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Original Paper

Detection of Residual Tumours in Postchemotherapy Testicular Cancer by FDG-PET

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The aim of this study was to investigate whether 2-(F-18)-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) could reliably detect testicular cancer in patients following chemotherapy. Twenty FDG-PET studies were performed on 15 patients with metastatic seminoma or non-seminoma. Tracer uptake in the PET study was measured by calculating the standardised uptake value (SUV) for the tracer. Nine lesions out of 20 were judged to be positive based on high FDG uptake. Three proved to represent inflammatory changes in non-cancerous tissue. Eleven PET studies were negative. In one of these, viable tumour was found at retroperitoneal lymphadenectomy. The median SUV values of metastatic tumours and benign residual tumours were 2.7 (range 1.6–9.5, $n = 10$) and 1.7 (range 0.7–5.5, $n = 15$), respectively. The large overlap of SUVs between these groups was due to the relatively high FDG uptake in inflammatory tissue (median 4.2, range 2.0–5.5, $n = 4$). The results indicate that FDG imaging of metastatic testicular cancer after chemotherapy has limited value because of a potentially high accumulation of FDG in inflammatory tissues. © **1997 Published by Elsevier Science Ltd.**

Key words: Positron emission tomography, fluorodeoxyglucose, testicular cancer, residual tumour

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INTRODUCTION

TESTICULAR CANCER is one of the most common neoplasms among 20–40 year old men [1]. The aetiology is unknown although cryptorchism predisposes to this malignancy [2]. Histologically, germ cell testicular cancer can be divided into seminomas and non-seminomas. Non-seminomas include mainly embryonal carcinoma, choriocarcinoma and teratoma [3]. The prognosis of patients with testicular cancer has dramatically improved over the last 20 years following the development of combination chemotherapy with bleomycin, etoposide and cisplatin. Over 70% of all testicular cancer patients are alive five years after diagnosis [4].

The response of metastatic testicular cancer to chemotherapy is usually evaluated by computed tomography (CT) and by measuring the serum levels of two well-established tumour markers, beta human chorionic gonadotropin (HCG) and alpha fetoprotein (AFP). Twenty per cent of testicular tumours are marker-negative. After chemotherapy, 30% of the patients still have residual tumour at CT [5, 6]. It is not possible to differentiate between malignant and scar tissue with CT or magnetic resonance imaging (MRI) [7]. Often surgery and histopathological analysis is necessary to disclose the nature of residual tumour after chemotherapy. In non-seminomas, this is a standard procedure [8].

The role of 2-(^{18}F)-fluoro-2-deoxy-D-glucose (FDG) as a tumour-seeking agent has been established in different types of cancer [9]. Because of its low rate of dephosphorylation and further metabolism, FDG is trapped into cells as fluorodeoxyglucose-6-phosphate [10]. The association between the grade of malignancy and high uptake of FDG has been established in lymphomas [11], brain tumours [12] and musculoskeletal tumours [13]. The detection of recurrent

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cancer is also possible with FDG-PET (position emission tomography) in cases where both CT and MRI show inconclusive findings [14].

The aim of the present study was to investigate whether residual testicular cancer seen in CT after chemotherapy could be reliably detected by FDG-PET.

PATIENTS AND METHODS

Patients

Fifteen patients aged 21–54 years (median 32 years) with radiographical abnormalities at CT after chemotherapy for metastatic testicular cancer were admitted to the study conducted in the Department of Oncology and Radiotherapy, Turku University Central Hospital and the Department of Oncology, Helsinki University Central Hospital between May 1995 and May 1996. All patients had CT scanning of the abdomen and thorax and the primary staging was performed according to the Walter Reed system [15]. Serum tumour markers and histopathological verification were obtained in each case before the start of therapy. The patient characteristics are presented in Table 1.

Four patients had seminomas and 11 had non-seminomas. One patient had recurrent disease. Primary histological verification was based on analysis of samples taken at surgery from the primary tumour ($n = 13$) or metastasis ($n = 2$). After standard chemotherapy with cisplatin, etoposide and bleomycin, histological verification of the residual tumour was obtained in 7 patients (47%). All PET scans were performed before surgery. The median time from PET scans to surgery was 18 days (range 6–58). Verification of the nature of the residual tumours in the remaining patients (53%) was based on information obtained from morphological studies, serum tumour markers and the length of event-free follow-up time of the PET study (median 16 months, range 8–20).

