Eur J Nucl Med Mol Imaging (2008) 35:1786–1795
DOI 10.1007/s00259-008-0806-1

ORIGINAL ARTICLE

Chemotherapy response assessment in stage IV melanoma patients—comparison of ^{18}F-FDG-PET/CT, CT, brain MRI, and tumormarker S-100B

Klaus Strobel · Reinhard Dummer · Hans C. Steinert · Katrin Baumann Conzett · Karin Schad · Marisol Pérez Lago · Jan D. Soyka · P. Veit-Haibach · Burkhardt Seifert · V. Kalff

Received: 14 December 2007 / Accepted: 1 April 2008 / Published online: 6 May 2008

Abstract
Purpose This study aims to compare the use of 18F-FDG-PET/CT, CT, brain MRI, and tumormarker S-100B in chemotherapy response assessment of stage IV melanoma patients.
Methods In 25 patients with stage IV melanoma, FDG-PET/CT and S-100B after 2–3 months (three cycles) of chemotherapy was compared with baseline PET/CT and baseline S-100B. Retrospectively, the response was correlated with the outcome. In patients with clinical suspicion for brain metastases, MRI or CCT was performed.
Results There was agreement between FDG-PET/CT and CT regarding response to chemotherapy in all patients. There was a clear trend to a longer OS of PET/CT responders (n=10) compared with PET/CT non-responders (n=15; p=0.072) with remarkably better 1-year OS of 80% compared to 40% (p=0.048). There was a significant longer PFS of PET/CT responders compared with PET/CT non-responders (p=0.002). S-100B was normal at baseline in eight of 22 patients where it was available. Chemotherapy response assessment with S-100B failed to show correlation with OS or PFS. Eleven patients developed brain metastases during treatment, first detected by PET/CT in two and by MRI or CCT in nine of 11 patients. Appearance of brain metastases was associated with a poor survival.
Conclusions 18F-FDG-PET/CT and CT alone are equally suitable for chemotherapy response assessment in melanoma patients and clearly superior to S-100B. PET/CT responders have better early survival, but this is shortlived due to late therapy failure—often with brain recurrence. Additional brain MRI for therapy response assessment in such high-risk patients is mandatory to detect brain metastases missed by PET/CT.

Keywords 18F-FDG-PET · Metastasis · Therapy · Oncology PET/CT PET

K. Strobel (✉) · H. C. Steinert · M. P. Lago · J. D. Soyka · P. Veit-Haibach · V. Kalff
Division of Nuclear Medicine, Department of Medical Radiology, University Hospital Zurich,
Raemistr. 100,
8091, Zurich, Switzerland
e-mail: klaus.strobel@usz.ch

R. Dummer · K. B. Conzett · K. Schad
Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

B. Seifert
Biostatistics Unit, University of Zurich, Zurich, Switzerland

V. Kalff
Department of Nuclear Medicine, Alfred Hospital Melbourne, Melbourne, Australia

Introduction

Stage IV melanoma with distant metastases remains an incurable disease with a poor 5-year survival of 6% [1, 2]. Melanoma metastases are characterized by relevant chemoresistance, and the use of systemic therapy for patients with multiple unresectable distant metastases is still controversial [3, 4]. Many patients with metastases are included in clinical trials in an attempt to determine any benefit from new treatment regimes. The currently used drugs have severe side effects and are expensive. Therefore, methods to assess the early success or failure of chemotherapy are important to both the patient and the health care system.

^{18}F-FDG-PET/CT is increasingly used for initial staging of patients with high-risk melanoma. ^{18}F-FDG-PET/CT with its unique combination of metabolic and morphologic information has a high accuracy for metastases in these patients and is superior to PET alone, CT alone, or conventional imaging methods in the M-staging situation [5–7]. Preliminary studies showed that PET imaging may help to select the patients for surgery and has influence on the survival [8]. ^{18}F-FDG-PET and-PET/CT is increasingly used for neoadjuvant, adjuvant, curative, or palliative chemotherapy response assessment in different malignant tumors such as lymphoma [9–11], esophageal cancer [12, 13], lung cancer [14], and breast cancer [15], but publications regarding PET or PET/CT for therapy response assessment in melanoma patients are still very limited [16, 17].

