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FULL PAPER

Diagnostic accuracy of integrated ^{18}F -FDG PET/CT for restaging patients with malignant germ cell tumours

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Objective: Evaluation of utility of fluorine-18 fludeoxyglucose (^{18}F -FDG) positron emission tomography/CT (PET/CT) for restaging patients with primary malignant germ cell tumours (GCTs).

Methods: Data of 92 patients (age, 31.94 ± 10.1 years; male/female, 86/6) with histopathologically confirmed malignant GCTs (gonadal, 88; mediastinal, 4; seminomatous, 47 and non-seminomatous, 45) who underwent ^{18}F -FDG PET/CT for restaging (suspected recurrence/post-therapy evaluation) were retrospectively analysed. Two experienced nuclear medicine physicians reviewed the PET/CT images in consensus, qualitatively and semi-quantitatively [maximum standardized uptake value (SUVmax)]. Histopathology (if available) and clinical/imaging/biochemical follow-up (minimum of 6 months) were employed as the reference standard.

Results: ^{18}F -FDG PET/CT was interpreted as positive in 59 and negative in 33 patients. Local disease was seen in 5, nodal disease in 50 and distant metastasis in 22 patients. PET/CT was true positive in 49, false positive in 10, true negative in 30 and false negative in 3 patients. ^{18}F -FDG

PET/CT showed sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 94.2%, 75.0%, 83.0%, 90.9% and 85.8% overall; 90.0%, 74.0%, 72.0%, 90.9% and 80.8% in seminomatous GCT; and 96.8%, 76.9%, 91.1%, 90.9% and 91.1% in non-seminomatous GCT, respectively. Difference in PET/CT accuracy for seminomatous and non-seminomatous GCTs was not significant ($p = 0.263$). PET/CT demonstrated disease in 13 patients with negative/equivocal conventional imaging findings and in 9 patients with normal tumour markers. No site- or histology-based difference was seen in SUVmax.

Conclusion: ^{18}F -FDG PET/CT demonstrates high diagnostic accuracy for restaging patients with malignant GCTs. It has comparable diagnostic performance in both seminomatous and non-seminomatous malignant GCTs.

Advances in knowledge: The present article demonstrates high diagnostic accuracy of ^{18}F -FDG PET/CT for restaging both seminomatous and non-seminomatous malignant GCTs in a large patient population.

Germ cell tumour (GCT) is the commonest malignancy in males aged between 20 and 35 years.¹ With cisplatin-based chemotherapy, high long-term cure rates can be achieved in patients with GCTs.² Traditionally, the follow-up of patients with GCT is carried out with clinical examination, measurement of serum tumour markers [alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β -HCG) and lactate dehydrogenase (LDH)], and with conventional imaging investigations such as CT or MRI.³ A major issue in the management of GCTs is post-chemotherapy residual masses, which harbour viable tumour cells in about 11–37% of cases.⁴ Unfortunately, CT or MRI cannot predict the histology of residual masses and has limited specificity in post-therapy setting.⁵

Fluorine-18 fludeoxyglucose (^{18}F -FDG) positron emission tomography (PET) improves the visualization of tumour cells by imaging their upregulated glucose metabolism. Based on this unique feature, ^{18}F -FDG PET improves the differentiation of viable tumour from non-viable tissue.⁶ In many previous studies, ^{18}F -FDG PET had been evaluated in patients with seminomatous and non-seminomatous GCTs with post-chemotherapy residual masses, demonstrating promising but variable results.^{7–12} However, these studies had mostly employed PET alone, which suffers the limitations of having a lack of anatomical correlation, especially for detection of abdominopelvic disease, which can be overcome by the use of integrated PET/CT.¹³ Since few studies are available regarding the utility of integrated

PET/CT in restaging of patients with GCTs, in the present study, this issue has been addressed. Also, since the utility of ^{18}F -FDG PET/CT is limited for benign GCTs,¹¹ we only included patients with malignant GCTs in the present study.