The study protocol was approved by the Ethical Committee of Turku University Central Hospital. Informed oral consent was obtained from each patient.

PET imaging

Twenty PET studies were performed in 15 patients. Five patients were studied twice. For 7 patients, the PET study was performed after four courses of chemotherapy, for the other 8 patients the number of courses of chemotherapy ranged from three to nine at the time of PET evaluation.

Table 1. The characteristics of 15 patients evaluated with FDG-PET

Patient no.	Age (years)	Histology	Stage
1	53	seminoma	IIA
2	50	seminoma	III
3	22	teratocarcinoma	III
4	32	embryonal carcinoma	IIC
5	36	embryonal carcinoma	III
6	32	teratocarcinoma	IIC
7	32	choriocarcinoma	III
8	28	embryonal carcinoma with teratoma	IIA
9	25	embryonal carcinoma with teratoma	IIB
10	24	embryonal carcinoma	III
11	21	choriocarcinoma	III
12	54	seminoma	IIC
13	26	embryonal carcinoma	III
14	54	seminoma	IIC
15	37	teratocarcinoma	IIB

FDG was synthesised as described by Hamacher and associates with slight modifications [16]. The radiochemical purity of the tracer was greater than 99%.

An ECAT 931/08-12 PET scanner (Siemens/CTI Corp., Knoxville, Tennessee, U.S.A.) was used for PET imaging. The device acquires 15 contiguous slices simultaneously with a slice thickness of 6.7 mm; the physical transaxial FWHM (full-width half-maximum) in the centre of the field of view is 6.7 mm [17].

To correct for photon attenuation, a transmission scan was obtained prior to emission imaging with a removable ring source containing ^{68}Ge (total collected counts over 150×10^6). A bolus of FDG (median 371 MBq, range 311–446 MBq) was injected into a peripheral vein of an upper extremity. An emission scan was acquired 45 min after injection for 15 min (3×300 s). Ten patients were studied at two bed positions. All data were corrected for deadtime, decay and photon attenuation and were reconstructed in a 128×128 matrix with a Hann filter (cut-off frequency 0.5).

The patients fasted for at least six hours before the PET study. At the beginning of the study, the median plasma glucose level was 5.3 mmol/l (range 4.7–6.3 mmol/l). None of the patients had diabetes.

Methods for PET analysis

Images were summed together over a period of 45–60 min and localisation of the tissues of interest were confirmed using the corresponding transmission and CT images. The visual analysis was graded as clearly positive (++) when high FDG uptake as a hot spot was seen, or suspect (+) when slightly enhanced accumulation of FDG compared with the expected normal distribution in the surrounding region was detected. Otherwise the image was interpreted as negative (–) for malignancy.

Elliptical regions of interest (ROIs) were drawn on the hot spots of the tumour and on the residual tumour seen at CT in the last frame of the dynamic imaging (or 60 min after FDG injection). The relative standard deviation of the measured average radioactivity concentration in a ROI was less than 13%. Each positive FDG accumulation in a tumour area was also calculated with an automated system defining a 3×3 mm maximum ROI within a larger, user-defined ROI [18].

Tracer accumulation in the ROIs was measured using the standardised uptake value (SUV), which is the radioactivity concentration in a ROI divided by the injected dose and the patient's weight [19]. The ROIs with the maximum average counts were selected to represent FDG uptake in the tissues.

CT imaging

CT scanning was performed every two months for all patients to evaluate the response of the tumours to chemotherapy. Scans were performed with General Electric or Philips scanners, for the area with the metastatic lesions at 5 or 10 mm intervals. Intravenous contrast enhancement was administered in all except two cases. The median interval between the PET study and the CT scanning was 17 days (range 0–52). The CT images were interpreted by an experienced radiologist without knowledge of the PET results or surgical or histological findings.

