FDG PET for Detection and Therapy Control of Metastatic Germ Cell Tumor

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We investigated the use of PET and 2-[18F]fluoro-2-deoxy-D-glucose (FDG) for detection and therapy control of metastatic germ cell cancer in comparison to CT. Methods: Fifty-four PET studies were performed in addition to CT in 33 patients with histopathologically proven germ cell tumors (14 seminomas, 18 nonseminomas, 1 not classified). The scans were done either after initial diagnosis (Group 1; n = 12), within 2 wk after completion of chemotherapy (Group 2; n = 13) or 14-375 days after chemotherapy (Group 3; n = 29). PET and CT were validated either by histology (n = 19) or clinical follow-up for 182-1704 days (n = 35). Focal pathological uptake with PET was quantified using standardized uptake values (SUVs).

Results: PET was significantly more accurate than CT (0.86 versus 0.59; p < 0.025) for detection of residual viable tumor in Group 3. While sensitivities of PET and CT did not differ markedly, PET was significantly more specific than CT. No significant differences between PET and CT were found in Groups 1 and 2. PET scans after therapy resulted in false-negative findings in five of nine cases of Group 2 but only in two of nine cases of Group 3. False-positive PET findings occurred in three inflammatory processes. SUV of seminomas was significantly higher than in nonseminomas (p < 0.01). Conclusion: PET using FDG is superior to CT for assessment of residual tumor after chemotherapy of germ cell cancer and may thus have an increased effect on patient management in the future. PET must be performed at least 2 wk after completion of therapy. Further data are necessary to determine the role of FDG PET for initial staging of germ cell cancer.

Key Words: germ cell tumor; staging; therapy control; PET; fluoride-18-fluorodeoxyglucose


Testicular cancer is now the most frequent malignancy among men between 20 yr and 40 yr. Incidences of 4-10 of 100000 have been reported in most industrialized countries (1). Germinal cell tumors are categorized into pure seminomas (40%) and into the heterogeneous group of nonseminomatous tumors comprising teratoma, choriocarcinoma, embryonal and mixed or combination tumors (2).

Metastatic spread is found in 70% of nonseminomatous tumors and 30% of seminomas at the time of diagnosis. With radiotherapy and the introduction of cisplatin combination chemotherapy, prognosis of metastatic testicular cancer has been dramatically improved. Cure rates of 80%-90% were reported in Stage II and III patients; cure is also possible in patients who failed to achieve complete remission after initial therapy (3).

Staging after initial diagnosis determines whether systemic chemotherapy, abdominal radiotherapy or no further therapy is necessary. Diagnosis of metastatic spread is usually made by CT of abdomen and chest and/or elevated tumor markers (human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP) and lactate dehydrogenase). CT-based clinical staging has been shown to have a false-negative rate in clinical Stage I patients of 30%-40% even with third- and fourth-generation CT scanners (4,5). As a consequence, Stage I seminomas undergo abdominal radiation therapy, whereas different therapeutic strategies are presently performed in clinical Stage I nonseminomas. These strategies comprise retroperitoneal lymph node dissection (RPLND), chemotherapy or surveillance. Due to excellent cure rates in early testicular cancer, therapy-induced morbidity (disturbances of ejaculation, infertility, surgical complications, induction of secondary tumors) has become an important matter. The development of better noninvasive imaging techniques would be a key to a more individualized therapy.

Another problematic issue is the occurrence of indeterminate residual masses in CT after completion of chemotherapy in 15%-75% of patients. Surgical resection of the mass is usually performed and histological examination shows necrosis/fibrosis in 40%-50% of the cases, differentiated teratoma in 12%-40% of the cases and persistent viable malignancy in 20%-40% of
the cases (3,6). Although teratomas should be resected because tumor progression may occur (7), approximately 40% of patients with residual masses after chemotherapy would not need laparotomy if viable residual tumors could be excluded noninvasively.

PET with 2-[18F]-fluoro-2-deoxyglucose (FDG PET) has been used successfully for staging and assessing therapy response in various malignancies (8). Only preliminary data were reported so far on the use of 18F FDG PET in testicular cancer patients, suggesting a role for PET in the detection and management of metastatic germ cell tumors (9–13).

The aim of our study was to compare the diagnostic potential of FDG PET and CT for detection and follow-up of germ cell tumor metastases. We focused on detection of residual or recurrent disease in patients with a residual mass after chemotherapy. Retrospective analysis of PET studies acquired over a longer time period was done to clarify the influence of the histopathological subtype on the results and to optimize timing of post-therapeutic PET scans.