Serum S-100B is a useful tumormarker in melanoma patients, indicating the presence of distant metastases and reflecting the tumor burden. In addition, S-100B has prognostic implications [18–23].

The aim of this study was to compare the value of ^{18}F-FDG-PET/CT, CT, brain MRI, and tumormarker S-100B in chemotherapy response assessment of stage IV melanoma patients in correlation with the survival.

Materials and methods

Patients

This retrospective study contains 25 consecutive patients (14 women, 11 men; mean age 62.3 years; range 31–82 years) which fulfilled the following criteria: diagnosis of melanoma with proven distant metastases; metastases were proven by biopsy in 15 patients and by typical appearance on PET/CT imaging (multiple focal lesions with increased FDG uptake not fitting to physiological, inflammatory lesions or other tumors) and/or rising S-100B tumormarker or other clinical findings in the remaining ten patients. ^{18}F-FDG-PET/CT was performed at baseline (PET/CT 0) and after 2–3 months (three cycles) of chemotherapy (PET/CT 1). Contemporaneous S-100B 0 and S-100B 1 measurements were available for comparison with ^{18}F-FDG PET/CT data in 22 cases. Overall, 14 CCTs and 18 brain MRI scans were performed if there was a suspicion for brain metastases. Imaging and therapy of the patients were performed between September 2004 and September 2007.

We received approval from our institutional review board to undertake this retrospective study.

Therapy

All the patients had stage IV melanoma with distant metastases and were included in clinical trials which used various chemotherapy regimes. In all the patients, the distant metastases were not detected at primary staging but during follow-up after resection of the primary tumor. In two patients, the primary tumor was unknown. The different localization of the primary tumors, Breslow thickness, and localizations of the distant metastases are described in Table 1. All the patients started with a first-line therapy: nine patients were treated with temozolomide alone, nine patients with dacarbazine alone, and seven patients with a combination of dacarbazine and thalidomide. In nine patients, first-line chemotherapy was changed to second-line chemotherapy because of progression of the metastases. In the most cases, cisplatin and vindesine were used for second-line treatment. In two patients, additional immunotherapy was administered. Seven patients underwent surgery during the follow-up. The localization of the resected metastases were as follows: lung (n=3), brain (n=2), stomach, and the inguinal region. Nine patients received additional radiotherapy of the following localizations: brain (n=5, one of them together with radiotherapy of a bone metastasis in the knee), thigh (n=3), and spine (n=1).

Determination and therapy response assessment with S-100B

The determination of serum S-100B was performed with a commercially available immunoassay (ELISA) KIT (Sangtec 100 ELISA, Dia Sorin, Stillwater, NM, USA) according to the instructions of the manufacturer. A definitely normal cut-upper limit was defined as 0.2 μg/l (the 95 percentile of blood donor samples). Values ≥0.3 μg/l were determined as indicative of definite melanoma metastases. The detection limit is 0.03 μl/l (BO+3 SD). Intra-assay and inter-assay precision was estimated by analysis of variance (ANOVA). The within and total run reproducibility is within 10%.

In all the patients, S-100B levels were determined before and during therapy. All together, 87 single S-100B measurements were performed in 25 patients (mean 3.48 measurements per patient). The percentage change of S-100B levels between S-100B 0 and S-100B 1 was assessed, and an increase or decrease of <30% of S-100B during therapy was determined as no response to chemotherapy, a decrease of ≥30% or a decrease from pathologically elevated S-100B value to a normal value (≤0.2 μg/l) was determined as response to chemotherapy.

PET/CT imaging protocol

All data were acquired on a combined PET/CT in-line system (Discovery LS or Discovery ST, GE Health Systems, Milwaukee, WI, USA).

