

Is Positron Emission Tomography Reliable to Predict Post-Chemotherapy Retroperitoneal Lymph Node Involvement in Advanced Germ Cell Tumors of the Testis?

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Purpose: To evaluate if 18 fluorodeoxyglucose positron emission tomography (18FDG-PET) scan could identify post-chemotherapy retroperitoneal lymph node (RPLN) involvement in advanced germ cell tumors of the testis.

Materials and Methods: Between January 2005 and January 2009, 16 patients with advanced germ cell tumors of the testis underwent RPLN dissection (RPLND) following chemotherapy. Before RPLND, abdominal computed tomography (CT), magnetic resonance imaging (MRI), and 18FDG-PET were performed in all the patients. Findings on 18FDG-PET were compared with pathological evaluation of the removed lymphatic tissue.

Results: Both abdominal CT and MRI demonstrated retroperitoneal masses in all the patients following chemotherapy. Although PET did not demonstrate any activity in 8 patients, tumor was detected histopathologically. In 1 patient, 18FDG-PET demonstrated activity; however, no tumor was detected on pathology. Of the remaining 7 patients, 18FDG-PET findings were concordant with the histopathological findings. No activity was detected in 2 patients with no tumors whereas all 5 patients harboring viable tumor cells showed positive 18FDG-PET activity. In our study, sensitivity and specificity of 18FDG-PET in detecting RPLN involvement were detected to be 39% and 67%, respectively.

Conclusion: 18FDG-PET imaging does not seem to be a reliable method in detecting RPLN involvement in advanced germ cell tumors of the testis following chemotherapy. Therefore, we neither recommend routine use of 18FDG-PET scanning nor decide the treatment work-up by solely relying on the 18FDG-PET findings in this patient group.

Keywords: testicular neoplasms, lymph nodes, positron-emission tomography, sensitivity and specificity

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INTRODUCTION

Chemotherapy is a treatment modality for patients with or without retroperitoneal lymph node (RPLN) involvement after radical orchiectomy.⁽¹⁾

Those patients with a residual retroperitoneal mass after chemotherapy are subject to

retroperitoneal lymph node dissection (RPLND). Since it is impossible to determine whether these lymph nodes harbor viable tumor cells postoperatively. Even tumor markers are within normal limits. Conventional radiographic evaluations, including computed tomography (CT) or

magnetic resonance imaging (MRI) fall short to identify viable tumor cells in such situations. Positron emission tomography with the use of 18 fluorodeoxyglucose (18FDG-PET) has been developed to identify viable tumor cells depending on the presumed metabolic activity in viable tissues. It has been so far shown that this holds true for several different tumors, including breast cancer, malignant melanoma, and colorectal cancer.⁽²⁻⁴⁾

The purpose of present study is to investigate if 18FDG uptake on PET scans after chemotherapy is an efficient way of identifying viable tumor cells in patients with testicular tumors who received chemotherapy and underwent RPLND for their residual retroperitoneal masses.

MATERIALS AND METHODS

Between January 2005 and January 2010, we performed RPLND on 16 patients with advanced germ cell tumors of the testis following chemotherapy. Before RPLND, abdominal CT, MRI, and 18FDG-PET were performed in all the patients. Tumor markers, including alpha-fetoprotein, beta subunit of human chorionic gonadotropin, and lactate dehydrogenase were all within normal limits in all the patients before performing RPLND. Patients' characteristics are summarized in Table 1.

We retrospectively evaluated if 18FDG uptake on PET scans after chemotherapy is an efficient way of identifying viable tumor cells in patients with testicular tumors who received chemotherapy and underwent RPLND for their residual retroperitoneal masses.

18FDG-PET scan was performed on full-ring PET and PET-CT cameras. The assessment included scanning of an image quality phantom, establishment of image reconstruction parameters, and assessment of local quality control procedures. Following 6-hour fasting, 350 to 400 MBq 18FDG was administered and a non-attenuation-corrected "halfbody" scan was performed. The emission scan was carried out to initiate 1 hour following injection. An attenuation-corrected local view was obtained over an approximately 20-cm field of view from

the celiac lymph nodes (LNs) to the iliac LNs. Reconstruction of the images was performed due to the ordered subset expectation maximization algorithm. All PET scans were reviewed and reported by the department of nuclear medicine. In case of increased 18FDG uptake detection compared to the normal surrounding tissue, the 18FDG-PET scan was considered as positive regarding metastatic disease.⁽⁵⁾