METHODS AND MATERIALS

We retrospectively analysed the data of patients with GCTs who underwent ^{18}F -FDG PET/CT between May 2007 and December 2012. The inclusion criteria were histopathologically confirmed malignant GCT, previous treatment for GCT, restaging PET/CT (carried out either for suspected recurrent disease based on the findings of clinical examination/tumour marker/conventional anatomical imaging or for post-treatment assessment) and the presence of a definite reference standard (histopathology/a minimum of 6 months of clinical/imaging follow-up after PET/CT). The exclusion criteria were patients without any previous treatment and/or patients with PET/CT carried out less than 4 weeks before treatment and/or non-availability of a definite reference standard. A total of 92 patients satisfying these inclusion and exclusion criteria were finally analysed. Approval of the institutional ethical committee (All India Institute of Medical Sciences, New Delhi, India) was obtained for this retrospective study. In view of the retrospective study design, written informed consent was waived.

Fluorine-18 fludeoxyglucose positron emission tomography/CT acquisition

Prior to PET/CT, all patients fasted for 6 h or more. Blood glucose was $<7.7\text{ mmol l}^{-1}$ in all of them. After intravenous injection of 370 MBq (10 mCi) of ^{18}F -FDG, the patients rested in a quiet room. PET/CT imaging was performed 45–60 min later. PET/CT acquisition was performed on a dedicated hybrid scanner (Biograph 2; Siemens Medical Solutions, Erlangen, Germany). For the CT part of PET/CT, no intravenous contrast agent was administered. Patients were given additional water as negative contrast or iodinated oral contrast (70–100 ml; Ultravist® 370; Bayer Schering Pharma, Berlin, Germany) before PET/CT acquisition. CT was acquired on a spiral dual slice CT with the following parameters—tube potential of 130 kV, tube current of 60 mAs, slice thickness of 4 mm, pitch of 1, matrix of 512×512 pixels and pixel size of 1 mm. After completion of CT acquisition, PET acquisition of the same axial range was carried out with the patient in the same position. Three-dimensional (3D) PET acquisition was performed for 2–3 min per bed position, with a matrix of 128×128 pixels and slice thickness of 1.5 mm. CT-based attenuation correction of the PET emission images was employed. PET images were reconstructed by an iterative method with ordered subset expectation maximization algorithm (two iterations and eight subsets). The reconstructed attenuation-corrected PET images, CT images and fused PET/CT images were available for review in three planes (the axial, coronal and sagittal) along with maximum intensity projections and 3D cine mode.

Image analysis

Two experienced nuclear medicine physicians (PS and RK) with more than 6 years' experience in PET/CT retrospectively evaluated the studies in consensus. At the time of review, they were unaware of clinical/imaging findings. A focus of non-physiological ^{18}F -FDG uptake was searched for. Any positive findings on ^{18}F -FDG PET were anatomically localized on non-enhanced CT. However,

pulmonary lesions showing the characteristic appearance of metastasis on CT scans were taken as positive even in the absence of significant ^{18}F -FDG uptake. Based on these criteria, a PET/CT study was interpreted as either positive or negative for disease. Lesions seen on PET/CT were grouped into local disease, nodal metastasis and distant metastasis. Maximum standardized uptake value (SUVmax) was used for the purpose of semi-quantitative analysis. This SUV measurement was carried out using the default body weight [SUV = mean region of interest activity (MBq g^{-1})/injected dose (MBq)/body weight (g)]. The lesion with the highest SUVmax was taken for each group.