MATERIALS AND METHODS

Patients

Included in the study were 33 patients (age range 19–71 yr; mean age 30 yr) with histopathologically proven germ cell tumor. The histological diagnosis was seminoma in 14 (42%), combined tumor in 6 (18%), teratocarcinoma in 5 (15%), choriocarcinoma in 3 (9%), embryonalcarcinoma in 3 (9%) and teratoma in 1. One tumor was not classified and diagnosis was made by CT-guided biopsy only. Tumor staging was assessed according to the international workshop on staging and treatment of testicular cancer in Lugano (14). Stage I represents tumors limited to the testis, Stage II represents lymphatic spread into subdiaphragmatic lymph nodes and Stage III represents supradiaphragmatic lymph node and/or hematogenous metastases. The final staging was Stage I in 4 (12%), Stage II in 11 (33%) and Stage III in 18 (55%) patients. Eight patients suffered from metastatic tumor relapse and five tumors were primarily located extragonadal. Twenty-eight patients received polychemotherapy, 9 received additional salvage chemotherapy and 3 also received autologous bone marrow support. Five patients underwent abdominal radiotherapy and one patient underwent radiotherapy of the involved testis.

A total of 54 PET scans were performed. Individual patients were studied up to four times either after initial diagnosis (Group 1; n = 12) or after chemotherapy. Informed consent was obtained from all patients. The post-therapy scans were divided into patients studied 1–13 days after the last therapy cycle (Group 2; n = 13) and those studied 14–37 days after the last therapy cycle (Group 3; n = 29). These time intervals were chosen retrospectively from an analysis of false PET findings in our study. Only PET scans, which could be validated for the existence or absence of viable tumor tissue, were included.

PET Imaging

Forty-two studies were performed after patients fasted overnight, 12 studies were performed 3–6 hr after patients had breakfast. Plasmaglucose levels at the time of FDG injection ranged between 3.0 and 8.8 mmol/liter (median 5.15 mmol/liter); hyperglycemia was present in four studies. FDG was purchased from the Institute of Radiochemistry, Research Center (Jülich, Germany). Patients received 120–309 MBq (median 182 MBq) FDG by intravenous bolus injection.

PET scanning was performed using an ECAT 953/15 scanner (Siemens-CTI, Knoxville, TN), allowing simultaneous acquisition of 15 contiguous cross-sectional slices with a slice thickness of 3.375 mm. In-plane resolution of the device was around 7 mm FWHM using iterative image reconstruction and 128 × 128 matrix size. Emission scans were corrected for photon attenuation by measured transmission scans using a retractable 68Ge ring source; scatter correction was not involved.

PET studies were performed between September 1990 and August 1996. During this period, new software was developed in our institution and was implemented into routine evaluation of oncological PET studies. The most important addition for these studies was iterative image reconstruction based on maximum likelihood expectation maximization using a formula developed by Shepp and Vardi (15). The method has been explained elsewhere (16). The resulting dataset was reoriented and additionally smoothed by linear interpolation of neighboring voxels in x-, y-, and z-axis. Coronal, sagittal and transversal images of 7-mm slice thickness were used for visual image interpretation and quantitative image analysis. Thus, the quality of low-count images was substantially improved, making whole-body scans comprising thorax and abdomen with minimum emission scan times of 5 min per bed position possible. The acquisition of emission scans was changed from initial 3–6 bed positions (equivalent to 15–25 cm axial field of view [FOV]) and 15 min per bed position during the first years to 8–16 bed positions (40–80 cm axial FOV) and 5–10 min per bed position. Acquisition of emission data was always started 40–60 min after injection and lasted for 45–80 min. Transmission scans of the abdomen were routinely performed. Thoracic studies were corrected for attenuation only, when metastases were suspected from visual interpretation of noncorrected images. Transmission scan time was 12–15 min per bed position, and scanning was performed either before FDG injection or after decay of injected activity. A reference cross was drawn on the patients’ skin to ensure correct repositioning using the built-in laser equipment.