Advanced germ cell testis tumor is regarded as presence of systemic disease, including the retroperitoneum detected by radiological imaging modalities, such as CT, MRI, and PET. According to American Joint Committee on Cancer Staging System, advanced germ cell testis tumors are regarded as stage IIc and stage III for advanced seminoma and stage IIb and higher stages for advanced nonseminomatous germ cell tumors (NSGCT).⁽⁶⁾

At our department, in compliance with the advancements in technique of RPLND, we have adopted modification of surgical templates and used modified template for RPLND. In our technique, we strictly adhere to the surgical techniques and through a midline abdominal incision, we thoroughly remove all the interaortocaval and ipsilateral LNs between the level of renal vessels and bifurcation of the common iliac artery. We minimize the contralateral dissection, particularly below the inferior mesenteric artery. On the left side, the following LNs are dissected: left iliac, pre-aortic, para-aortic, and interaortocaval nodes. On the right side, right iliac, paracaval, interaortocaval, pre-aortic, and para-aortic LNs are dissected.⁽⁶⁾

RESULTS

The mean patients' age was 29 ± 7 years (range, 23 to 46 years). The pathological findings were mixed germ cell tumor ($n = 11$), embryonal carcinoma ($n = 2$), teratoma ($n = 2$), endodermal sinus tumor ($n = 1$), and seminoma ($n = 1$). The chemotherapeutic regimens were as below: Bleomycin (B), etoposide (E) and cisplatin (P): BEP (4 cycles, $n = 13$), BEP (3 cycles, $n = 1$), BEP (2 cycles, $n = 1$), and BEP (4 cycles) + EP (2 cycles) ($n = 1$).

Table 1. Characteristics of patients who underwent RPLND for testis tumor and comparison of their abdominal CT, MRI, and PET findings with RPLND pathologies*

Patient Number	Testis tm age	Testis tumor pathology	CT & MRI findings	Maximum RPLN size on CT & MRI	18FDG-PET findings	Pre-operative chemotherapy	Operative findings	RPLND pathology
False (-) Group (n = 8)								
1	34	Left Embryonal carcinoma, intratubular germ cell neoplasia	Left para-aortic, left renal hilar masses	6.0 × 3.0 × 3.0 cm	No activity	BEP (4 cycles)	Interaorticaval and para-aortic masses	Mature cystic teratoma
2	35	Right Mixed germ cell tm (seminoma, yolk sac tm, immature teratoma)	Para-aortic, pericaval, left parailiac masses	5.0 cm	No activity	BEP (4 cycles)	Inter aorta-caval and para-caval masses	Mature cystic teratoma
3	28	Left Teratoma	Left para-aortic, pre-aortic, left renal hilar masses	4.5 × 3.8 × 3.2 cm	No activity	BEP (4 cycles)	Left renal hilar mass	Mature cystic teratoma
4	29	Left Mixed germ cell tm (embryonal carcinoma, choriocarcinoma, yolk sac tm, seminoma)	Left renal hilar, para-aortic masses	3.0 × 5.0 cm	No activity	BEP (4 cycles)	Inter aorta-caval, para-aortic, renal hilar masses	Metastatic teratoma and yolk sac tm
5	23	Left Embryonal carcinoma, mature teratocarcinoma	Left para-aortic, renal hilar masses	2.0 cm	No activity	BEP (4 cycles)	Left para-aortic, interaorta-caval, and renal hilar 2 × 2 cm mass	Immature teratoma
6	24	Right Mixed germ cell tm (embryonal carcinoma, yolk sac tm)	Left para-aortic mass	2.5 cm	No activity	BEP (4 cycles)	Interaorta-caval and right external iliac masses	Mature teratoma
7	33	Left Embryonal carcinoma	Left renal hilar, left iliac masses	5.0 × 5.0 cm	No activity	BEP (4 cycles) and EP (2 cycles)	Left renal hilar and interaorta-caval masses	Mature cystic teratoma
8	23	Right Embryonal carcinoma	Right para-aortic mass	9.0 cm	No activity	BEP (4 cycles)	Paracaval 10 × 5 cm mass	Teratocarcinoma
False (+) Group (n = 1)								
1	25	Right Mixed germ cell tm (embryonal carcinoma, yolk sac tm, teratoma)	Para-aortic mass	6.8 × 6.5 cm	Para-aortic mass activity	BEP (4 cycles)	Interaorta-caval and paracaval masses	Tm necrosis
Concordant Group (n = 7)								
1	26	Left Mixed germ cell tm	Para-aortic masses	1.8 cm	Para-aortic mass activity	BEP (4 cycles)	Interaorta-caval, precaval, para-aortic, left and para-caval masses	Immature teratoma
2	25	Right Seminoma	Para-aortic mass	3.0 × 1.0 cm	Right common iliac and external iliac activity	BEP (4 cycles)	4 cm mass next to right common iliac vein	Seminoma
3	46	Right Immature teratoma	Para-aortic, retro-caval masses	8.0 × 6.0 cm	Para-aortic, retro-caval and interaorta-caval activity	BEP (3 cycles)	Para-aortic, interaorta-caval, paracaval maximum 12 cm masses	Mature cystic teratoma
4	29	Left Endodermal sinus tm	Left renal hilar mass	10 × 7 × 8 cm	Activity on left psoas muscle at L3 level	BEP (4 cycles)	Para-aortic 8 × 6 cm mass	Melanistic findings secondary to chemotherapy
5	36	Left Teratoma, yolk sac tm	Left renal hilar mass	3.8 × 4.0 cm	Left para-aortic mass activity and mass activity between right mediastinum and liver	BEP (4 cycles)	Masses located on left paraaorta-caval superior to inferior mesenteric artery	Yolk sac tm
6	41	Left Embryonal carcinoma, seminoma	Left para-aortic mass	2.8 × 3.0 × 2.4 cm	No activity	BEP (4 cycles)	Interaorta-caval, left para-aortic masses	Lymphocyst
7	29	Left Mixed germ cell tm (embryonal carcinoma, immature teratoma)	Para-aortic and para-caval lymph nodes	2.0 × 1.6 cm	No activity	BEP (2 cycles)	Interaorta-caval, left para-aortic masses	Sinus histiocytosis and reactive lymphoid hyperplasia