Table 2. The results of PET studies

Patient	PET Study	Site of suspected region	No. of lesions	Lesion size at CT (cm)	Visual score in PET	SUV	Histological diagnosis	Treatment or follow-up time after PET
Malignant								
1	1	mediastinum	1	1.8 × 1.8 × 2	+	3.4	not obtained	radiotherapy
7	2	lungs	2	1.5 × 1.5 and 2 × 1	+	2.3 and 3.0	choriocarcinoma	died
7	3	retroperitoneum	1	2.5 × 3 × 4	++	4.0	choriocarcinoma	died
10	4	lungs	2	2.5 × 3 × 2.5 and 2 × 2	++	2.4 and 9.5	not obtained	chemotherapy
11	5	lungs	2	6 × 6 and 3.5 × 3.5	+	1.6 and 1.6	not obtained	chemotherapy
14	6	retroperitoneum	1	3.5 × 1.5 × 3	++	3.8	not obtained	chemotherapy
15	7	retroperitoneum	1	4 × 2.5 × 3	−	1.6	teratocarcinoma	chemotherapy
Benign								
1	8	mediastinum	1	1.5 × 1.5	−	1.3	not obtained	14 months
1	8	lungs	1	5 × 3.5 × 4	++	5.5	radiation pneumonitis	14 months
2	9	mediastinum	1	3 × 2.5 × 4	−	1.6	not obtained	radiotherapy
2	10	mediastinum	1	3 × 2.5 × 4	−	1.9	not obtained	10 months
3	11	retroperitoneum	1	2 × 2	−	1.7	necrotic tissue	20 months
4	12	retroperitoneum	1	3 × 3 × 4	−	0.7	necrotic tissue	19 months
5	13	lungs	multiple	0.3 × 0.3	−	1.0	not obtained	20 months
6	14	retroperitoneum	1	4.5 × 4.5 × 4.5	−	1.9	not obtained	18 months
8	15	retroperitoneum	1	2.5 × 1.5	−	2.0	not obtained	18 months
9	16	retroperitoneum	1	4 × 4	−	2.0	chronic inflammation	19 months
11	17	lungs	2	3.5 × 3.5 and 2.2 × 2.2	−	0.8 and 1.0	not obtained	8 months
12	18	retroperitoneum	1	5 × 3.5 × 8	+	4.7	chronic inflammation	14 months
13	19	lungs	1	5.5 × 4	++	3.7	chronic inflammation	10 months
13	20	lungs	1	scar in 5 cm area	−	1.5	not obtained	8 months

+ +, clearly positive in visual analysis of PET study; +, suspect in visual analysis; −, negative in visual analysis.
PET study number is marked, because 5 patients were studied twice.

Statistical analysis

All patient data are expressed as median and range. The quantitative results between different groups were compared with the Mann–Whitney U-test. *P* values were calculated as two-sided comparisons.

RESULTS

In 20 PET studies, the uptake of FDG was measured in 25 regions because of a tumour detected at CT. Ten of these lesions were classified as malignant and 15 as benign, based on the histological findings ($n = 9$), or event-free follow-up time after PET study and the findings at CT or serum tumour marker levels ($n = 16$). The results of the PET findings are shown in Table 2.

Visual analysis: positive PET findings

In visual analysis, accumulation of FDG was detected in 9 out of 20 PET studies (45%). Five were graded as clearly positive (++) (Figure 1(a)) and four suspect (+). Six of the lesions with a high uptake of FDG were considered to represent persistent malignant tissue in final evaluation. Three proved to represent inflammatory changes in non-cancerous tissue.

Two of the six positive findings considered to represent malignant tissue were confirmed surgically: both were seen in one patient with choriocarcinoma (Patient no. 7, Table 2), who died after chemotherapy for intra-abdominal haemorrhage and at autopsy malignant tissue was found both in the lungs and the retroperitoneum (Figure 1(b)). Four patients with positive findings at PET were not operated upon (Patient nos. 1, 10, 11, 14) but were judged clinically to have active disease and therapy was continued. Two of these (Patient nos. 1 and 14) had large bulky seminoma. Patient no. 10 had advanced disease (stage III) and only three courses of chemotherapy had been given prior to the positive PET study. Two patients (nos. 7 and 11) had a positive PET study and an elevated HCG level (27 U/l and 424 U/l). The other 13 patients had normal serum tumour markers at the time of the PET study.