Due to software improvements, earlier studies were reconstructed again as described previously. Image interpretation was done by an experienced observer without knowledge of follow-up data but with respect to CT findings known at the time of PET imaging. Focally hypermetabolic lesions not explained by urinary excretion, intestinal activity or other physiological reasons were suspected for viable tumor metastasis. In cases where viable tumor tissue was suspected, the lesion with the highest apparent FDG uptake was subject to quantitative analysis. For comparison, FDG uptake was also assessed in several normal tissues (lung, mediastinum, blood, liver, intestines, bone marrow), which represent the regional background of typical germ cell tumor metastases.

Quantitative image analysis yielded standardized uptake values (SUVs) according to the formula: $SUV = \frac{\text{radioactivity concentration in region of interest (ROI) [Bq/ml] \times injected dose [Bq]}}{\text{body weight [g]}}$. Radioactivity concentration was corrected for calibration and decay. ROIs of suspected tumor hot spots were defined semiautomatically with a software tool developed in our institution from the 50% isocontour after background subtraction (17). Background ROIs were traced manually. ROIs of normal tissue were drawn manually from 10 patient studies of chest and abdomen, which were selected at random. The cavity of the left ventricle was used to assess blood background, and studies with considerable myocardial uptake were excluded. A lower lumbar spine was chosen for bone marrow quantification. Intestines were quantified only when intestinal activity was clearly visible. Transversal or coronal 7-mm slices were used for SUV analysis.

CT Imaging

Correspondent CTs were available in all PET studies. The time interval between PET and CT study was 1–38 days (median 15 days). CT scans used for comparison were obtained with third- or fourth-generation CT scanners from different institutions. Transversal cross-sections of 7–10 mm slice thickness were used, oral
TABLE 1
Diagnostic Accuracy of PET, CT and Tumor Markers

<table>
<thead>
<tr>
<th>Method</th>
<th>TP</th>
<th>FN</th>
<th>TN</th>
<th>FP</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
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<td>8 of 24</td>
<td>27 of 30</td>
<td>3 of 30</td>
<td>0.67*</td>
<td>0.90†</td>
<td>0.80*</td>
<td>0.84*</td>
<td>0.77*</td>
</tr>
<tr>
<td>CT</td>
<td>18 of 24</td>
<td>6 of 24</td>
<td>18 of 30</td>
<td>12 of 20</td>
<td>0.75*</td>
<td>0.60†</td>
<td>0.67*</td>
<td>0.60*</td>
<td>0.75*</td>
</tr>
<tr>
<td>TM</td>
<td>11 of 21</td>
<td>10 of 21</td>
<td>22 of 23</td>
<td>1 of 23</td>
<td>0.52</td>
<td>0.96</td>
<td>0.75</td>
<td>0.92</td>
<td>0.89</td>
</tr>
<tr>
<td>PET + TM</td>
<td>15 of 21</td>
<td>6 of 21</td>
<td>20 of 23</td>
<td>3 of 23</td>
<td>0.71*</td>
<td>0.87*</td>
<td>0.80*</td>
<td>0.83*</td>
<td>0.87*</td>
</tr>
<tr>
<td>CT + TM</td>
<td>17 of 21</td>
<td>4 of 21</td>
<td>16 of 23</td>
<td>7 of 23</td>
<td>0.81*</td>
<td>0.70*</td>
<td>0.75*</td>
<td>0.71*</td>
<td>0.80*</td>
</tr>
</tbody>
</table>

* = ns.
† p < 0.01.

TM = tumor markers; TP = true-positive; FN = false-negative; TN = true-negative; FP = false-positive; PPV = positive predictive value; NPV = negative predictive value.

contrast was generally applied in abdominal scans and intravenous contrast medium was given when tumor lesions were suspected. CT scans for initial staging were interpreted as suspicious for metastatic lymphatic spread if lymph node enlargement of >1.5 cm was found. CT scans for follow-up were performed in patients of Group 2 with a median of 11 days after completion of chemotherapy (PET 7 days) and in Group 3 with a median of 56 days after therapy (PET 60 days). All follow-up studies were classified as complete remission (CR), partial remission (PR), stable disease (SD) or progression (PRO) regarding the course of the patient. In the case of CR or PR, CT was assumed to indicate good therapy response and absence of residual viable tumor; in the case of SD or PRO, CT was assumed to indicate residual viable tumor. This valuation yielded the best diagnostic accuracy; a different valuation of CT results would have yielded lower accuracy.

Tumor Markers

Tumor marker levels of AFP and HCG at the time of PET scanning were available in 44 of 54 studies. AFP > 7 kU/l and HCG > 10 U/l were considered pathological.