*CT indicates computed tomography; MRI, magnetic resonance imaging; 18FDG-PET, 18fluorodeoxyglucose positron emission tomography; RPLND: retroperitoneal lymph node dissection; tm, tumor; RPLN, retroperitoneal lymph node; BEP: bleomycin, etoposide, cisplatinum; and EP, etoposide, cisplatinum.

Both abdominal CT and MRI demonstrated retroperitoneal masses in all the patients following chemotherapy. Mean retroperitoneal mass size detected on CT or MRI was 4.9 ± 2.6 cm (range, 1.8 to 10 cm). Characteristics of CT, MRI, and 18FDG-PET scans are demonstrated in Table 1 with histopathological findings.

Of 16 patients, PET was not able to detect residual tumor in the RPLND specimen following chemotherapy in 8 (50%) patients (False Negative Group). Positron emission tomography was able to correctly detect residual tumor in the RPLND specimen in 7 (43.8%) patients (Concordant Group) (Table 1). In the remaining 1 (6.2%) patient, although PET detected activity, necrosis was demonstrated pathologically following RPLND (False Positive Group) (Table 1). Other patients' parameters are summarized in Table 1.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 18FDG-PET in detecting RPLN involvement were 39%, 67%, 83%, and 20%, respectively (Table 2).

Pathological findings detected following chemotherapy and RPLND included mature cystic teratoma (n = 5), metastatic teratoma and yolk sac tumor (n = 1), immature teratoma (n = 2), mature teratoma (n = 1), teratocarcinoma (n = 1), seminoma (n = 1), metastatic findings secondary to chemotherapy (endodermal sinus tumor) (n = 1), yolk sac tumor (n = 1), tumor necrosis (n = 1), lymphocysts (n = 1), and sinus histiocytosis and reactive lymphoid hyperplasia (n = 1).

Including 16 patients in our study, CT and MRI demonstrated mass lesion(s) in the retroperitoneal area. Following RPLND, tumor was detected histopathologically in all, but 3 patients. Necrosis, lymphocyst, and lymphoid hyperplasia were detected in these 3 patients (Table 1).