Reference standard

For validation of PET/CT findings, a combination of clinical or imaging findings (contrast CT, PET/CT, bone scan and MRI) or follow-up of blood tumour marker levels (minimum 6 months; median, 13 months; and range, 6–26 months) and/or histopathology (if available) was employed as the reference standard. Lesions that increased in size on follow-up imaging and/or showed increased ^{18}F -FDG uptake on follow-up PET/CT were classified as true positive (TP). Lesions that responded to anticancer therapy were also classified as TP. Lesions that did not show any change in size or showed decrease in size/ ^{18}F -FDG uptake on follow-up imaging without any intervening therapy were classified as false positive (FP). Also, patients with positive PET/CT but progressively falling tumour marker levels were classified as FP. Patients with negative PET/CT and increasing tumour marker levels were taken as false negative (FN).^{14,15}

Statistical analysis

The statistical software package SPSS® v. 11.5 (SPSS Inc., Chicago, IL) was used for statistical analyses. Mean and standard deviation were used for presenting continuous data. Numbers and percentages were used for presenting categorical data. Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated with 95% confidence interval for ^{18}F -FDG PET/CT on a per study basis. Continuous variables were compared among groups using Mann–Whitney test with two-tail probability. For comparison of proportions, χ^2 test was used. A $p < 0.05$ was considered significant.

RESULTS

Patients

Table 1 demonstrates the demographic, clinical and pathological characteristics of the 92 patients included in the present study. Of the 92 patients, 88 had primary gonadal and 4 had primary mediastinal GCTs. On the basis of the reference standard described in the Methods and materials section, at the time of PET/CT, 52/92 (56.5%) patients were positive and 40/92 (43.5%) patients were negative for recurrent/residual disease. A diagnosis was established with histopathology/fine needle aspiration cytology in 26 patients (30 lesions). Since pathological confirmation of all lesions was not technically or ethically feasible, the diagnosis was established with clinical/imaging/tumour marker follow-up for the remaining 66 patients. The follow-up imaging were contrast-enhanced CT ($n = 40$), ultrasound ($n = 6$), MRI ($n = 4$), bone scan ($n = 6$) and PET/CT ($n = 11$). A combination of these was available in many patients.

Table 1. Demographic and clinicopathological characteristics of the patients

Variable	Frequency	%
Age (years)		
Mean $\pm$ standard deviation	31.9 $\pm$ 10.1	–
Range	3–66	–
Sex		
Male	86	93.5
Female	6	6.5
Histopathology		
Seminomatous GCT	47	51.1
Seminoma	44	47.8
Dysgerminoma	3	3.3
Non-seminomatous GCT	45	49.0
Mixed GCT	12	13.0
Yolk sac tumour	4	4.3
Embryonal carcinoma	2	2.2
Choriocarcinoma	1	1.0
Endodermal sinus tumour	2	2.2
Immature teratoma	3	3.3
Not otherwise specified	21	22.8
Treatment before positron emission tomography/CT		
Surgery	6	6.5
Chemotherapy	9	9.8
Radiotherapy	1	1.1
Chemoradiotherapy	1	1.1
Surgery + radiotherapy	4	4.3
Surgery + chemotherapy	61	66.3
Surgery + chemoradiotherapy	10	10.9

GCT, germ cell tumour.

Fluorine-18 fludeoxyglucose positron emission tomography/CT results

Diagnostic accuracy

^{18}F -FDG PET/CT was interpreted as positive for recurrence/residual disease in 59/92 (64.1%) and negative in 33/92 (35.9%) patients. When compared with the reference standard, PET/CT was TP in 49, true negative in 30, FP in 10 and FN in 3 patients (Figures 1–3). The sensitivity, specificity, PPV, NPV and accuracy of ^{18}F -FDG PET/CT are detailed in Table 2. We have also separately calculated the sensitivity, specificity, PPV, NPV and accuracy of ^{18}F -FDG PET/CT in seminomatous (seminoma and dysgerminoma) and non-seminomatous GCTs (all others) groups. These are also detailed in Table 2. Between seminomatous and non-seminomatous GCT groups, no significant difference was seen in the sensitivity ($p = 0.372$), specificity ($p = 0.941$) and accuracy ($p = 0.263$) of ^{18}F -FDG PET/CT. ^{18}F -FDG PET/CT demonstrated disease in 13 patients with negative/

equivocal conventional imaging findings and 9 patients with normal tumour markers.