Validation and Statistics

Validation was done either by histology (n = 19) or clinical follow-up for 182–1704 days (median 483 days; n = 35). In the latter group, residual viable tumor tissue was assumed if lesions were documented by CT, and either tumor markers were positive at the time of the PET scan, or progression was found in CT during follow-up. Absence of viable tumor after therapy was assumed if the patient was without progression in CT and tumor markers were negative for at least 6 mo without further therapy. Histology was gained by RPLND (n = 14), thoracotomy (n = 3) or CT-guided biopsy (n = 2).

Sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were determined for PET, CT and tumor markers. SUVs of different histologic subtypes were compared by the Mann–Whitney U test. Differences between PET and CT for parameters of diagnostic accuracy were evaluated by Pearson's chi-square test where appropriate or by Fisher's exact test. A statistical software package for the PC was used (SPSS for Windows, SPSS Inc., Chicago, IL).

RESULTS

The diagnostic accuracy for the detection of viable metastatic tumor tissue of PET in comparison to CT and tumor markers is shown in Table 1. PET was more exact than CT or tumor markers, but this difference was not yet statistically significant. Although sensitivity and negative predictive value were in the same range as in CT, specificity was significantly higher in PET (p < 0.01). Tumor markers yielded the highest specificity but the lowest sensitivity; diagnostic accuracy was in between PET and CT. Similar information was obtained by the combination of PET and tumor markers compared to CT and tumor markers. Sensitivity was higher for CT and tumor markers, whereas specificity was inferior to PET and tumor markers, but these differences were not statistically significant (Table 1).

Accuracy of PET was different in the three patient groups as shown in Table 2. PET studies performed in patients shortly after the last day of chemotherapy (1–13 days) were false-negative in 5 of 9 cases. Accuracy of PET in these patients was much lower than in patients studied before or more than 13 days after therapy. PET revealed significantly higher specificity and diagnostic accuracy (p < 0.025) than CT in patients studied more than 13 days after therapy. Differences were not significant during initial staging after orchiectomy and within 2 wk after completion of chemotherapy.

In Groups 1 and 3, there were no false-negative PET results in seminomas but there were three false-negatives in nonseminomas. Two false-positive PET results were found in seminomas and one in nonseminomas. The accuracy of PET was higher than the accuracy of CT in both histopathological subgroups (Table 3) but the difference was significant only in nonseminomas (p < 0.05).

Quantitative analysis of FDG uptake by the SUV method

TABLE 2
Diagnostic Accuracy of PET Versus CT in Patient Groups 1–3

<table>
<thead>
<tr>
<th>Group</th>
<th>Method</th>
<th>TP</th>
<th>FN</th>
<th>TN</th>
<th>FP</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>5 of 6</td>
<td>1 of 6</td>
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<td>1 of 6</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>5 of 6</td>
<td>1 of 6</td>
<td>5 of 6</td>
<td>1 of 6</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
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<td>5 of 9</td>
<td>4 of 4</td>
<td>0 of 4</td>
<td>0.44</td>
<td>1.00</td>
<td>0.62</td>
<td>1.00</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>7 of 9</td>
<td>2 of 9</td>
<td>2 of 4</td>
<td>2 of 4</td>
<td>0.78</td>
<td>0.50</td>
<td>0.69</td>
<td>0.78</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>PET</td>
<td>7 of 9</td>
<td>2 of 9</td>
<td>18 of 20</td>
<td>2 of 20</td>
<td>0.78</td>
<td>0.90*</td>
<td>0.86*</td>
<td>0.78</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>6 of 9</td>
<td>3 of 9</td>
<td>11 of 20</td>
<td>9 of 20</td>
<td>0.67</td>
<td>0.55*</td>
<td>0.59*</td>
<td>0.40</td>
<td>0.79</td>
</tr>
</tbody>
</table>

* p < 0.025 (vertical reading).

TP = true-positive; FN = false-negative; TN = true-negative; FP = false-positive; PPV = positive predictive value; NPV = negative predictive value; Group 1 = PET before chemotherapy; Group 2 = PET less than 14 days after chemotherapy; Group 3 = PET minimum 14 days after chemotherapy.