Patients fasted for at least 4 h prior to the scanning, which started approximately 60 min (median 66 min; range

Table 1 Characteristics of 25 patients with chemotherapy response assessment with ^{18}F-FDG-PET/CT, CT and S-100B and follow-up

No	Breslow (mm)	Localization	Mets at baseline	First-line chemo	PET/CT response	CT response	S-100B response	Survival (months)	Follow-up (months)	Final tumor load
1	15.0	Thigh	Lung, adrenal, in-transit	TMZ	No	No	Not available	4		High load
2	1.7	Flank	Lung, mediastinal, hilar ln	TMZ	Yes	Yes	Yes	18		Low load, brain mets
3	4.9	Foot	Lung, soft tissue	DTIC	Yes	Yes	Yes	18		High load
4	5.5	Arm	Lung, ln, soft tissue, abdominal	DTIC	Yes	Yes	Not suitable		17	No tu
5	6.5	Arm	Liver, lung, bone, ln, pleural effusion	TMZ	Yes	Yes	Yes		19	No tu
6	U	Chest	Pulmonal	DTIC	No	No	Not suitable	10		Low load, brain mets
7	13.0	Ear	Lung, liver	TMZ	No	No	No		16	Low load
8	5.3	Knee	Lung, liver, ln, soft tissue	TMZ	Yes	Yes	Yes	12		Only brain mets
9	6.0	Shoulder	Liver, ln	DTIC	No	No	No	11		High load
10	8.0	Foot	ln mediast und iliacal	DTIC	No	No	Yes	11		Low load, brain mets
11	7.0	Arm	Lung, bone, ln	TMZ	No	No	Not suitable	4		High load
12	1.7	Chin	Lung	DTIC	No	No	Not suitable		16	No tu
13	3.5	Flank	Liver, soft tissue	TMZ	No	No	No	9		High load, brain mets
14	U	Rectal	Liver, lung, soft tissue	DTIC	Yes	Yes	Not suitable	15		High load, brain mets
15	4.3	Abdomen	Liver, bone, ln	TMZ	Yes	Yes	Yes	7		High load
16	4.1	Knee	Lung, in-transit	DTIC	Yes	Yes	Yes		14	No tu
17	1.0	Foot	Bone, ln	TMZ	No	No	Not suitable	5		High load
18	1.8	Arm	Lung, liver, soft tissue	DTIC	No	No	Yes		14	High load, brain mets
19	U	Vagina	Pleura, stomach, ln	DTIC + THAL	Yes	Yes	Not available	24		High load
20	3.5	Back	Choledochus, lung	DTIC + THAL	No	No	Not suitable	16		Low load, brain mets
21	U	Unknown	In-transit	DTIC + THAL	No	No	No		28	Low load, brain mets
22	2.1	Arm	Lung	DTIC + THAL	No	No	Not suitable	17		Low load, brain mets
23	1.4	Lumbar	Lung, liver	DTIC + THAL	No	No	Yes	6		Low load, brain mets
24	2.5	Occipital	Lung	DTIC + THAL	No	No	No	4		High load
25	U	Unknown	ln, soft tissue	DTIC + THAL	Yes	Yes	Not available	34		Low load, brain mets

U unknown; *ln* lymph node; *mets* metastases; *chemo* chemotherapy; *TMZ* temozolomide; *DTIC* dacarbazine; *THAL* thalidomide

54–73 min) after the injection of 370–400 MBq of ^{18}F-FDG. All the patients were tested for a normal glucose level before scanning. The patients with elevated glucose levels were rescheduled and scanned with normal glucose levels. No intravenous contrast agent was given. Initially, the CT scan was acquired starting from the level of the head using the following parameters: 40 mAs, 140 kV, 0.5 s per tube rotation, slice thickness 4.25 mm, scan length 867 mm, data-acquisition time 22.5 s. The CT scan was acquired during breath holding in the normal expiratory position. In the patients with primary tumors in the lower extremities, the scanning of the lower legs was added.

Immediately following the CT acquisition, a PET emission scan was acquired with an acquisition time of 3 min per cradle position with a one-slice overlap in 2D mode (matrix 128×128). The eight to nine cradle positions starting from the head to the knees resulted in an acquisition time of approximately 24–27 min. In the patients with primary tumors of the lower extremities, scanning of the lower legs was added. The CT data were

used for the attenuation correction, and the images were reconstructed using a standard iterative algorithm (OSEM). The acquired images were viewed with a software providing multiplanar reformatted images of PET alone, CT alone, and fused PET/CT with linked cursors using AW workstation (GE Health Systems, Milwaukee, WI, USA). PET/CT imaging was performed according to the recently published "procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0" [24].