Table 2. Demonstration of 18FDG-PET results related to presence of live tumor cells in the RPLND specimens.*

Presence of live tumor cells in the RPLND specimens	18FDG-PET (+)	18FDG-PET (-)
	(n)	(n)
Live tumor cells (+)	5	8
Live tumor cells (-)	1	2

*18FDG-PET indicates 18 fluorodeoxyglucose positron emission tomography; and RPLND, retroperitoneal lymph node dissection.

DISCUSSION

In the recent years, PET has very commonly been used in oncologic urology. Positron emission tomography provides images of physiologic and metabolic processes by using positron emitters. The metabolic PET tracer that is most commonly used in oncology scans is 18FDG. Increased cellular proliferation in malignant tumors leads to increased FDG use.⁽⁷⁾ Positron emission tomography scan gives functional information of the tissues; however, its ability to localize lesions is poor.⁽⁸⁾ On the other hand, CT is superior in giving anatomical details of the lesions. Therefore, these imaging modalities are combined as 18FDG-PET scan in order to obtain both anatomical and functional tissue images in clinical practice.⁽⁸⁾ 18FDG-PET scan has been suggested to be superior to standard imaging modalities in detection of disease extent in a number of tumors;⁽²⁻⁴⁾ however, it is increasingly being used in evaluation of metastatic testis tumors.

Currently, limited number of publications exist in the literature regarding testis tumors (seminomatous versus nonseminomatous) and the use of PET. Our study included patients who all underwent RPLND following chemotherapy with normal serum tumor markers; and they were mostly patients with nonseminomatous germ cell testis tumors (Table 1). In our series of 16 patients, PET was not able to detect residual tumor in the RPLND specimens following chemotherapy in 8 patients (Table 1). The impact of chemotherapy on the use of 18FDG by the tumor tissues in patients with testis tumor is not clear, which might affect PET findings and warrant further research. Current guidelines suggest post-chemotherapy RPLND in advanced seminomas with residual retroperitoneal masses if PET scan performed 6 to 8 weeks after chemotherapy is positive and also in NSGCTs for all residual radiographic lesions with negative or plateauing markers.⁽⁹⁾

Sensitivity, Specificity, PPV, and NPV of 18FDG-PET

In our study, sensitivity, specificity, PPV, and NPV of 18FDG-PET in detecting RPLN involvement were 39%, 67%, 83%, and 20%,

respectively. In a study on 46 patients with stage I NSGCT who did not receive chemotherapy, 18FDG-PET detected 70% of subjects who subsequently relapsed with metastatic disease. The sensitivity, specificity, and accuracy of PET were 70%, 100%, and 93%, respectively.⁽¹⁰⁾ Cremerius and colleagues obtained similar results comparing 18FDG-PET and RPLND findings in 12 patients with testis tumors.⁽¹¹⁾ De Santis and associates evaluated the clinical value of 18FDG-PET as a predictor of viable tumor in post-chemotherapy seminoma residuals (n = 19). The specificity, sensitivity, PPV, and NPV of 18FDG-PET were 100%, 80%, 100%, and 96%, respectively.⁽¹²⁾ Lower sensitivity, specificity, PPV, and NPV of 18FDG-PET detected in our series compared to the literature might be due to the effect of previous chemotherapy administered to our patients.

PET and Seminomatous testis tumors

18FDG-PET was suggested as a predictor of viable residual tumor in post-chemotherapy seminoma residuals.⁽¹²⁾ In that study, all the patients with residual lesions > 3 cm (n = 19) and 35 of 37 patients with residual lesions ≤ 3cm were correctly predicted by 18FDG-PET.⁽¹²⁾ Becherer and coworkers reported no false positive results whereas they had 3 false negative PET scans in a series of 56 patients with advanced seminomas.⁽¹³⁾ In our series, we had 1 patient with pure seminoma in which 18FDG-PET correctly detected RPLN involvement. We had additional 3 patients with mixed germ cell testis tumors having seminomatous components. Of these 3 patients, 18FDG-PET findings were false negative in 2 patients whereas they were concordant with the RPLND pathology in only 1 patient. Further studies with larger number of patients are needed in order to find out if 18FDG-PET could correctly detect RPLN involvement following chemotherapy in patients with advanced seminomas.