Three patients had a high uptake of FDG, but no viable tumour was found. One of these was a patient with an embryonal carcinoma and lung metastases (Patient no. 13, Table 2). After chemotherapy, the upper tumour in his left lung was resected and only necrosis was found. After 3 months, positive FDG accumulation was found in the left inferior lung (Figure 2(a)). The patient was re-operated upon and chronic inflammatory reactive tissue consisting mainly of large macrophages, was found (Figure 2(b)). After reoperation, a new PET study was negative. Patient no. 12 had accumulation of FDG in the tumour near the left kidney (Figure 2(c)). At surgery, benign granulomatous tissue was found. Also, this lesion consisted mainly of large macrophages with clear cytoplasm (Figure 2(d)). One other patient showed positive accumulation of FDG outside the suspected residual tumour area (Figure 2(e)). A radiation pneumonitis was diagnosed two months after radiotherapy at CT (Figure 2(f)), which resolved radiographically without any treatment in the follow-up CT scans.

Visual analysis: negative PET findings

Eleven PET studies were negative. In one of these (Patient no. 15), viable tumour was found at retroperitoneal lymphadenectomy.

Nine patients had negative findings at PET (Patient no. 2 twice), which were in agreement with their clinical and histological findings. Three patients underwent surgery, where necrotic tissue (Patient nos. 3 and 4) or granulomatous tissue (Patient no. 9) was found. The other 6 patients have been disease free after PET study during a median follow-up time of 16 months (range 8–20 months).

Patient no. 2 with seminoma was studied twice, although the first PET study after four courses of chemotherapy was negative. He had a very large bulk tumour in the mediastinum and two more cycles of chemotherapy and radiotherapy to a dose of 25 Gy were given. The tumour did not decrease in size at CT after additional treatment and no increased activity was found at PET. Since the second PET study, no progressive disease has occurred during a follow-up time of 16 months.

Findings in patient no. 15 were interpreted as false-negative. The PET study showed a high tracer accumulation in the bowel, which was considered normal and no increased activity in the nearby tumour area was seen. At surgery a 2.2 cm tumour with histologically active teratocarcinoma was found.

Quantitative analysis; standardised uptake value

In the PET study, tracer uptake was quantitated by calculating the standardised uptake value (SUV) for the tracer. Tracer uptake measurements obtained by the visually and automatically defined maximum ROIs were fully comparable. All except one metastatic testicular cancer accumulated FDG at PET. The median SUV value of metastatic tumours was 2.7 (range 1.6–9.5, $n = 10$) and that of benign residual tumours was 1.7 (range 0.7–5.5, $n = 15$). The difference between these groups was not significant, although a trend for difference was detected ($P = 0.063$) (Figure 3). The median SUV of inflammatory lesions was 4.2 (range 2.0–5.5, $n = 4$). When inflammatory SUV values were excluded from the analysis, the difference between malignant and benign tissue was significant ($P = 0.004$). The specificity, sensitivity and accuracy of FDG-PET were 77%, 86% and 80%, respectively. There was no difference in FDG uptake between different histological groups.

DISCUSSION

FDG-PET has been reported to have the potential to detect recurrent and residual testicular cancer [20, 21]. It is also well documented that inflammatory tissue accumulates FDG [22]. Our study confirms the applicability of FDG-PET to image postchemotherapy lesions, but also shows that it has limited sensitivity (86%) and specificity (77%) to disclose the nature of the imaged tissue after treatment. One malignant lesion was not detected in the visual and quantitative evaluation of FDG-PET scans and we found three false-positive cases, where increased FDG uptake was present in inflammatory tissue. In 2 patients, the inflammatory nature of the lesion was confirmed at surgery. The third case was diagnosed as radiation pneumonitis at CT. The single false-negative case of a residual teratocarcinoma was located in the retroperitoneal area close to a strong accumulation of FDG, that was considered as normal FDG uptake in the bowel. Consequently, no clear differentiation between bowel and tumour uptake could be made with certainty.

Figure 1. (a) Metastatic lesion of embryonal carcinoma in the inferior lobe of the left lung. A positive FDG accumulation with an SUV of 9.5. (b) Metastatic choriocarcinoma in the retroperitoneal area with an SUV of 4.0.

