L-[1-Carbon-11]Tyrosine Imaging of Metastatic Testicular Nonseminoma Germ-Cell Tumors

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The aim of this study was to investigate whether PET with L-[1-^{11}C]tyrosine (TYR) can be used to visualize metastatic disease of nonseminoma testicular germ-cell tumors and to monitor the effect of systemic cisplatinum-based polychemotherapy in a noninvasive fashion to reduce the number of operations in patients with a residual retroperitoneal tumor mass. **Methods:** Ten patients with retroperitoneal nonseminoma testicular germ-cell tumors metastases were studied with TYR PET before the start of cisplatinum-based polychemotherapy. A dose of 370 MBq of TYR was injected intravenously, and a 30-min TYR image was acquired 20 min after injection. The standardized uptake value of TYR was calculated in visualized lesions. **Results:** PET showed increased focal uptake of TYR in the retroperitoneum of 2 patients (20%). In 2 patients with large and inhomogeneous lesions on CT, PET showed decreased TYR uptake at the site of the lesion (20%). In the other 6 patients, the metastatic tumor masses were not depicted (60%). Because of these disappointing results, no posttreatment scans were obtained. Standardized uptake values of the visualized lesions varied from 1.05 to 2.87 for the lesions with increased metabolism and from 0.29 to 0.34 for lesions with decreased metabolism. **Conclusion:** PET with TYR is not suited to visualize the apparently slowly proliferating nonseminoma testicular germ-cell tumors or determine the nature of a residual retroperitoneal mass after chemotherapy.

Key Words: PET; germ-cell cancer; tyrosine; metastases

J Nucl Med 1998; 39:1027–1029

Patients with metastatic nonseminoma testicular germ-cell tumors, including those with retroperitoneal disease, are treated with intensive cisplatinum-based polychemotherapy. Staging is performed by CT, and tumor marker assessment is performed by radioimmunoassay (*1*). Before therapy, 40% of the patients with metastatic disease have elevated plasma α-1-fetoprotein (AFP) levels, and 75% have elevated human β-choriogonadotropin (HCG) levels. In 85% of patients, at least one of these tumor markers is present (*2*). The effectiveness of the treatment can be monitored by measuring these tumor markers. If tumor markers normalize and CT of the abdomen shows no residual retroperitoneal tumor masses, then the patient is considered to be in complete remission. However, despite normalization of the tumor markers, CT shows a residual retroperitoneal tumor mass in a majority of patients (*3,4*). Although effective anatomical localization of the residual mass can be achieved with the aid of MRI and CT, conventional imaging techniques do not allow determination of the nature of these masses (*5*). Therefore, all patients with residual disease after chemotherapy are treated with adjuvant surgery (*3,6*). Histology reveals scar tissue or necrosis in 45% of these patients, mature teratoma in 42% and viable tumor tissue in 13% (*1,7*). Information about the nature of residual retroperitoneal tumor mass after chemotherapy is crucial for subsequent treatment. Second-line chemotherapy is necessary when viable malignant tumor tissue is present. The surgical removal of residual tumor tissue has been proven to be beneficial, as has the removal of mature teratoma, because it can degenerate into malignancy, and the patient can develop growing teratoma syndrome (*4*). The surgical removal of necrotic tissue, however, places an unnecessary surgical strain on patients.

Different metabolic processes (protein synthesis, uptake of disaccharides, glycolysis and transamination) are enhanced in tumors as compared to normal tissues (*8*). This fact is exploited in PET. The glucose analog [^{18}F]fluoro-2-deoxy-D-glucose (FDG) can be used to calculate glucose consumption, and the amino acid L-[1-^{11}C]tyrosine (TYR) can be used to calculate the protein synthesis rate in tissues (*9*).

The aim of this study was to investigate whether PET with TYR can be used to visualize metastatic disease before the start of chemotherapy and to monitor the effect of chemotherapy noninvasively to reduce the number of operations in these patients.

