Can We Rely on PET in the Follow-Up of Advanced Seminoma Patients?

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Key Words

Fluorodeoxyglucose-positron emission tomography ·
Seminoma · Residual lesions

Abstract

The management of residuals after completion of chemotherapy in advanced seminoma is controversial. It has been proposed that fluorodeoxyglucose-positron emission tomography (FDG-PET) can be used as a follow-up. In this study we investigated FDG-PET as a follow-up tool in advanced seminoma patients treated previously with chemotherapy or radiotherapy. Thirty-seven patients assigned to an advanced seminoma group based on CT and/or FDG-PET/CT and then treated with chemotherapy were included in the study. All these patients underwent FDG-PET/CT examination as a part of the follow-up scheme. Patients underwent retroperitoneal lymph node dissection (RPLND), radiotherapy, or were followed clinically by CT and/or PET/CT every 6 months. In 8 cases FDG-PET was positive: 5 of them underwent RPLND and 3 radiotherapy. Two patients with negative FDG-PET but posi-

tive CT also underwent RPLND. The remaining patients with negative FDG-PET results were followed up. FDG-PET/CT was false positive in one case >3 cm and one <3 cm, in 6 cases >3 cm it was true negative. While FDG-PET can find a viable tumor, there also is an important question of false positive results. It was clinically proven that a negative FDG-PET was correlated with stable disease, but we were unable to examine specimens in these cases. Copyright © 2012 S. Karger AG, Basel

Introduction

Although seminoma is a relatively rare tumor, its incidence in Europe has been rising over the last 30 years. Approximately 25% of patients present with advanced stage disease [1]. After chemotherapy, radiologically detectable residual masses are found in about 60% of them [2–5] and relapses occur in 10–15% of these patients [6].

The optimal treatment of patients with persistent masses is not defined and differs among oncological cen-

Fig. 1. Histological specimens. **a** Residual lesion specimen, complete response after chemotherapy – necrosis of neoplastic tissue, $\times 200$. **b** Residual lesion specimen, partial response after chemotherapy – partial necrosis with presence of viable neoplastic tissue, $\times 200$.

ters – some authors suggest surgery for lesions with a diameter >3 cm, others recommend observation as long as the lesions do not grow [4, 7, 8]. The role of positron emission tomography (PET), which has already been shown to be a useful diagnostic tool in the management of non-seminomatous germ cell cancers [9–13], in the follow-up of seminoma is not yet fully defined.

In this study we present our experience with fluorodeoxyglucose-positron emission tomography (FDG-PET) as a follow-up tool in advanced seminoma patients treated previously with chemotherapy or radiotherapy.

Patients and Methods

We performed a retrospective analysis of 60 patients with histopathologically confirmed advanced seminoma out of 192 diagnosed in the years 2006–2011 using FDG-PET/CT due to metastatic germ cell cancer (fig. 1). Twenty-three patients were excluded from evaluation due to insufficient follow-up time or incomplete data recorded in files. Thirty-seven patients were assigned to an advanced disease group based on CT and/or FDG-PET/CT, and then treated with chemotherapy and/or radiotherapy. All patients were classified as a good-prognosis group according to IGCCCG, i.e. no nonpulmonary visceral metastases [14]. Chemotherapy protocols were BEP (bleomycin, etoposide, cisplatin), EP (etoposide, cisplatin), CEP (carboplatin, etoposide, bleomycin) and carboplatin in 12, 16, 1 and 4 patients, respectively. Four patients underwent radiotherapy alone, 3 received radiotherapy because of clinical symptoms of progression after chemotherapy and 4 were treated with radiotherapy and chemotherapy because of bulky disease in retroperitoneal lymph nodes. All these patients underwent FDG-PET/CT examination 1–4 months after chemotherapy or radiotherapy as a part of the follow-up scheme. Patients underwent retroperitoneal lymph node dissection (RPLND) or were followed clinically by CT and/or PET/CT every 6 months (fig. 2). In each case, the decision to perform RPLND was made individually by the oncologist and urologist. Patients who had been treated with radiotherapy did not, except for one case, qualify for RPLND. Comparative analysis was performed.

Table 1. Correlation of FDG-PET results, residual tumor diameter in CT and presence of viable neoplastic tissue (documented by histology or clinical follow-up)

		Viable tumor		Nonviable tumor	
		histology	follow-up	histology	follow-up
>3 cm	PET+	3	3	1	0
	PET–	0	0	2	8
<3 cm	PET+	0	0	1	0
	PET–	0	0	0	19

Results

PET/CT scans of 37 patients were evaluated. In 8 cases FDG-PET was positive: 5 of them underwent RPLND and 3 radiotherapy. Two patients with negative FDG-PET but positive CT also underwent RPLND. The median follow-up time counted from the date of PET scan was 40 months.