Site of disease

The site of recurrent/residual disease as seen on ^{18}F -FDG PET/CT are detailed in Table 3. Lymph nodes were the commonest site of disease on PET/CT followed by distant metastasis. The lymph nodal groups involved included abdominal ($n = 37$), pelvic ($n = 12$), thoracic ($n = 10$), supraclavicular ($n = 3$), axillary ($n = 3$), cervical ($n = 2$) and inguinal ($n = 2$). In about 24% of patients, metastasis to distant organs was seen on PET/CT. Lungs were the commonest site of distant metastasis followed by the bone and liver. Ten patients had FP results (node, nine and lung, one), which were later found to be benign lesions. Of these nine nodal lesions, four were found to be residual post-therapy inflammation by histopathology ($n = 3$) and follow-up ($n = 1$). Three nodal lesions were confirmed to be tuberculosis on biopsy. The other two were non-specific inflammation. The lung lesion disappeared on follow-up CT without any treatment and was regarded as non-specific inflammation. All these patients had normal tumour markers. Of three patients in the present study with FN PET/CT results, one had mature teratomatous component on histopathology. The other two had small residual tumour in post-therapy masses on histopathology but negative PET/CT.

Semi-quantitative analysis

The lesion with the highest SUVmax value on each PET/CT study was used for semi-quantitative analysis. On semi-quantitative analysis, the overall mean lesion SUVmax was 5.2 ± 2.6 (median, 4.9 and range, 0.9–12.5). The mean SUVmax of local lesions was 6.2 ± 3.1 (median, 6 and range, 3.5–11.5), nodal metastasis was 5.1 ± 1.9 (median, 4.9 and range, 2.5–11.6) and organ metastasis was 5.2 ± 3.7 (median, 5.5 and range, 0.9–12.5). We did not find any significant difference between the SUVmax of local lesions and nodal lesions ($p = 0.473$) or local lesions and distant organ metastasis ($p = 0.617$). Similarly, the SUVmax of nodal metastasis was not significantly different from that of distant organ metastasis ($p = 0.713$). Comparison of lesion SUVmax between seminomatous and non-seminomatous GCTs did not reveal any significant difference (5.9 ± 2.5 vs 5.4 ± 2.7 ; $p = 0.575$).

DISCUSSION

Periodic measurement of serum tumour markers (AFP, β -HCG and LDH) is an easy tool for disease assessment in patients with GCTs.¹⁶ However, as it cannot localize the site of disease, supplementation with imaging is necessary. Contrast-enhanced CT is usually the modality of choice. However, it has significant limitations in post-treatment setting—an inability to differentiate viable from non-viable masses and to detect disease in normal-sized nodes.¹⁷ ^{18}F -FDG PET/CT might be a supplemental biomarker and is superior to CT for restaging patients with GCT.¹⁸ Currently, limited numbers of publications exist regarding the utility of ^{18}F -FDG PET/CT in GCTs, mostly in a small heterogeneous population with conflicting results. Although ^{18}F -FDG PET/CT is currently recommended for post-therapy evaluation of advanced stage seminomatous GCTs,¹⁹ it is not recommended in post-therapy evaluation of non-seminomatous GCTs, apart

Figure 1. A 32-year-old male with seminoma, post right inguinal orchiectomy. He presented with rising serum lactate dehydrogenase levels. The axial contrast-enhanced CT (a) image of the abdomen revealed centimetre-sized minimally enhancing left para-aortic lymph node (arrow). The maximum intensity projection positron emission tomography (PET) (b) image revealed focal fluorine-18 fludeoxyglucose (^{18}F -FDG) uptake in the abdomen (arrow). Also noted was the conspicuous physiological ^{18}F -FDG uptake in brown fat. The axial PET/CT (c) image revealed intense ^{18}F -FDG uptake in the para-aortic node (arrow; maximum standardized uptake value, 5.5). Fine needle aspiration cytology confirmed the diagnosis. The node disappeared after chemotherapy.

from the setting of clinical trials.²⁰ Therefore, further evidence pertaining to the usefulness of ^{18}F -FDG PET/CT in GCTs is needed.