FDG PET IN METASTATIC GERM CELL CANCER • Cremerius et al. 817
revealed significantly higher uptake in seminomas than in nonseminomas (p < 0.01). When we did not regard patients who were studied within 2 wk after therapy, we did not find an overlap between the two subgroups. SUV ranged from 7.2–13.5 in seminomas (n = 5) and from 1.4–5.0 in nonseminomas. This difference was even more obvious when pre- and post-therapeutic PET scans were evaluated separately (Fig. 1). Discrimination of seminomas from nonseminomas was possible with PET using a SUV threshold of 6.0. The differences between pre- and post-therapy SUVs as shown in Figure 1 were not significant. Table 4 gives a more detailed analysis of SUV in the different histopathologies: The lowest SUV was found in combined tumors, whereas teratocarcinoma, choriocarcinoma and embryonal carcinoma had intermediate FDG uptake compared to seminomas. The highest uptake was found in seminoma metastases before therapy. Table 5 shows SUVs of normal tissues for comparison. The highest physiological uptake (outside the brain and the myocardium) was found in liver and bone marrow, followed by blood, mediastinal and intestinal uptake. The lowest background was found in the lung.

TABLE 3
Influence of Histological Subtype on PET and CT Results*

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Method</th>
<th>TP</th>
<th>FN</th>
<th>TN</th>
<th>FP</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>PET</td>
<td>5 of 5</td>
<td>0 of 5</td>
<td>12 of 14</td>
<td>2 of 14</td>
<td>1.00</td>
<td>0.86</td>
<td>0.90†</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>5 of 5</td>
<td>0 of 5</td>
<td>10 of 14</td>
<td>4 of 14</td>
<td>1.00</td>
<td>0.71</td>
<td>0.79†</td>
</tr>
<tr>
<td>Nonseminoma</td>
<td>PET</td>
<td>6 of 9</td>
<td>3 of 9</td>
<td>11 of 12</td>
<td>1 of 12</td>
<td>0.67</td>
<td>0.92</td>
<td>0.81‡</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>5 of 9</td>
<td>4 of 9</td>
<td>6 of 12</td>
<td>6 of 12</td>
<td>0.56</td>
<td>0.50</td>
<td>0.52‡</td>
</tr>
</tbody>
</table>

* Patient Groups 1 and 3 only.
† = ns.
‡ p < 0.05.
TP = true-positive; FN = false-negative; TN = true-negative; FP = false-positive.

Detailed clinical, CT and PET data of all patients with false-negative or false-positive PET findings are given in Table 6. All three false-positive PET scans were due to inflammatory processes: sarcoidosis with affection of mediastinal lymph nodes in one patient, extensive retroperitoneal inflammation after chemotherapy and radiotherapy of an extragonadal seminoma in a second case and pericholangitis of the liver demonstrated by CT-guided biopsy in the third patient who was also suffering from hemosiderosis. The SUVs of the false-positive cases ranged from 3.7–9.2. These values were comparable to SUVs of germ cell tumor metastases. False-negative PET scans could be verified by histology in three cases. In two cases, differentiated teratoma was found in subsequent surgery of the residual mass after chemotherapy. PET scanning had been performed 9 and 40 days after therapy. One patient was found to have a negative PET scan and residual viable cancer in resected specimen; he was studied 10 days after therapy. PET for initial staging was false-negative in one patient with combined tumor. At RPLND, 1 of 25 resected lymph nodes was found to contain tumor; the size of the lymph node was 15 mm. CT was also negative in this patient.

Five individual patients were studied by FDG PET before and after polychemotherapy. Three of them received a third scan during follow-up. SUVs of reference metastatic lesions during the time course after diagnosis are demonstrated by Figure 2. In three patients (Patients 13–15), disappearance of hypermetabolic PET lesions correctly predicted complete remission. In Patient 1, PET and tumor markers were normalized after 3 mo (10 days after completion of chemotherapy), whereas CT showed stable disease in the liver and regression of retroperitoneal lymph node metastases. Laparotomy was performed and revealed residual vital tumor cells in the liver lesions but necrosis of retroperitoneal lymph nodes. Three months later, tumor relapse was documented by PET and tumor markers. In Patient 8, FDG uptake was still present after 7 mo of therapy; after second-line therapy (surgery and chemotherapy) another 7 mo later, PET and tumor markers were normalized. Neverthel-
Clinical Data of Patients with False-Negative or False-Positive PET Findings

