + HDCT<br>Outcome: CR | 74 |
| 825 | Resection (< 10% vital) | PRm positive (LDH) | 4.2 cm, retroperit and pelvis | 4.8 | 8, after resection | CT | Retroperit and pelvis | TIP<br>Outcome: CR | 4 |
| 742 | Biopsy (necrosis) | PRm negative | 11 cm, retroperit | 7.0 | 10, after biopsy | hCG increase | Retroperit and new lung | HDCT × 3<br>Outcome: death on PD | NA |
| 773 | Biopsy (schwannoma) | SD | 4.8 cm, retroperit | 4.1 | 4, after biopsy | hCG increase | Retroperit | 1 × PEI + 3 × HDCT<br>Outcome: CR | 56 |
| 730 | FU imaging | PRm negative | 10.7 cm, retroperit | 3.8 | 18, after first PET | PET | Retroperit | 4 × TIP<br>Outcome: CR | 53 |
| 737 | FU imaging | PRm negative | 6 cm, retroperit | NA | 8, after first PET | PET | Retroperit | 1 × TI + 3 × HDCT; resection: necrosis<br>Outcome: CR | 34 |
| 745 | FU imaging | PRm negative | 2.2 cm, pelvis | NA | 9, after first PET | CT | Pelvis | 3 × HDCT + RT<br>Outcome: CR | 12 |
| 772 | FU imaging | PRm negative | 3.5 cm, retroperit, lung, and mediastinum | 4.2 | 13, after first PET | PET | Retroperit, lung, and mediastinum | 1 × PEI + 3 × HDCT; resection: necrosis<br>Outcome: CR | 17 |
| 800 | FU imaging | PRm negative | 7 cm, retroperit | 8.4 | 3, after first PET | CT | Retroperit | 3 × PEI<br>Outcome: residual but inactive | 35 |
| 803 | FU imaging | PRm negative | 4.5 cm, retroperit | 3.4 | 14, after first PET | PET | Retroperit | TI-CE HDCT<br>Outcome: residual but inactive | 33 |
| 804 | FU imaging | PRm negative | 3 cm, retroperit, pelvis, and lung | 9.2 | 5, after first PET | PET | Lung | TI-CE HDCT<br>Outcome: residual but inactive | 25 |
| 805 | FU imaging | PRm negative | 3.5 cm, pelvis | 3.3 | 17, after first PET | PET | Pelvis | TI-CE HDCT<br>Outcome: CR | 31 |
| 806 | FU imaging | PRm negative | 12 cm, retroperit | 9.0 | 7, after first PET | CT | Retroperit | TI-CE HDCT<br>Outcome: residual but inactive | 21 |
| 807 | FU imaging | PRm positive (LDH) | 3.2 cm, mediastinal, supraclavicular | 7.0 | 5, after first PET | CT | Mediastinum and supraclavicular | TI-CE HDCT; resection: necrosis<br>Outcome: CR | 10 |
| 826 | FU imaging | PRm negative | 2.2 cm, retroperit | 4.0 | 12, after first PET | PET | Retroperit and new bone | TI-CE HDCT + RT<br>Outcome: CR | 54 |

Abbreviations: CR, complete remission; CT, computed tomography; FU, follow-up; hCG, human chorionic gonadotropin; HDCT, high-dose chemotherapy; LDH, lactate dehydrogenase; NA, not applicable; PD, progressive disease; PEI, cisplatin, etoposide, and ifosfamide; PET, positron emission tomography; PRm, partial remission marker; retroperit, retroperitoneal; RT, radiotherapy; SD, stable disease; SUV, standardized uptake value; TI-CE, paclitaxel, ifosfamide, carboplatin, and etoposide; TI, paclitaxel and ifosfamide; TIP, paclitaxel, ifosfamide, and cisplatin; UPN, unique patient number.



 

**Table 3.** PPV for All Patients and for Predefined Subgroups

| Patient Group | No. of Patients | Viable Tumor Detection Method (No.) | | Result, No. (%) | | PPV (%) |
|---|---|---|---|---|---|---|
| | | Histology | FU | True Positive | False Positive | |
| All patients | 90 | 7 | 14 | 21 (23) | 69 (77) | 23 |
| PET equivocal | 28 | 2 | 1 | 3 (11) | 25 (89) | 11 |
| PET definite | 62 | 5 | 13 | 18 (29) | 44 (71) | 29 |
| PET ≤ 6 weeks | 37 | 4 | 7 | 11 (29) | 26 (71) | 29 |
| PET > 6 weeks | 53 | 3 | 7 | 10 (19) | 43 (81) | 19 |
| PET SUV ≥ 4 | 34 | 3 | 8 | 11 (32) | 23 (68) | 32 |
| PET SUV < 4 | 39 | 4 | 4 | 8 (21) | 31 (79) | 21 |
| Lesion < 3 cm | 8 | 1 | 2 | 3 (38) | 5 (62) | 38 |
| Lesion ≥ 3 cm | 82 | 6 | 12 | 18 (22) | 64 (78) | 22 |

Abbreviations: FU, follow-up; PET, positron emission tomography; PPV, positive predictive value; SUV, standard uptake value.