The present study analysed 92 patients with GCTs who underwent restaging ^{18}F -FDG PET/CT following treatment, either for suspected recurrence or for post-therapy monitoring. ^{18}F -FDG PET/CT analysis showed sensitivity, specificity, PPV, NPV and accuracy of 94.2%, 75.0%, 83.0%, 90.9% and 85.8%, respectively. These results correlate with the recently published study by Ambrosini *et al.*²¹ The specificity was, however, on the lower side, possibly because of the higher prevalence of infective/inflammatory pathology in our patient population from a developing country. A recent study by Ambrosini *et al.*²¹ showed

higher sensitivity of ^{18}F -FDG PET/CT for seminoma lesion detection compared with non-seminoma tumours (92% *vs* 77%). The heterogeneity of the patient population and inclusion of multiple PET/CT for the same patient was possibly responsible for the difference. In the present study, no significant difference was seen in the diagnostic performance of PET/CT between seminoma and non-seminoma GCTs, thereby highlighting its utility in both the histopathological groups.

Lymph nodes were the most common site of disease involvement on PET/CT. Abdominal nodes ($n = 37$) were most commonly involved followed by pelvic ($n = 12$) and thoracic nodes ($n = 10$). As expected, among the abdominal nodes, retroperitoneal lymph nodes were the most common involved. The lung

Figure 2. A 45-year-old male with yolk sac tumour of the right testis with scrotal skin involvement and retroperitoneal nodal metastasis. He underwent left orchiectomy and retroperitoneal lymph nodal dissection, followed by chemotherapy. He presented with raised serum α -fetoprotein levels, and restaging fluorine-18 fludeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/CT was performed. The maximum intensity projection PET (a) image showed focal ^{18}F -FDG uptake in the left scrotal region (arrowhead), bilateral lungs (solid arrows), mediastinal and supraclavicular region (broken arrows). Axial CT (b) and PET/CT (c) images revealed small ^{18}F -FDG avid [maximum standardized uptake value (SUVmax), 2.1] local recurrence in the left scrotal sac (arrowhead) along with hydrocoele. Also noted were metastases to the lungs (d, e: arrow; SUVmax, 7.5), supraclavicular node (f, g: broken arrow; SUVmax, 3.0) and mediastinal nodes (h, i: broken arrow; SUVmax, 5.6). He was started on chemotherapy but died of progressive disease 8 months later.

Figure 3. A 26-year-old male with seminoma left testis with retroperitoneal lymph nodal metastasis, who underwent left orchiectomy followed by chemotherapy. Post-treatment axial contrast CT images (a, b) revealed lobulated retroperitoneal lymph nodal masses (arrows) with large areas of necrosis and specks of calcification. Fluorine-18 fludeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/CT was done for evaluation of this post-therapy lymph nodal mass. Axial PET/CT images (c, d) revealed low-grade ^{18}F -FDG uptake (broken arrows; maximum standardized uptake value, 2.1) in the non-necrotic solid components of the nodal masses (arrows), suggestive of minimal residual disease. On maximum intensity projection PET (e) image, no other site of metastasis was seen. A note was made of physiological ^{18}F -FDG uptake in brown fat. The patient underwent retroperitoneal nodal dissection. Post-operative histopathology was negative for any viable tumour. ^{18}F -FDG PET/CT was false positive in this patient.