Overall, 96 PET/CT scans were performed in these 25 patients (mean 3.8 per patient).

Therapy response assessment with CT

The images were reviewed and analyzed by two radiologists experienced in oncologic CT imaging without knowledge of other imaging study results. The CT images were analyzed for the presence and nature of focal metastatic lesions suspicious for metastases.

For therapy response with CT, the CT part of the ^{18}F-FDG-PET/CT study was evaluated separately from the PET part. Response was assessed by comparing the CT part of PET/CT 0 with PET/CT 1 using the established RECIST criteria [25]. No response was assigned to (a) patients with new metastases and/or (b) if there was stability (<30% decrease of the sum of the longest diameter of the target lesions) or progression in size of the known metastases. A therapy response was defined as complete disappearance of the metastases or at least 30% decrease of the sum of the longest diameter of the target lesions.

PET/CT interpretation and measurement of SUV max

The ^{18}F-FDG-PET/CT images were reviewed and analyzed by two experienced nuclear-radiology physicians without knowledge of the results of other imaging studies. The PET images and the corresponding CT images of the PET/CT study were analyzed for the presence and nature of focal lesions with an increased ^{18}F-FDG uptake. For all the patients, the attenuation-corrected PET images were analyzed. Lesions were interpreted as metastases if the uptake was higher than the uptake of the surrounding background tissue, and thus, a focal lesion was clearly depictable. ^{18}F-FDG uptake in physiological or benign variants as in muscles or pulmonary infiltration was excluded from the analysis.

Semiquantitative analysis of FDG uptake in all suspicious lesions was performed by measuring the maximum standardized uptake value (SUV max).

Therapy response assessment with ^{18}F-FDG PET/CT

Response was assessed by comparing the baseline PET/CT (PET/CT 0) with PET/CT 1 after three cycles of chemotherapy. Therapy response assessment with ^{18}F-FDG PET/CT was determined with a combination of PET and CT criteria as previously described [16]: Briefly, no response was defined as increasing FDG uptake in the known metastases, if new metastases were detected or if there was no significant decrease of FDG uptake in the known metastases visible. SUV max measurements were occasionally used if visual evaluation was not sufficient. Chemotherapy response was diagnosed if the decrease in size and FDG uptake of the lesions was more than 30% or complete disappearance of pathological FDG uptake in the metastases occurred. The size of the lesions was measured on the CT part of the PET/CT. If new FDG-negative pulmonary nodules developed between the baseline and the restaging investigation, which were not calcified, this was described as progressive disease due to lung metastases.

Fig. 1 Overall survival of ^{18}F-FDG-PET/CT (**a**), CT (**b**) and S-100B (**c**) responders and non-responders ▶

Brain imaging with contrast enhanced CCT or MRI

Brain MRI or contrast enhanced CCT was performed at different institutions in patients with symptoms suspicious for brain metastases like headache or neurologic deficits or to confirm ^{18}F-FDG-PET/CT findings which were suspicious for brain metastases. So we do not have PET/CT and brain MRI contemporaneously in all patients. In all the patients who received MRI of the brain, at least T2- and T1-weighted images without contrast and T1-weighted images with intraveneous application of Gadolinium were performed. Metastases were diagnosed as contrast-enhancing parenchymal lesions in T1-weighted images with additional surrounding edema [26]. CCT was performed according to established protocols before and after intravenous contrast administration [27]. Brain images were evaluated by experienced neuroradiologists.

Statistical analysis

Data were analyzed on a patient basis using SPSS 15 for Windows (SPSS). Kaplan–Meier curves were obtained comparing the overall survival (OS) and the progression-free survival (PFS) of responders and non-responders for each response assessment tool (PET/CT, CT, or S-100B; Figs. 1 and 2). Statistical significance was assessed with the log-rank test and Chi-Square tests. $P<0.05$ was considered to indicate a significant difference (Figs. 3 and 4).