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Primary histology</th>
<th>Final staging</th>
<th>CT finding</th>
<th>PET finding</th>
<th>Time post Chx (days)</th>
<th>Secondary staging</th>
<th>Follow-up data*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Seminoma</td>
<td>Iic</td>
<td>SD</td>
<td>FN</td>
<td>10</td>
<td>Cancer</td>
<td>P/261 d</td>
</tr>
<tr>
<td>2</td>
<td>Seminoma</td>
<td>Iic</td>
<td>PRO</td>
<td>FN</td>
<td>7</td>
<td>nd</td>
<td>P/128 d</td>
</tr>
<tr>
<td>3</td>
<td>Seminoma</td>
<td>Iic</td>
<td>PR</td>
<td>FN</td>
<td>4</td>
<td>nd</td>
<td>P/165 d</td>
</tr>
<tr>
<td>4</td>
<td>Seminoma</td>
<td>la</td>
<td>FP#</td>
<td>FP#</td>
<td>—</td>
<td>Sarcoïdosis</td>
<td>R/254 d</td>
</tr>
<tr>
<td>5</td>
<td>Seminoma</td>
<td>Iic</td>
<td>PR</td>
<td>PR</td>
<td>90</td>
<td>inflammation</td>
<td>R/121 d</td>
</tr>
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<td>6</td>
<td>Terato ca</td>
<td>Iic</td>
<td>PR</td>
<td>FN</td>
<td>40</td>
<td>Teratoma</td>
<td>R/145 d</td>
</tr>
<tr>
<td>7</td>
<td>Terato ca</td>
<td>Iib</td>
<td>PR</td>
<td>FN</td>
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<tr>
<td>8</td>
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<td>Iib</td>
<td>CR</td>
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<tr>
<td>9</td>
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<td>Iic</td>
<td>SD</td>
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<td>nd</td>
<td>P/604 d</td>
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<td>Inflammation</td>
<td>R/1086 d</td>
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<tr>
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<td>Comb tu</td>
<td>Iib</td>
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<tr>
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<td>FN#</td>
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<td>Cancer²</td>
<td>—</td>
</tr>
</tbody>
</table>

* Patient outcome (P = progression; R = remission)/period of follow-up (days).
# Initial staging.
* Metastasis in 1 of 25 lymph nodes.

Time post Chx = time interval between chemotherapy and PET (days); terato ca = teratocarcinoma; chor ca = chorioncarcinoma; comb tu = combination tumor; SD = stable disease; PRO = progression; PR = partial remission; CR = complete remission; FN = false-negative; FP = false-positive; nd = not done.

less, tumor relapse occurred 8 mo later. Figure 3 shows the initial PET and CT scan of Patient 15.

Figures 4 and 5 demonstrate that differentiation between necrosis and well-differentiated teratoma in residual masses after therapy is not feasible by FDG PET. However, transformation of a known differentiated teratoma into poorly differentiated teratocarcinoma in a case of growing teratoma was detected by PET as shown in Figure 6. In this case, PET was also correct in assessing that the tumor did not respond to chemotherapy.

DISCUSSION

In the past few years, imaging of metastatic germ cell cancer has been the domain of CT and to a lesser degree ultrasonography. Lymphography has been usually replaced by CT. Functional imaging methods like 67Ga scintigraphy have been studied in seminoma but were not successful (18). Only three reports about PET using FDG in the evaluation of germ cell cancer have been published up to now (9,10,13). Wilson et al.

FDG PET IN METASTATIC GERM CELL CANCER • Cremerius et al. 819

FIGURE 2. PET follow-up of five patients. SUV of a reference lesion in relation to time after diagnosis. ID = identification; Histo = histological subtype; Se = seminoma; NS = nonseminoma; PRO = progression; CR = complete remission.

FIGURE 3. A 34-yr-old seminoma patient with multiple retroperitoneal lymph node metastases before therapy. (A) Coronal reformatted PET scan demonstrates pathological bilateral FDG uptake (SUV 13.5) of enlarged lymph nodes shown by the transversal CT image (B).
Thoracotomy after this three nomas (necrotic FDG nomas) (our performed high Wilson uptake) true-positive relevant teratomas aspect uptake. Although Wilson et al. (9) found from metastatic carcinoma. (A) PET shows low FDG uptake (SUV 1.7) in the residual mass demonstrated by CT (B). Thoracotomy was performed a few days after PET scanning and revealed necrotic tissue without viable tumor cells.

FIGURE 4. A 31-yr-old patient with a residual mass of the right basal lung after chemotherapy of metastatic chorion carcinoma. (A) PET shows low FDG uptake (SUV 1.7) in the residual mass demonstrated by CT (B). Thoracotomy was performed a few days after PET scanning and revealed necrotic tissue without viable tumor cells.