was the most common site of distant metastases on PET/CT. FP findings on PET/CT were seen in 10 patients. Because of the non-specific nature of ^{18}F -FDG, it can also accumulate in infective/inflammatory lesions, and therefore these FP results as not surprising.²² Also, low-grade ^{18}F -FDG uptake can be seen in the residual masses for a variable time after chemotherapy and radiotherapy. The inflammatory lesions resulting in FP ^{18}F -FDG PET/CT results have also been documented in results published by other groups.^{9,21} Hence, when there is discrepancy between tumour markers and PET/CT findings, tissue diagnosis should be obtained. Three patients in the present study had FN PET/CT results. Because of their low-grade glucose metabolism, teratomas can lead to FN results on ^{18}F -FDG PET/CT.²³ Similarly, microscopic disease or small tumour can also be the reason behind FN PET/CT results. We found no significant difference in the ^{18}F -FDG uptake (SUVmax) of lesion at various sites in the present study. Also, no significant

difference was seen in the ^{18}F -FDG uptake of seminomatous and non-seminomatous GCT lesions. This might represent the fact that biological aggressiveness and not the site of lesion or primary histopathology is the major determinant of ^{18}F -FDG uptake in GCTs.

In post-therapy patients with GCTs, ^{18}F -FDG PET/CT is extremely useful in identifying the sites of disease when circulating serum tumour markers are elevated. However, it can even detect disease in patients with normal tumour markers.²¹ In the present study population, ^{18}F -FDG PET/CT demonstrated recurrent lesions in nine patients with normal serum tumour markers. In the backdrop of known limitations of tumour markers for detection of recurrent disease in GCTs, this finding assumes important clinical significance. In addition, in 13 patients with negative/equivocal conventional imaging results, ^{18}F -FDG PET/CT was positive and helped in detecting the

Table 2. Performance of fluorine-18 fludeoxyglucose positron emission tomography/CT on per study-based analysis (results with 95% confidence interval)

Parameters	Overall	Seminomatous GCT	Non-seminomatous GCT
Sensitivity	94.2% (84.0–98.7)	90.0% (68.3–98.7)	96.8% (83.7–99.9)
Specificity	75.0% (58.8–87.3)	74.0% (53.7–88.8)	76.9% (46.1–94.9)
Positive predictive value	83.0% (71.0–91.5)	72.0% (50.6–87.9)	91.1% (76.3–98.1)
Negative predictive value	90.9% (75.6–98.0)	90.9% (70.8–98.8)	90.9% (58.7–99.7)
Accuracy	85.8%	80.8%	91.1%

GCT, germ cell tumour.

Table 3. Sites of recurrence/residual disease on fluorine-18 fludeoxyglucose positron emission tomography/CT (PET/CT)

Sites ^a	n (%)
Local	5 (8.4)
Nodes	50 (84.7)
Distant organs	22 (37.2)
Lung	14 (23.7)
Bone	7 (11.8)
Liver	4 (6.7)
Adrenal	1 (1.6)

^aOf the total 59 PET/CT studies positive for disease, many patients had more than one site of recurrence/residual disease.

disease. When there is discordance between tumour marker levels and conventional imaging findings, ¹⁸F-FDG PET/CT appears to be particularly beneficial, and this correlates with the published literature.¹³ A major advantage of ¹⁸F-FDG PET/CT is whole body nature of the study, which can detect or exclude viable tumours at different sites in a single examination.

We must acknowledge the limitations of the present study. First and foremost, the retrospective design of the present study is an important limitation. It might have introduced significant selection bias. Second, the lack of a pathological reference standard in all of the patients was also a limitation. Using clinical/tumour marker/imaging follow-up in place of the pathological reference standard can bias the specificity of test results. Although ideal, histopathology is difficult to obtain for all lesions, especially for distant sites, because of ethical and technical reasons. Finally, conventional imaging (CT/MRI) was not available for all patients, and hence no comparison was attempted. Although results favour PET/CT over conventional imaging, in the absence of systematic analysis, no definite comments could be made. Prospective multicentre studies addressing these shortcomings of the present study are warranted.

CONCLUSION

¹⁸F-FDG PET/CT demonstrates high diagnostic accuracy for restaging patients with malignant GCTs. It has comparable diagnostic performance in both seminomatous and non-seminomatous malignant GCTs. Further prospective studies addressing this topic are required for correctly delineating the role of ¹⁸F-FDG PET/CT for restaging malignant GCT.

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