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Meta-Analysis to Determine the Diagnostic Value of 2-^{18}Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography in Assessing Residual Tumors after Systemic Therapy for Metastatic Seminoma

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Abstract

Background: A meta-analysis was performed to determine the value of 2-^{18}fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for assessing viable tumor residuals after chemotherapy in patients with pure seminoma. Materials and methods: This review included five studies published between 1999 and 2010 with a total of 130 patients who underwent both computed tomography (CT) and FDG-PET scanning for residual tumor detection after systemic therapy. We compared the sensitivity and specificity of FDG-PET and CT (tumor size ≤ or > 3 cm) in identifying vital tumor tissue. Results: On the average, FDG-PET had higher specificity (92% vs. 59%) and sensitivity (72% vs. 63%) as well as a higher positive predictive value (PPV) than the solely size-based CT assessment of residual tumors (70% vs. 28%). PET *al*so tended to have a higher negative predictive value (93% vs. 86%). Conclusion: The present evaluation of currently available data indicates that FDG-PET is superior to CT in detecting viable tumor residuals after chemotherapy in patients with metastatic seminoma. Its application can thus be recommended.

Keywords: FDG-PET, Seminoma, Testicular Cancer, Diagnosis, Residual Disease

1. Introduction

Testicular germ cell tumors, the most common malignancies in young men, are classified as seminomas or nonseminomas. Seminomas comprise about 50% of all germ cell tumors, but their incidence has doubled in the last 30 years [1]. More than 97% of patients with clinical stage I disease can be cured by surgery and, if necessary, adjuvant radiotherapy or carboplatin-based chemotherapy. Approximately 25% are advanced-stage cases (Lugano classification IIC or higher) requiring platinum-containing polychemotherapy. The current guidelines of the European Germ Cell Cancer Consensus Group (EGCCCG) now recommend combination chemotherapy with cis-platinum, etoposide and bleomycin (PEB) [2,3]. Residual tumors are found in about 80% of patients with systemic treatment; they can be diagnosed immediately after chemotherapy [4,5].

The literature suggests that about 30% of residual lesions > 3 cm still contain vital tumor tissue; a biopsy or resection followed by a histological workup was therefore advocated according to the recommendation of the Sloan-Kettering Cancer Center [6,7]. However, resection of these residual tumors by retroperitoneal lymphadenectomy is associated with high morbidity, mainly due to changes after chemotherapy [8,9]. Monitoring the lesions by alternative diagnostic imaging techniques thus seems a useful modality to avoid overtreating patients. However, size alone does not appear to be an optimal criterion for identifying residual tumors or necrosis; sensitivity and specificity are limited when applying the specified 3 cm cut-off value [10,11]. The required imaging technique should enable precise differentiation between tumor tissue and necrosis. Since 2-^{18}fluoro-2-deoxy-D-glucose positron emission tomography (FDG- PET) is suitable for localizing tissue areas of enhanced metabolic

activity, it has the potential for better detection of vital tumors [12]. This is true for pure seminomas, but FDG-PET is of limited value in detecting residual tumors of nonseminomas, because it cannot differentiate mature teratoma components from fibrosis or necrosis [13,14]. The fact that pure seminomas contain no teratoma components could render this examination particularly valuable for detecting vital seminoma residuals.

In other malignant diseases, FDG-PET is already regarded as a valuable tool for diagnosing vital residual tumors. High-quality data are available here particularly for Hodgkin's and non-Hodgkin's lymphoma [15-18].

For seminomas, on the other hand, the available data are sometimes not entirely consistent. The vast majority of studies have demonstrated the usefulness of FDG-PET in the follow-up of seminomas [19-22]. Only one study reported no diagnostic gain: a study by Ganjoo *et al*. [23] that dates back to 1999, a time when the FDT-PET technique was still in the early stages of development.

The present review study analyzes all current publications on this topic with the aim of determining whether FDG-PET may provide a useful tool for assessing residual tumors of pure seminomas after chemotherapy and whether it may offer an advantage over the solely size-based CT assessment of residual tumors.

2. Materials and Methods

The electronic databases Pubmed and MEDLINE were used to carry out a systematic literature search for original studies on the value of FDG-PET for assessing residual tumors in the follow-up of patients with metastatic seminoma after systemic therapy. The five studies published on this topic thus far were examined, analyzed and summarized with regard to relevant information (number of patients, number of residual tumors examined, lesion size, and FDG uptake). SPSS 17.0 software was used to perform statistical calculations based on the data obtained within the context of this meta-analysis.