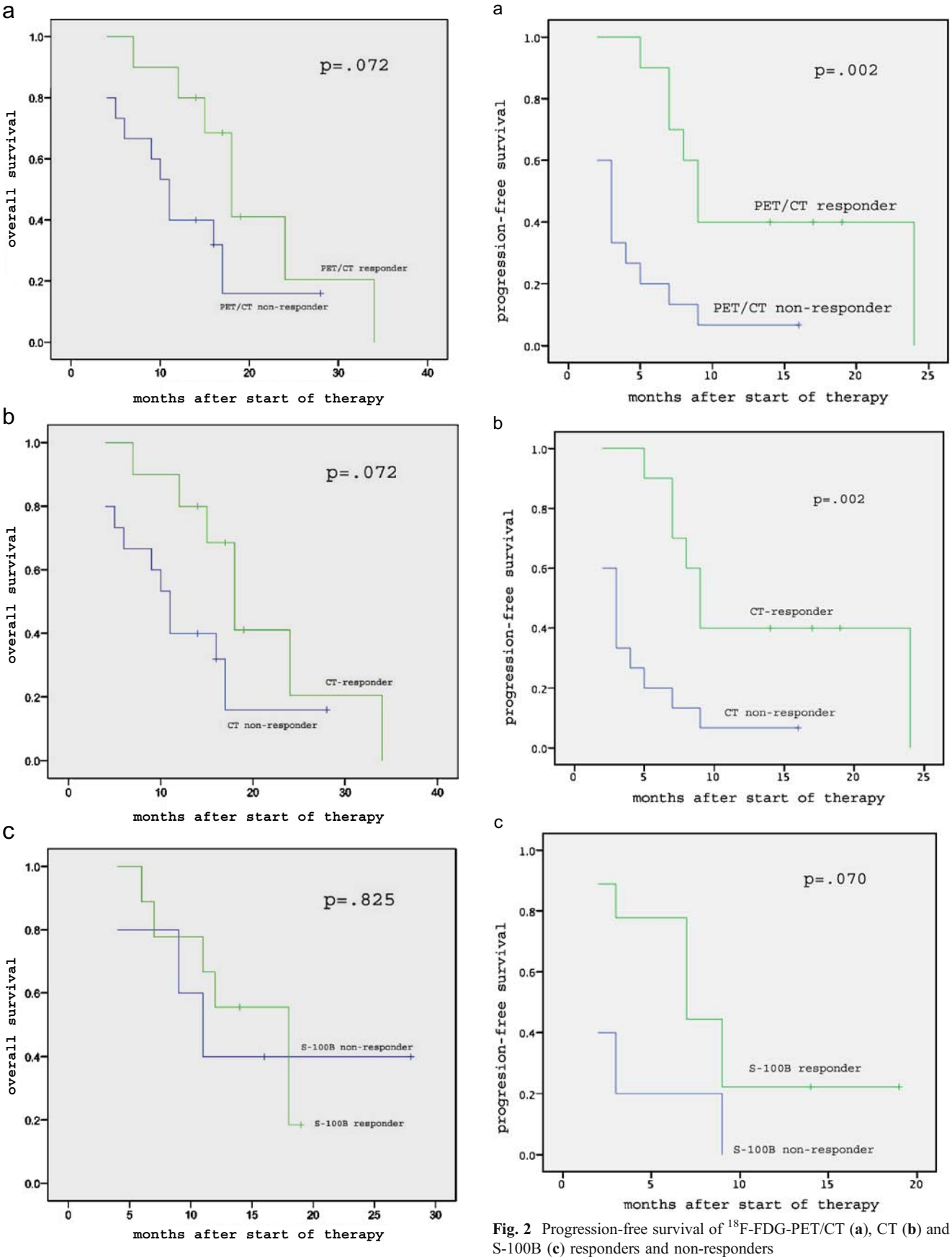

Fig. 2 Progression-free survival of ^{18}F-FDG-PET/CT (**a**), CT (**b**) and S-100B (**c**) responders and non-responders