FIGURE 5. A 25-yr-old patient with a residual pulmonal mass after chemotherapy of metastatic combined testicular tumor. (A) PET reveals faint tumoral uptake (SUV 1.4) visible only due to low pulmonal background activity. The residual lesion is clearly shown by CT (B). Subsequent surgery was performed and differentiated teratoma was found histopathologically.

(9) have reported on 21 patients (4 seminomas and 17 nonseminomas) and found avid FDG uptake in 8 of 14 cases with known metastatic spread. Although Wilson et al. (9) used a PET camera with only modest sensitivity, they found PET to be useful for therapy monitoring and were able to predict response to therapy by comparing pretreatment and on-treatment FDG uptake. They also showed limitations of the method: PET was negative in four patients with lesions smaller than 1 cm and in three patients with differentiated teratomas at surgery. The latter aspect has been recently demonstrated in a larger series by Stephens et al. (10). They evaluated 30 patients with nonseminomas before surgical resection of a residual mass and found a significant different uptake between residual carcinoma and necrosis or teratomas but no significant difference between teratomas and necrosis.

In this study, we report about a larger series that includes a relevant number of seminomas. In this patient population, true-positive PET scans revealed significantly higher FDG uptake in seminomas than in nonseminomas. In the series of Wilson et al. (9), this difference was not found, but they had only two positive PET scans in seminomas. In agreement with this finding, diagnostic accuracy of PET in seminomas was as high as 90% with no false-negative cases if studies that were performed earlier than 2 wk after therapy were excluded from our series. In contrast to seminomas, FDG uptake of nonseminomas was only low to moderate with a wide range of SUVs from 1.4–5.0. The lowest uptake was found in a residual mass confirmed to be a differentiated teratoma at surgery. SUV of differentiated teratoma was comparable to normal mediastinal or abdominal background tissue, thus detection was possible only in the lung, where the lowest background SUV was measured. All other differentiated teratomas in residual masses after therapy were negative in the PET scan. This resulted in a lower diagnostic accuracy of 81% for nonseminomas, which was still significantly higher than the accuracy of CT (Table 3). The advantage of PET over CT in nonseminomas was based mostly on its higher specificity. Our quantitative results in nonseminomas were comparable to the results of Stephens et al. (10), who found SUVs of 1.3–4.8 in teratomas after chemotherapy. The lowest FDG uptake in our series was found in combined tumors. SUV quantification may not be exactly comparable between different institutions due to different methodologies (use of mean or maximum values, methods of ROI delineation, lack or use of scatter correction), thus comparisons between different institutions regarding absolute SUV values should be done with caution.

The question of optimal timing of post-treatment scans has been raised by Wilson et al. (9) but could not be answered in their study. We showed that PET scanning during the first 2 wk after the completion of chemotherapy was obviously too early and resulted in a loss of sensitivity and diagnostic accuracy. A similar observation was earlier reported in brain tumors and head and neck tumors under radiation therapy, where a tempo-
False-positive PET scans occurred only in patients with histopathologically proven inflammatory processes. This limitation is well known in PET imaging using FDG and has been reported as a major problem in its use in oncological patients (22). Avid FDG uptake in inflammation has also been demonstrated by microautoradiography (23). This problem may not be solved by SUV quantification because SUVs of inflammatory processes were in the same range as SUVs of tumor lesions. Thus, laboratory parameters indicating inflammation should be screened routinely in these patients. If histopathological diagnosis is not possible, $^{99m}$Tc-granulocyte antibody scans or other imaging methods may be used to exclude granulocyte accumulations.

The role of PET in comparison with tumor markers has only been partly addressed in our study because tumor markers were not available from all patients at the time of PET scanning. The type of information gained by PET and tumor markers seems to be quite similar; both reflect the volume of the metabolically active tumor mass. This is illustrated in our study by the fact that adding tumor markers to PET did not enhance the information given by PET alone. On the other hand, adding PET to tumor markers improved sensitivity and negative predictive value. Small volumes of viable tumor may remain undetected by PET and tumor markers as shown by the example of Patient 8. Thus, for follow-up and treatment control, SUV in FDG PET may be regarded as an additional biologic tumor marker, especially valuable in cases where plasma tumor markers were negative at the time of diagnosis and could not be used for therapy monitoring.