MATERIALS AND METHODS

Patients

Ten consecutive patients (mean age = 34 yr; age range 19–60 yr) participated in the study. Written informed consent was obtained from all the patients, and the study protocol was approved by the Medical Ethics Committee of the Groningen University Hospital. All patients had retroperitoneal nonseminoma testicular germ-cell tumors metastatic disease. This information was based on the combination of positive abdominal CT and elevated plasma AFP and/or HCG levels. Patient characteristics are shown in Table 1. PET studies were performed before the start of cisplatinum-based polychemotherapy. Depending on the results of these pretreatment PET scans, a second scan could be performed after therapy, in case of residual retroperitoneal tumor mass. To maintain a constant plasma tyrosine level throughout the study, the patients fasted for at least 10 hr (except for water) before the study.

PET Studies

All PET sessions were performed using an ECAT 951/31 PET camera (Siemens/CTI, Knoxville, TN). This device has a 56-cm-diameter patient aperture and acquires 31 planes simultaneously over a 10.8-cm axial field of view. The spatial resolution is 6.1 mm FWHM. The patients were positioned in the camera by locating the target lesion relative to the pelvic bones, as visualized on CT. A transmission scan to correct for attenuation of photons by the body tissues in the imaged area was obtained before injection. A dose of 370 MBq of TYR was injected intravenously, and a 30-min TYR image was acquired 20 min after injection. Images were assessed visually with knowledge of the CT findings. Around visualized lesions, a region of interest (ROI) was drawn, and from this, the standardized uptake value (SUV) was calculated based on lean body mass, using the equations reported previously (*10*).

Received May 3, 1997; revision accepted Oct. 9, 1997.
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TABLE 1
Patient Characteristics*

Patient no.	Histology	Tumor markers	Size (cm)	PET	SUV_{tumor}
1	Choriocarcinoma, seminoma	HCG ↑	1	–	–
2	Embryonal carcinoma, mature teratoma	AFP ↑, HCG ↑	1.5	–	–
3	Choriocarcinoma, embryonal carcinoma, yolk sack tumor, immature teratoma	AFP ↑, LDH ↑	1.5	–	–
4	Embryonal carcinoma, mature teratoma, seminoma	AFP ↑, LDH ↑	1.5	+ (several)	2.03–2.87
5	Embryonal carcinoma	AFP ↑, HCG ↑	2.5	+	1.05
6	Choriocarcinoma, embryonal carcinoma, yolk sack tumor, mature teratoma, seminoma	AFP ↑, HCG ↑, LDH ↑	4	–	–
7	Embryonal carcinoma, yolk sack tumor, seminoma	AFP ↑, HCG ↑, LDH ↑	5	–	–
8	Yolk sack tumor, mature teratoma	AFP ↑	6	–	–
9	Embryonal carcinoma, yolk sack tumor, mature teratoma	AFP ↑, HCG ↑, LDH ↑	6	+ (due to cyst)	0.34
10	Choriocarcinoma, embryonal carcinoma, yolk sack tumor	AFP ↑, HCG ↑, LDH ↑	12	+ (due to cyst)	0.29

*Characteristics include histology of the primary tumor, elevated tumor markers at the time of PET, size of the retroperitoneal lesion as measured with CT, visibility with PET and calculated TYR uptake in the visualized tumors.
HCG = human chorionic gonadotropin; AFP = alpha-fetoprotein; LDH = lactate dehydrogenase.

RESULTS

In all patients, the intestines showed relatively high TYR uptake. However, due to the uptake of TYR in the bone marrow of the vertebral column, the retroperitoneum was easily located. PET showed increased focal uptake of TYR in the retroperitoneum of two patients (20%) (Fig. 1). When compared to CT, the focal TYR uptake appeared to be at the location of the known retroperitoneal lesion. In two other patients with large and inhomogeneous lesions on CT, PET showed decreased TYR uptake at the site of the lesion (20%) (Fig. 2). This can be attributed to the presence of cystic or necrotic tumor components. In the other six patients, the metastatic tumor masses were not depicted (60%). Because of these disappointing results, no post-treatment scans were performed.