The 8 patients with a positive FDG-PET result had been treated with the following chemotherapy schemes: 5 of them received BEP, 2 received EP and 1 KEP. FDG-PET was false positive in the patient treated with KEP and one of the patients treated with EP. The time interval between the completion of chemotherapy and PET was 5 and 12 weeks in these patients.

Seven residual lesions were resected, 6 of which were >3 cm. Viable cancer was present in three histological specimens, all of which were >3 cm and positive in FDG-PET/CT. FDG-PET/CT was false positive in 1 case >3 cm and 1 case <3 cm; in 2 cases >3 cm it was true negative (table 1).

The remaining 30 patients who were not operated were followed clinically. In 3 of them the presence of a viable

Fig. 2. FDG-PET images. **a** A false positive result, no viable neoplastic cells were found in a specimen from RPLND. **b** A true positive result.

Table 2. Literature reports of application of FDG-PET in patients with seminoma

Study	Patients	Results
De Santis et al. [15], 2001	33 patients with postchemotherapy residuals	PET is a useful predictor of viable tumor, especially in residuals >3 cm
Ganjoo et al. [16], 1999	29 patients with postchemotherapy residuals	PET has no benefit in evaluation of postchemotherapy residuals
Becherer et al. [17], 2005	54 patients with postchemotherapy residuals	positive PET is highly predictive of viable tumor
Müller-Mattheis et al. [18], 1998	54 patients, 27 with pure seminoma, different stages	PET is useful in evaluation of postchemotherapy residuals, but not in staging
De Santis et al. [24], 2004	51 patients with postchemotherapy residuals	PET is the best predictor of viable residual tumor
Nuutinen et al. [25], 1997	15 patients with metastatic seminoma (4) or nonseminoma	PET has limited value in imaging of metastatic testicular cancer after chemotherapy
Johns Putra et al. [26], 2004	38 patients with metastatic germ cell tumors (8 with seminoma)	PET is a promising tool in detection of viable germ cell tumor after chemotherapy

tumor was reflected by clinical signs of progression in PET/CT and CT; they were treated with radiotherapy. Twenty-seven patients remained disease-free.

Discussion

Several papers comparing FDG-PET or PET/CT to CT in follow-up of advanced seminoma patients have been published, including three describing the results of prospective studies [15–17]. Müller-Mattheis et al. [18] analyzed 27 patients with pure seminoma and found that in 21 of them FDG-PET results were identical with those of the abdominal CT; therefore, PET does not add relevant information for this group of patients. In the next 6 patients with pure seminoma stage II B and II C, results were not conclusive. The authors noticed that FDG-PET cannot be considered a standard diagnostic tool in the

staging examinations in testicular cancer. It is of clinical relevance in patients who present residual tumor after chemotherapy, being helpful in finding viable tumor in residual masses, but cannot replace RPLND. The European Association of Urology recommends a CT scan every 6 months as a follow-up for advanced seminoma patients after chemotherapy. FDG-PET scan is also recommended in lesions >3 cm (if available); however, CT but not FDG-PET is recommended for disease staging [14].

Ganjoo et al. [16] conducted a prospective study of 29 patients with seminoma and residual disease. CT and PET scans were performed. In 19 patients negative PET scan results correlated with stable or decreasing residual mass size after primary chemotherapy in median follow-up of 11.5 months. More problematic were 10 patients after salvage chemotherapy. In this group, 1 patient had a positive PET scan in posterior mediastinum, but only necrotic tissue was found. The same patient had a negative

PET scan of the retroperitoneal mass, but relapsed in that area. Overall, 5 patients in this group had stable or decreasing mass, and 5 had disease relapse, but PET scans had no apparent benefit in evaluation of residual masses in seminoma. Literature reports of application of FDG-PET in patients with seminoma are shown in table 2.