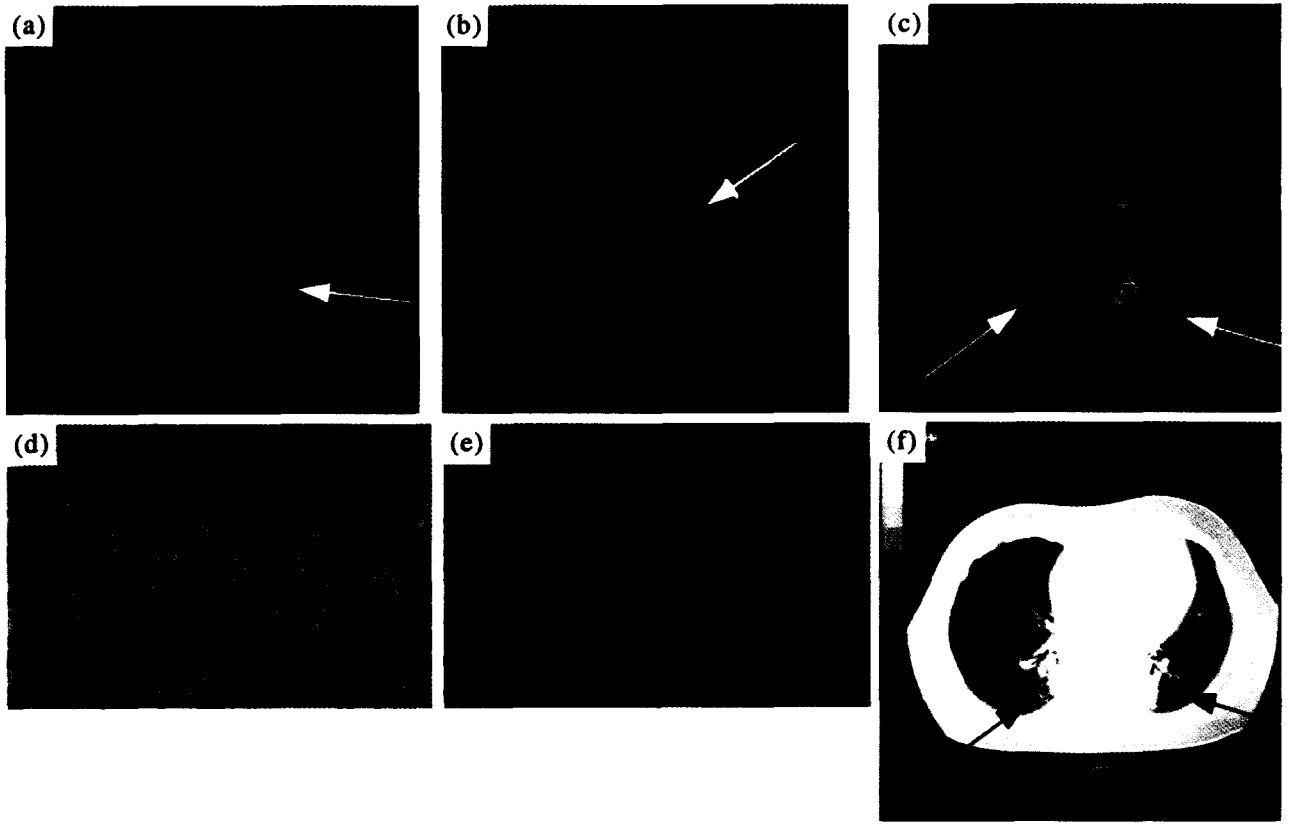

Figure 2. (a) A postchemotherapy PET scan of patient no. 13 with a positive accumulation of FDG in inferior lobe of left lung. (b) Histology of the pulmonary lesion in patient no. 13. The lesion was composed mainly of macrophages with an abundant clear cytoplasm. Among the macrophages, a few small lymphocytes are found. Some multinucleated giant cells are also seen in the lesion (magnification 400 ×, haematoxylin–eosin stain). (c) A positive accumulation of FDG in the tumour of patient no. 12 near the left kidney. (d) Histology of the lesion in patient no. 12 close to the left kidney. Most of the cells were large macrophages. Between the cells, some cholesterol clefts were found. Also a few lymphocytes were present (magnification 250 ×, haematoxylin–eosin stain). (e) FDG-accumulation in the posterior lung close to the vertebra in patient no. 1. The areas of high uptake were included in the volume of irradiation performed two months previously. (f) Concurrent CT scan at the same plane. The opacity seen in the lesion was suggestive of radiation pneumonitis. In the follow-up, the radiographic abnormality was resolved completely.