3. Results

Our analysis included only four of the five studies published on this topic, because two of them had overlapping patient populations. In these studies, a total of 130 patients with residual tumors after chemotherapy for high-stage seminomas were examined with regard to FDG uptake by the lesions. The patients had a mean age of 39.5 years.

Gonadal seminomas were initially diagnosed in 102 patients, while 20 had retroperitoneal and 8 mediastinal primary tumors. All these patients had residual tumors after primary first-line chemotherapy with a platinum-based regimen. Moreover, the studies included 16 patients after relapse and salvage chemotherapy and another 16 after high-dose chemotherapy and peripheral stem cell transplantation (**Table 1**). The total number of lesions examined and analyzed after systemic therapy amounted to 161 because some of the patients had several lesions and also because some of those in the studies by Becherer *et al.* [19] and de Santis *et al.* [20] were examined several times due to relapses and repeat FDG-PET scans.

FDG-PET was used to examine all residual masses for vital tumor tissue after systemic chemotherapy. The residual tumor status over time was determined by either histological examination or clinical follow-up (mean 23.6 months) and imaging procedures. A total of 43 lesions (27%) were resected and submitted for histological workup; 118 residual tumors (73%) were observed using CT as a diagnostic aid.

Altogether, 33 of 161 residual tumors showed positive FDG-PET findings (**Table 2**).

Of the 33 positive results, 23 were true-positive with a sensitivity of 72% and a specificity of 92% (**Table 3**). The diagnostic value of tumor size (maximum tumor diameter > 3 cm or ≤ 3 cm) as the sole criterion was used for comparison. It proved to be markedly less sensitive and specific than the FDG-PET examination in its ability to detect vital tumor tissue in residual masses (**Table 3**). Moreover, only 20 of 71 tumors larger than three centimeters contained vital tumor tissue (positive predictive value, PPV = 28%). Here tumor measurement alone had a sensitivity of only 63%. On the other hand, vital seminomas were detected in 12 of 86 tumors ≤ 3 cm (negative predictive value, NPV = 86%).

In addition, the results of this meta-analysis clearly indicate that, compared to the solely size-based assessment of residual tumors, the use of FDG-PET can reduce the probability of both over- and undertreatment. An evaluation of the relatively small number of cases from the various studies reviewed here suggests that the rate of overtreated patients could be significantly reduced from 72% to 30% ($p < 0.001$; Fisher's exact test) and that of undertreated patients from 14% to 7% ($p = 0.11$; **Table 3**).

4. Discussion

The management of residual tumors after chemotherapy for seminoma is still controversially discussed. Retrospective analyses disclosed no advantage in additionally irradiating the lesions after systemic therapy for metastatic seminoma [24-26]. Thus there still remain the options of surgical excision or an "active surveillance" strategy. There is general consensus that residual tumor

Table 1. Overview of the patient population and residual tumors in the four publications comparing the two examination modalities.

	Becheree *et al*. 2005	Hinz *et al*. 2008	Ganjoo *et al*. 1999	De Santis *et al*. 2001	TOTAL
Total patient population	48	20	29	33	130
Mean age	39	42	38	39	39.5
Primary testicular tumor	39	18	19	26	102
Primary retroperitoneal tumor	7	2	6	5	20
Primary mediastinal tumor	2	0	4	2	8
Total number of lesions	74	20	30	37	161
Status based on histology	13	20	1	9	43
Status based on follow-up	61	0	29	28	118
First-line chemotherapy	40	21	19	28	108
Second-line chemotherapy	7	1	3	5	16
High-dose chemotherapy	5	0	7	4	16

Table 2. Correlation of FDG-PET findings with measurements of the largest tumor diameter (≤ or > 3 cm) and with the real presence of vital seminoma cells.

	Becheree *et al*. 2005	Hinz *et al*. 2008	Ganjoo *et al*. 1999	De Santis *et al*. 2001	TOTAL
Residual tumor > 3 cm	27	12	18	14	71
Vital tumor (true positive)	11	1	1	7	20
No vital tumor (false positive)	16	11	17	7	51
Residual tumor ≤ 3 cm	47	8	8	23	86
No vital tumor (true negative)	43	6	4	21	74
Vital tumor (false negative)	4	2	4	2	12
Positive PET	12	12	1	8	33
True positive	12	3	0	8	23
False positive	0	9	1	0	10
Negative PET	62	8	29	29	128
True negative	59	8	23	28	119
False negative	3	0	5	1	9
Relapse	15	3	5	9	32

Table 3. Comparison of the specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV) and the theoretical over- or undertreatment associated with the solely size-based assessment of residual tumors vs. the FDG-PET examination.