The optimal management of residual masses remains a controversial matter, with the two main options being surgery and surveillance. Resection of residuals may be technically demanding and connected with increased morbidity; therefore, it is reserved only for patients with a high risk of viable tumor. A cutoff of >3 cm lesion size is commonly used, with some authors suggesting resection of all residual lesions >3 cm [3, 4, 8, 19, 20]. This strategy, however, results in overtreatment of nearly 60% of patients, as viable cancer cells are reported to be found only in 30–50% (37.5% in our study) of residuals >3 cm [4, 5, 7, 21–23]. Still, De Santis et al. [15] consider, based on their results and review of other studies, surgery to be the treatment of choice for residuals with a high risk of relapse, with more favorable results than surveillance. This opinion seems justified, especially if the high-risk group is defined as the ones with lesions >3 cm and positive in FDG-PET, as they found FDG-PET to be highly specific and observed no false negative results for residuals >3 cm [15, 24]. They showed that FDG-PET is the best predictor of viable neoplastic tissue in postchemotherapy seminoma residuals and should be used as a standard tool for clinical decision-making in this patient group.

While CT evaluates the number and size of residuals, FDG-PET provides information about the tissue metabolism rate, a potentially better indicator of viable neoplasm. Imaging of metastatic testicular cancer after chemotherapy, however, is difficult because of a potentially elevated accumulation of FDG in inflammatory tissues, which may lead to false positive results. Nuutinen et al. [25] in their study indicated a large overlap of standardized uptake values between metastatic and benign residual tumors. It should be emphasized that this study was extremely small and heterogeneous: 15 patients with metastatic seminoma or non-seminoma.

According to European Association of Urology guidelines, the treatment of choice in metastatic seminoma is radiotherapy on a para-aortic and ipsilateral iliac region, BEP or EP scheme chemotherapy in low-volume disease, and BEP or EP scheme chemotherapy in advanced metastatic disease [14]. The vast majority of patients included in this study received such treatment. One patient was treated with KEP scheme chemotherapy and radiotherapy because of kidney toxicity.

In our observations, FDG-PET was able to identify all 6 cases of viable residual lesions, all of them >3 cm, with only one false positive result. Another false positive PET result was observed in a case <3 cm. It must be emphasized that we have observed no false negative PET scans. Therefore, a conclusion can be drawn that patients with residual lesions, even >3 cm, can safely undergo mere surveillance, provided that FDG-PET is negative.

It is also worth mentioning that many studies critically assessing the role of PET in seminoma management were published before the era of PET/CT. It is known that PET alone can create much more false positive results than PET/CT.

Our study can be somewhat limited by the fact that it was not designed as a prospective one but rather is a retrospective analysis of application of FDG-PET in follow-up after chemotherapy of advanced seminoma. A further limitation is the small number of patients and heterogeneity of treatment.

Conclusions

FDG-PET can find a viable tumor – no false negative results were observed. Despite a considerable number of false positive results, FDG-PET/CT has an advantage over CT alone. It was clinically proven that a negative FDG-PET was correlated with stable disease, but we were unable to examine specimens in these cases. On the other hand, it has to be emphasized that 2 of 5 positive FDG-PET scans were proven false positive in surgical specimens. This can cause unnecessary surgical treatment. Small groups of patients and lack of pathological reports are limitations of this and other similar studies.

References

- 1 Thomas GM, Rider WD, Dembo AJ, et al: Seminoma of the testis: results of treatment and patterns of failure after radiation therapy. *Int J Radiat Oncol Biol Phys* 1982;8:165–174.
- 2 Peckham MJ, Horwich A, Hendry WF: Advanced seminoma: treatment with cis-platinum-based combination chemotherapy or carboplatin (JM8). *Brit J Cancer* 1985;52:7–13.
- 3 Motzer R, Bosl G, Heelan R, et al: Residual mass: an indication for further therapy in patients with advanced seminoma following systemic chemotherapy. *J Clin Oncol* 1987;5:1064–1070.