CONCLUSION

FDG PET is more accurate than CT in detecting residual viable tumors after chemotherapy of metastatic germ cell tumors. PET scanning should not be performed earlier than 2 wk after completion of therapy. After this time interval, patients with a negative PET scan possess a 90% probability of having only necrosis or fibrosis if a residual mass is still present on CT. Probability of a residual tumor for a positive PET scan at that time is around 80%.

These results may have important implications for the management of patients after chemotherapy of metastatic germ cell tumors. In case of a positive PET scan, further therapy such as salvage chemotherapy or salvage surgery seems advisable because tumor relapse and incomplete therapy response are very likely. In case of a negative PET scan, surgery may be postponed even in residual masses shown by CT. If viable tumor tissue is present, it will very probably be a differentiated teratoma, which may be operated on later when further follow-up by CT shows no significant regression over a longer time period.

Our preliminary results in patients studied during initial staging demonstrate that smaller lymph node metastases in the retroperitoneum may not be reliably detected by PET similar to CT. Thus, from our study, PET seems to be useful for initial staging, but its advantage over CT is not discernible at the moment. Further studies are necessary and should probably focus on seminoma because of its higher FDG uptake compared to nonseminoma.

FDG PET IN METASTATIC GERM CELL CANCER • Cremerius et al. 821
Hürthle Cell Tumor Dwelling in Hot Thyroid Nodules: Preoperative Detection with Technetium-99m-MIBI Dual-Phase Scintigraphy

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Single injection dual-phase scintigraphy (early and late acquisitions) with 99mTc-MIBI was used to differentiate benign and malignant hot thyroid nodules. Methods: Thirteen euthyroid and two hyperthyroid patients displaying a hot thyroid nodule on the 99mTc scan due to an autonomously functioning thyroid nodule (AFTN) underwent early (15–30 min) and late (3–4 hr) thyroid scintigraphy after the administration of 740–1000 MBq 99mTc-MIBI. Visual scoring was done to assess nodular tracer uptake and retention. In addition, the nodular-to-thyroid (N/T) uptake ratio in the early and late image and the washout rates (WO) from the nodule and thyroid tissue were measured. All patients underwent thyroid surgery. Results: Histopathology revealed a Hürthle cell tumor in three nodules, a benign adenoma with oxyphilic metaplasia in two nodules and a benign adenoma without oxyphilic cells in the remaining 10 nodules. The Hürthle cell tumors displayed intense and persistent uptake of 99mTc-MIBI (N/T was 2.81 ± 0.52 and 5.53 ± 1.06 in early and late images, respectively; WO from the nodule was 12.33 ± 0.47, WO from the thyroid tissue was 22.00 ± 3.56). The benign nodules showed intense uptake in the early image and intense uptake to absent retention in the late image (N/T was 2.94 ± 1.31 and 1.62 ± 0.50 in the early and late images, respectively; WO from the nodule was 20.25 ± 2.92, WO from the thyroid tissue was 20.33 ± 2.92). Conclusion: Single injection dual-phase 99mTc-MIBI scintigraphy of the thyroid with AFTN can identify nodules as a result of the activity of a Hürthle cell tumor, since these tumors cause intense and persistent tracer uptake in contrast with a benign AFTN.

Key Words: thyroid scintigraphy; technetium-99m-sestamibi; hot nodules; Hürthle cells tumor


The rate of malignancy in thyroid nodules is fortunately very low, representing about 6% of all nodules (1,2); however, the rate of malignancy is higher in those nodules where 99mTc or radioiodine demonstrate to be scintigraphically cold than in those that are found to be hot (3–6). These latter sometimes appear hot with 99mTc and cold with radioiodine, since this tracer is rapidly removed from such nodules because they either have lost their ability to organify the iodine (7) or may be autonomous and enact a rapid turnover of iodine (8). In such cases, some authors have suggested reimaging with radioiodine those nodules that appear hot with 99mTc (3–6,9–12). Others (13) claim that this procedure is not necessary since the risk of cancer in such nodules is very low, accounting for 4%–11% of all hot nodules (14). Papillary or follicular cancer have been found to coincide and be associated with hot nodules, rather than cause the hot nodule (14). When present, a Hürthle cell tumor was found in the histology of these surgical specimens (14–16). Since in such cases total thyroidectomy is mandatory, its preoperative detection is of paramount importance.

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Received May 23, 1997; accepted Aug 4, 1997.
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822 The Journal of Nuclear Medicine • Vol. 39 • No. 5 • May 1998