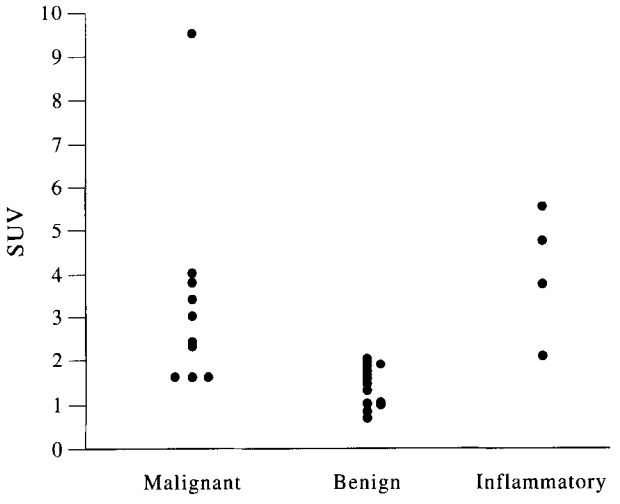

Figure 3. The SUV of malignant (n = 10), benign (n = 11) and inflammatory (n = 4) lesions.

It is interesting that in both false-positive lesions where histology was available, the lesions consisted mainly of macrophages. The number of lymphocytes was relatively small. In one true-negative case, histology after PET study indicated a benign granulomatous lesion, but only a few macrophages were found among lymphocytes. This suggests that macrophages were the major cellular compartment present in at least two out of the three false-positive findings [22]. The impact of accumulation of FDG in macrophages has been demonstrated previously in sarcoidosis, which clearly shows the limited specificity of FDG-PET to evaluate thoracic lesions [23].

Dohmen and associates [24] have also reported false-positive and -negative cases in testicular cancer imaged with FDG-PET. In a study of 19 postchemotherapy germ cell cancer patients, they found visually 2 false-positive and 7 false-negative cases. No quantitation of tracer uptake was made to facilitate comparison of their findings with the current study. However, Stephens and associates [20] could not quantitatively differentiate teratomas from residual necrosis or fibrosis, whereas Wahl and associates [25] have reported increased FDG uptake in the lung of a patient who was proven to have a teratoma. These studies suggest that FDG-PET is a valuable adjunct to select candidates for postchemotherapy surgical evaluation, but also indicates that it is not safe to refrain from surgery based on PET findings only.

Generally, SUV has been reported to be higher in tumour areas than in necrotic or scar tissue [14, 26]. Stephens and associates [20] reported a cut-off SUV of 5 for metastatic testicular cancer and for necrotic or fibrotic tissue. Only one case was reported as false-negative with a SUV of 3.2 in a series of 30 patients. By contrast, the difference between malignant and benign lesions was not significant in our study, when inflammatory findings (false-positives) were included ($P = 0.063$). The SUVs of inflammatory lesions (median 4.2, range 2.0–5.5) clearly overlapped the SUVs of malignant tissues (median 2.7, range 1.6–9.5) (Figure 3). If these inflammatory SUV values were excluded from the analysis, the difference between malignant and benign tissue became significant ($P = 0.004$), but this type of a priori classification is not feasible in the clinical setting.

The use of SUV to assess FDG uptake has been recently criticised [27]. SUV precludes analysis of FDG uptake kinetics which presumably allows a better characterisation of FDG metabolism in tumour tissue [28]. Loss of count recovery and partial volume effects may cause underestimation of true uptake when small lesions are evaluated. Because of the large size of the evaluated lesions in the current study, results are unlikely to be altered by correcting for differences in the object size. The improved diagnostic accuracy obtained by using algorithms to correct for object size remains to be demonstrated in future studies.

Advanced testicular cancer is a highly curative disease. It is very important that first-line-chemotherapy is adequate. Our study demonstrates that false-positive and -negative findings are seen when imaging residual tumour with FDG-PET and indicates a limited clinical use of FDG-PET. We feel that interpretation of FDG-PET scans should be made with caution when evaluating the presence of residual metastatic testicular cancer in FDG-positive lesions. A negative FDG-PET following chemotherapy of testicular cancer suggests eradication of malignant disease, but increased activity may represent either viable cancer or inflammatory tissue.

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