	Specificity	Sensitivity	PPV	NPV	Overtreatment	Undertreatment
Size ≤ or ≥ 3 cm	59.3%	62.5%	28.2%	86%	71.8%	14%
FDG-PET	92.2%	71.9%	69.7%	93%	30.3%	7%

size is associated with the probability of tumor relapse. Residuals larger than three centimeters carry an approximately 30% risk of containing vital tumor tissue [4,6,7,27]. However, surgical management of these lesions involves a high risk of postoperative morbidity such as retrograde ejaculation and lymphatic or pancreatic fistulas [6]. On the other hand, a survival advantage of operated seminoma patients was demonstrated by de Santis *et al.* in 2004 [21], who compared analyses on "active surveillance" vs. resection of residual tumors. In

fact, 6% (8 of 132) of the patients in the "active surveillance" group died of the tumor disease or as a consequence of salvage therapy, while no deaths (0 of 58) occurred in the operated group [21].

FDG-PET is now a standard diagnostic technique for detecting vital tumor tissue after chemotherapy, since it identifies metabolically active areas in the examined masses and thus enables easy and specific vital tumor detection.

Five study groups have thus far investigated the usefulness of FDG-PET and have published partially controversial results [19-23]. For this reason, it has not yet been possible to recommend FDG-PET as a standard procedure in the follow-up of seminoma patients. In the meantime, however, the study group of Heidenreich *et al*. [28] and the EGCCCG [2,3] generally recommend performing retroperitoneal lymphadenectomy only after obtaining positive PET results in patients with seminomatous residual tumors after chemotherapy.

This study has re-evaluated and summarized the studies published thus far. The summary of all studies has demonstrated that FDG-PET may be regarded as a highly valuable tool for identifying true negative findings. The negative predictive value was 93% and thus exceeded the negative predictive value of the solely size-based tumor assessment (≤3 cm, 86%). Avital residual tumors could be detected with a specificity of 92% by FDG-PET and only 59% by size determination. Residual tumors ≤3 cm contained vital seminoma tissue in 14% of the cases; regardless of tumor size, FDG-negative lesions showed vital tumor tissue in only 7%. FDG-PET thus seems able to better identify a group of patients who do not require primary surgery for residual tumors after systemic therapy. In patients with FDG-negative lesions, the increased postoperative morbidity makes it seem justified to adopt a watchful waiting attitude with observation of residual tumors and to only consider resection if they grow larger.

However, false-positive findings in FDG-PET must still be regarded as a problem. Comprising 30% of all positive findings in FDG-PET, they would lead to overtreatment of one third of all patients with FDG-PET-positive residual tumors. At just under 70%, however, the positive predictive value of the FDG-PET examination here was still significantly above that of using residual tumor size alone (28%) as the basis for making treatment decisions. Nevertheless, a significant weak point of the examination method is evident here [29].

In conclusion, an analysis of studies published thus far indicates that FDG-PET may indeed be regarded as a valuable diagnostic tool for examining postchemotherapy tumor residuals in cases of pure seminoma. In particular, it has proved superior to solely size-based tumor assessment in its sensitivity and specificity as well as its positive and negative predictive value. Given that surgical removal of residual tumors exceeding three centimeters is widely recommended [20,21], overtreatment could be reduced in more than half of all cases by relying on the FDG-PET findings.

Considering the (false) positive findings in FDG-PET, which include avital tissue in 30%, the decision to surgically remove the lesions should, in some cases, be partly based on the tumor size and resectability and possibly also the growth tendency and perioperative risk.

Moreover, the rate of false positive findings can be further reduced by making sure that there is a time interval of at least six weeks between the completion of chemotherapy and the diagnostic FDG-PET scan. Performing the examinations too early increases the false positive rate. On the other hand, combined FDG-PET/CT examinations are better able to morphologically assess foci of increased FDG uptake, which optimizes the diagnostic value. In addition, PET examinations should be assessed by an experienced nuclear medicine specialist; if necessary, a second opinion should be sought at a specialized center. There are no data thus far on the use of an alternative tracer, nor does it seem useful to repeat the examination after a certain interval in view of the high costs and low diagnostic gain.

5. Summary

In summary, the data presented here confirm that 2-^{18}fluoro-2-deoxy-D-glucose positron emission tomography corresponds to the current clinical standard in the follow-up of residual tumors after systemic therapy for advanced pure seminoma.

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