The SUV of the visualized lesions varied from 1.05 to 2.87 for the lesions with increased metabolism and from 0.29 to 0.34 for the cystic lesions. There was no clear relationship between the different tumor marker levels and the visibility of the lesion or the SUV. The SUVs of bone marrow varied from 1.59 to 3.13, whereas a large ROI placed ventrally in the abdomen showed an intestinal SUV that varied from 1.63 to 2.66.

DISCUSSION

Although the number of patients was small, the results presented indicate no role for amino acid PET in patients with metastatic nonseminoma testicular germ-cell tumors. Retroperitoneal metastases were visualized in only 2 of 10 untreated patients. Histological examination of the retroperitoneal dissection after chemotherapy revealed no tumor in 5 patients (Table 1; Patients 1, 2, 3, 5 and 6), a completely viable yolk sack tumor in 1 patient (*8*), focal mature teratomas within large necrotic areas in 3 patients (*4,9,10*) and an exclusively mature teratoma within large necrotic areas in only 1 patient (*7*). Furthermore, all patients had elevated tumor markers at the time of the PET scan. This makes it very likely that the majority of the retroperitoneal masses did consist of viable tumor (and not mature teratoma only). Therefore, we conclude that TYR is not suited to visualize viable nonseminoma testicular germ-cell tumors.

The ability to metastasize is generally associated with poor differentiation and a high proliferation rate, although this rule may not apply to metastases to lymph nodes, as in nonseminoma testicular germ-cell tumors (*11*). The uptake of amino acids in breast cancer was shown to be related to differentiation and proliferation rate (*12*). Therefore, the inability to visualize nonseminoma testicular germ-cell tumors with TYR PET might be due to the fact that eight of our patients may have had well-differentiated, slowly proliferating tumors. The fact that even the two most bulky tumors, which are likely to be among the faster proliferating tumors, showed hypometabolism was somewhat surprising. Mature teratoma is well differentiated and proliferates even slower than malignant tumor tissue. On the other hand, because the detection of tumors depends merely on the difference between the intensity of the signal from the tumor and that from the background, the relatively high uptake of TYR in intestinal tissue and bone marrow may also impair the identification of tumors with slightly increased TYR uptake.

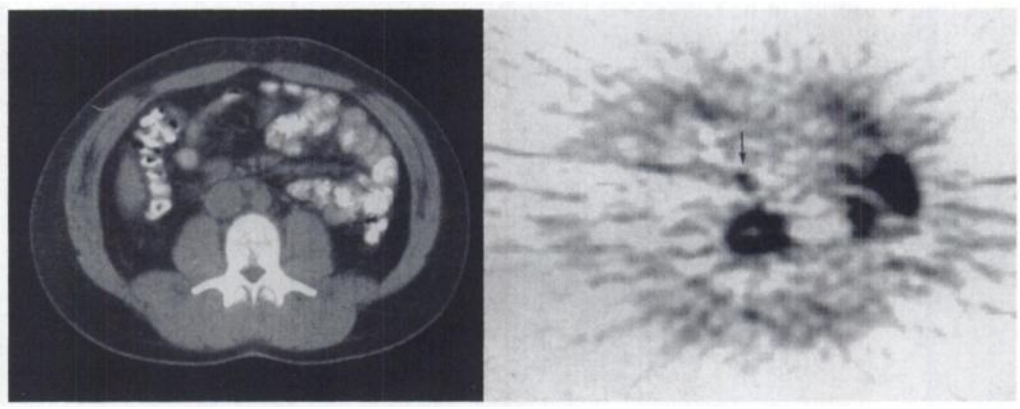

FIGURE 1. Abdominal CT and PET images of Patient 5. The CT scan shows an enlarged prevertebral lymph node between the aorta and the caval vena. With PET, increased tyrosine uptake is seen at the same location.