The high rate of false-positive PET scans can be explained by the histologic findings. Among 41 patients with further evaluation of positive scans by either biopsy or resection, vital seminoma was only found in seven (17%) of 41 patients. Necrosis was the most frequent finding, but other histologies such as sarcoidosis, fibrosis, inflammation, and benign tumors were also associated with false-positive FDG activity.

Relapses were detected in 17% of patients, all at the site of residual disease and all within 4 months after the end of chemotherapy. Importantly, all patients with relapse except one were treated successfully with salvage treatment using conventional-dose or high-dose chemotherapy. This suggests that intensified or prolonged follow-up of PET-positive patients with seminoma or repeated PET scanning is unnecessary because patients with residual vital seminoma will eventually be identified by regular follow-up schedules.

Patients undergoing surgical resections of PET-positive residual masses had a low relapse rate of only 8% as compared with 22% in case of follow-up using repeated imaging. This corresponds to an absolute risk reduction of 14% and a relative risk reduction of 64%. On the basis of these figures, the number needed to resect to prevent one relapse would be eight. Resections of large post-chemotherapy masses in seminoma are challenging, however, and often associated with severe complications.[16] Moreover, the fact that necrosis was the only histologic finding in approximately 80% of resected patients confirms that PET is an inappropriate tool to reliably predict viable seminoma after chemotherapy or to identify patients who might benefit from additional postchemotherapy treatments. In the near future, novel serum biomarkers such as microRNA might help to identify patients with vital residual tumor.[17]

None of four PET-positive patients experienced relapse after additional radiotherapy. However, because no histologic information is available in those patients, the impact of additional radiotherapy cannot be assessed. The use of additional radiotherapy is nevertheless discouraged in patients with PET-positive residual lesions because the likelihood of overtreatment is high[18,19] and late toxicities after treatment with both chemotherapy and radiotherapy are known to be markedly increased.[20,21]

An unexpected finding of our analysis is the fact that patients who presented initially with large seminoma masses may have been exposed to overtreatment; although only 9% of patients were classified as intermediate risk according to the International Germ Cell Cancer Consensus Group classification, a total of 29% of patients received four cycles of a cisplatin-based three-drug combination. Hence, one of five patients may have received a fourth cycle possibly based on the impression of large tumor masses and/or elevated lactate dehydrogenase, which is not recommended by current guidelines.

This report has all the limitations inherent in a retrospective study and is only hypothesis generating. The data are susceptible to selection bias and may not be representative for all patients with seminoma; for example, among eight patients with residual lesions < 3 cm, the rate of viable seminoma or relapse was unexpectedly high. Moreover, because we did not centrally reassess the original PET scans, we had to rely on assessments by local investigators, which might have introduced interobserver bias. The facts that technical improvements in PET scanning and reporting had occurred during the study period and that current state-of-the-art SUV measurements are not available for all patients in this series are other drawbacks.

Although our report represents the largest analysis in this patient population, the total number of patients is still small. Without prospective randomized studies, no definite recommendations as to the optimal management of patients with seminoma with residual masses after chemotherapy can be made. Because the probability of vital seminoma is reported to be low in most series, there is consensus among experts that PET should not be used in residual lesions measuring < 3 cm in the largest diameter.[3] Such patients can be observed according to published guidelines,[3,4] with imaging (magnetic resonance imaging or CT) after 6 and 12 months and annually thereafter up to 5 years. For residual lesions ≥ 3 cm, we recommend to perform PET not earlier than 6 weeks after completion of chemotherapy. In view of the high negative predictive value of 96%,[11] PET-negative patients can be observed according to the aforementioned schedule. In case of a positive PET scan after chemotherapy, we propose to closely monitor patients with repeated imaging (CT or magnetic resonance imaging), tumor marker measurements, and clinical assessment after 2 and 4 months and every 4 months thereafter in the first year, every 6 months in the second year, and then annually up to 5 years. On the basis of the results of the current analysis, biopsies of residual lesions are discouraged. Surgical resection of PET-positive residual lesions may be considered on an individual basis on the basis of size, location, resectability, and patient preference. For patients with unequivocal progression, salvage chemotherapy is recommended and will result in a high rate of cure.

Despite its limitations, the results of this retrospective study challenge the clinical relevance of positive PET scans in patients with metastatic seminoma and residual masses after chemotherapy and caution against additional treatments on the basis of PET positivity alone. Given their rarity and complexity, such patients should be referred to centers with expertise in managing germ cell tumors.

  

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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**Questioning the Value of Fluorodeoxyglucose Positron Emission Tomography for Residual Lesions After Chemotherapy for Metastatic Seminoma: Results of an International Global Germ Cell Cancer Group Registry**

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