PET and Nonseminomatous testis tumors

Nonseminomatous germ cell tumors are reported to avidly take up 18FDG.⁽⁵⁾ In a study on 46 patients with stage I NSGCT, 18FDG-PET

detected 70% who subsequently relapsed with metastatic disease.⁽¹⁰⁾ In a multicenter study on patients with clinical stage I NSGCT, it was concluded that although PET identified some patients with disease not detected by CT scan, the relapse rate among PET-negative patients remained high suggesting that 18FDG-PET scanning does not seem to be sensitive enough in identification of patients at low risk of relapse.⁽⁵⁾ On the other hand, in a study by Hain and colleagues evaluating 31 patients with testis tumor, 18FDG-PET scan identified metastatic disease in 10 and was negative in 16 patients. There were no false positives, but 5 false negatives. They concluded that 18FDG-PET is capable of detecting metastatic disease at diagnosis that has not been identified by other imaging modalities.⁽¹⁴⁾

The German Multicenter Positron Emission Tomography Study Group evaluated the accuracy of 18FDG-PET for prediction of pathology compared with CT scan and serum tumor markers in a series of 121 patients with stage IIC or III NSGCT scheduled for secondary resection after cisplatin-based chemotherapy. Prediction of tumor viability with 18FDG-PET was accurate in 56% of the patients and sensitivity and specificity of 18FDG-PET were 70% and 48%, respectively. They concluded that 18FDG-PET is unable to give a clear additional clinical benefit to the standard diagnostic procedures, CT scan and serum tumor markers, in prediction of tumor viability in residual masses.⁽¹⁵⁾

Impact of RPLN size on 18FDG-PET findings

In our study, the smallest tumor size was 2 cm both in the false positive and false negative groups. Additionally, we had 3 patients with a 3-cm or less RPLN and 18FDG-PET correctly identified histopathologic findings in RPLND materials. On the other hand, 18FDG-PET was not able to identify correctly the histopathologic findings in RPLND specimens in 2 patients with mixed germ cell tumors, including seminoma components both having 5-cm RPLN. Some authors suggested tumor size as a parameter in detecting viable tumor in 18FDG-PET,^(16,17) whereas others did not find such a

relationship.^(18,19) It was reported that lesions particularly smaller than 1 cm in size can not be detected by 18FDG-PET.⁽¹⁹⁾ According to our results, we do not believe either RPLN size or tumor type affects the tumor detection reliability of 18FDG-PET.

Pitfalls and limitations related to 18FDG-PET

Pitfalls could be summarized as follows: 1) the problem of accurate image alignment; 2) misregistration errors; 3) artefactual mislocalization errors; 4) misplacement and mislocation of the lesions; 5) inflammatory and granulomatous tissues also show extensive FDG uptake; 6) lesions < 1 cm in size can not be detected; and 7) mature teratoma is indistinguishable from normal and necrotic tissue.^(8,19,20)

These pitfalls are explained to occur due to the possibility of misregistration of the CT and PET images and movement artifacts occurring due to respiration effects.^(8,19) Therefore, these scans have been suggested to be reviewed by experienced experts.⁽⁸⁾ In order to sort out these problems, respiration-averaged CT matching PET images, respiratory gating of the PET acquisition in improving misregistration issues, and using more detector rows in the scanner are currently being used.^(8,21,22)

Teratoma and 18FDG-PET findings

In our series, most of the RPLND pathologies were teratoma (mature or immature) in the false negative group and PET was able to correctly detect only 2 patients with teratoma following RPLND. In the literature, it was reported that FDG uptake was very low in teratomas and PET failed to detect or distinguish mature teratoma from necrosis or fibrosis because both accumulate very little or no FDG.^(19,23,24)

CONCLUSION

In conclusion, CT and MRI are frequently used in detection of RPLN and masses in advanced testis tumors; however, controversial reports exist regarding the use of 18FDG-PET scan in this setting. Although the number of patients in our study is limited, our results demonstrated

that 18FDG-PET imaging does not seem to be a sufficiently sensitive method in detecting RPLN involvement in advanced germ cell tumors of the testis following chemotherapy. Decision making solely relying on 18FDG-PET scan findings could easily lead to overtreatment or vice versa, particularly in this patient group. Therefore, pathologic evaluation of the surgically removed masses seems to be the most reliable method in final diagnosis, which would guide the final treatment approach.

CONFLICT OF INTEREST

None declared.

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