- 4 Puc HS, Heelan R, Mazumdar M, et al: Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan-Kettering Cancer Center. *J Clin Oncol* 1996;14:454–460.
- 5 Fossa SD, Oliver RT, Stenning SP, et al: Prognostic factors for patients with advanced seminoma treated with platinum-based chemotherapy. *Eur J Cancer* 1997;33:1380–1387.
- 6 Fléchon A, Bompas E, Biron P, et al: Management of postchemotherapy residual masses in advanced seminoma. *J Urol* 2002;168:1975–1979.
- 7 Herr HW, Sheinfeld J, Puc HS, et al: Surgery for a postchemotherapy residual mass in seminoma. *J Urol* 1997;157:860–862.
- 8 Schultz SM, Einhorn LH, Conces DJ Jr, et al: Management of postchemotherapy residual mass in patients with advanced seminoma: Indiana University experience. *J Clin Oncol* 1989;7:1497–1503.
- 9 Stephens AW, Gonin R, Hutchins GD, et al: Positron emission tomography evaluation of residual radiographic abnormalities in postchemotherapy germ cell tumor patients. *J Clin Oncol* 1996;14:1637–1641.
- 10 Sanchez D, Zudaire JJ, Fernandez JM, et al: 18F-fluoro-2-deoxyglucose-positron emission tomography in the evaluation of non-seminomatous germ cell tumours at relapse. *BJU Int* 2002;89:912–916.
- 11 Bomanji JB, Costa DC, Ell PJ: Clinical role of positron emission tomography in oncology. *Lancet Oncol* 2001;2:157–164.
- 12 Cerfolio RJ, Ojha B, Mukherjee S, et al: Positron emission tomography scanning with 2-fluoro-2-deoxy-d-glucose as a predictor of response of neoadjuvant treatment for non-small cell carcinoma. *J Thorac Cardiovasc Surg* 2003;125:938–944.
- 13 Becherer A, Jaeger U, Szabo M, et al: Prognostic value of FDG-PET in malignant lymphoma. *Q J Nucl Med* 2003;47:14–21.
- 14 Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, Horwich A, Laguna MP, European Association of Urology: EAU guidelines on testicular cancer: 2011 update. *Eur Urol* 2011;60:304–319.
- 15 De Santis M, Bokemeyer C, Becherer A, Stoiber F, Oechsle K, Kletter K, Dohmen BM, Dittrich C, Pont J: Predictive impact of 2-18fluoro-2-deoxy-D-glucose positron emission tomography for residual postchemotherapy masses in patients with bulky seminoma. *J Clin Oncol* 2001;19:3740–3744.
- 16 Ganjoo KN, Chan RJ, Sharma M, et al: Positron emission tomography scans in the evaluation of postchemotherapy residual masses in patients with seminoma. *J Clin Oncol* 1999;17:3457–3460.
- 17 Becherer A, De Santis M, Karanikas G, Szabó M, Bokemeyer C, Dohmen BM, Pont J, Dudczak R, Dittrich C, Kletter K: FDG PET is superior to CT in the prediction of viable tumour in post-chemotherapy seminoma residuals. *Eur J Radiol* 2005;54:284–288.
- 18 Müller-Mattheis V, Reinhardt M, Gerharz CD, Fürst G, Vosberg H, Müller-Gärtner HW, Ackermann R: Positron emission tomography with [18 F]-2-fluoro-2-deoxy-D-glucose (18FDG-PET) in diagnosis of retroperitoneal lymph node metastases of testicular tumors (in German). *Urologe A* 1998;37:609–620.
- 19 Horwich A, Paluchowska B, Norman A, et al: Residual mass following chemotherapy of seminoma. *Ann Oncol* 1997;8:37–40.
- 20 Friedmann EL, Garnick MB, Stomper PC, et al: Therapeutic guidelines and results in advanced seminoma. *J Clin Oncol* 1985;3:1325–1332.
- 21 Ravi R, Ong J, Oliver RT, et al: The management of residual masses after chemotherapy in metastatic seminoma. *BJU Int* 1999;83:649–653.
- 22 Fléchon A, Bompas E, Biron P, et al: Management of postchemotherapy residual masses in advanced seminoma. *J Urol* 2002;168:1975–1979.
- 23 Gietema JA, Willemse PH, Mulder NH, et al: Alternating cycles of PVB and BEP in the treatment of patients with advanced seminoma. *Eur J Cancer* 1991;27:1376–1379.
- 24 De Santis M, Becherer A, Bokemeyer C, Stoiber F, Oechsle K, Sellner F, Lang A, Kletter K, Dohmen BM, Dittrich C, Pont J: 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. *J Clin Oncol* 2004;22:1034–1039.
- 25 Nuutinen JM, Leskinen S, Elomaa I, Minn H, Varpula M, Solin O, Söderström KO, Joensuu H, Salminen E: Detection of residual tumours in postchemotherapy testicular cancer by FDG-PET. *Eur J Cancer* 1997;33:1234–1241.
- 26 Johns Putra L, Lawrentschuk N, Ballok Z, Hannah A, Poon A, Tauro A, Davis ID, Hicks RJ, Bolton DM, Scott AM: 18F-fluorodeoxyglucose positron emission tomography in evaluation of germ cell tumor after chemotherapy. *Urology* 2004;64:1202–1207.