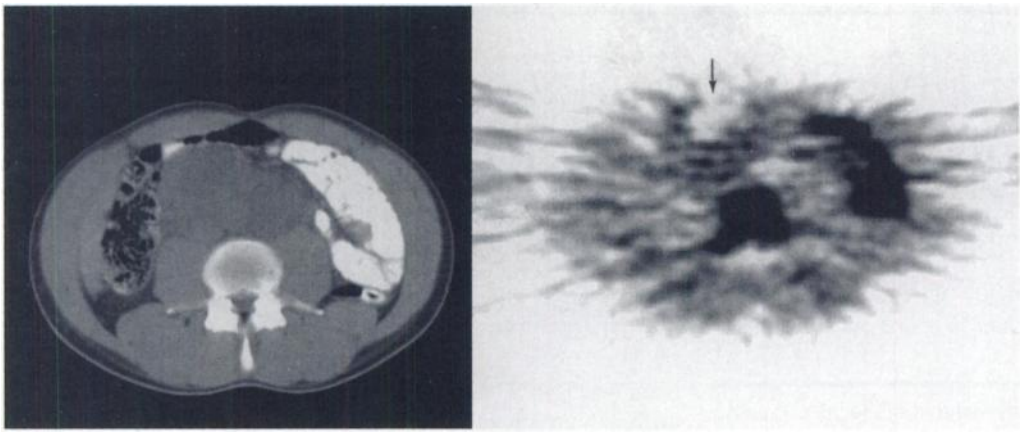

FIGURE 2. Abdominal CT and PET images of Patient 10. The CT scan shows a retroperitoneal tumor mass in which cystic or necrotic parts are visible. With PET, decreased tyrosine uptake is seen at the location of the largest cystic portion.

Different groups have investigated PET with FDG to determine the nature of a residual mass after chemotherapy for testicular cancer (*13–16*). It appeared possible to differentiate viable tumor tissue (larger than 1-cm diameter) from necrosis and scar tissue. It was not possible to differentiate mature teratoma from necrosis or scar tissue. Because mature teratoma is not malignant in itself, the inability of FDG PET to identify mature teratoma adds to the general accuracy of FDG PET in discriminating benign from malignant tissue, but surgery was, thus, still unavoidable for all patients. Furthermore, FDG imaging of metastatic testicular cancer after chemotherapy has limited value because of potentially high accumulation of FDG in inflammatory tissues (*16*). In this study, the patients were not studied with both TYR and FDG, because this would have meant that patients were scanned twice before and twice after chemotherapy, due to the original protocol, which included monitoring of chemotherapy. We thought that this would be too much of a burden for these patients (receiving high-dose chemotherapy).

Steyerberg et al. (*1*) have developed a statistical model that predicts the histological outcome after chemotherapy for nonseminoma testicular germ-cell tumors. The absence of teratoma elements in the primary tumor, prechemotherapy normal AFP and HCG and elevated lactate dehydrogenase levels, a small prechemotherapy mass and a large shrinkage of the mass during chemotherapy are used as predictive factors. This model can discriminate necrosis very well from mature teratoma and viable tumor (area under receiver operating characteristic curve = 0.84) but is less effective in distinguishing mature teratoma from viable malignant tissue (area = 0.66) (*1*). In theory, a combination of FDG PET and the Steyerberg model can discriminate between all three histologies of interest and might be worth exploring.

CONCLUSION

Although there may be a role for FDG PET in localizing metastatic disease and monitoring response to chemotherapy, thus aiding patient management, TYR PET is not suited to visualize the apparently slowly proliferating nonseminoma testicular germ-cell tumors or to determine the nature of a residual mass after chemotherapy.

ACKNOWLEDGMENTS

This study was supported by Dutch Cancer Society Grant RuG 94-786.

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