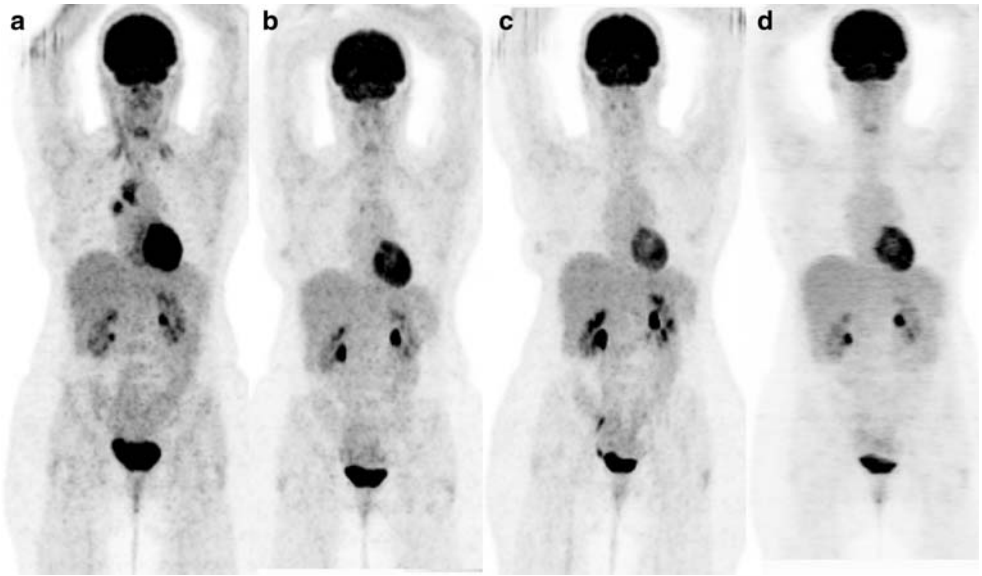

Fig. 3 A 46-year-old female patient (no. 2) with a melanoma resected at the flank 1 year before (Breslow 1.7 mm). After detection of lung and mediastinal metastases in the baseline ^{18}F-FDG-PET (**a**) with an increased S-100B (0.6 μg/l) the patient received temodal chemotherapy. Follow-up ^{18}F-FDG-PET/CT (**b**) showed a partial response with decrease of the size and FDG-uptake in the metastases. Correspondingly S-100B dropped to normal values (0.2 μg/l). The next ^{18}F-FDG-PET/CT (**c**) showed a complete response with disappearance of the metastases and the S-100B remained normal (0.2 μg/l**).** The last ^{18}F-FDG-PET/CT (**d**) showed no extracerebral metastases but raised the suspicion of brain metastases, which was confirmed by an MRI of the brain (Fig. 4). S-100B failed to indicate new distant metastases (0.1 μg/l). The patient received radiotherapy of the brain but died 18 months after the beginning of the chemotherapy and 9 months after the detection of brain metastases

Results

SUV max of the most active metastases showed median values of 6.8 (mean 10.52; range 1.2–40.0) before therapy and 5.5 (10.58; 1.2–52.6) after three cycles of chemotherapy. Eighteen of 25 patients had died after a mean follow-up of 14 months (median 14, range 4–34 months). Advanced melanoma was the cause of death in all the patients (Figs. 3, 4). Seven patients were alive, four in complete remission (nos. 4, 5, 12, 16) and three with progressive disease (nos. 7, 18, 21). Mean follow-up time in the surviving patients was 18 months (range 14–28 months). Median overall survival was 18 months in PET/CT responders (n=10) and 11 months in PET/CT non-responders (n=15; p=0.072, log-rank test). One-year survival was 80% and 40%, respectively. Thus, 1-year-survival was significantly better in responders compared with non-responder (p=0.048, chi-square test). Median progression-free survival was 9 months in PET/CT responders and 3 months PET/CT non-responders (p=0.002).

In 11/25 patients, S-100B values could not be used for follow-up: in three patients, S-100B was not performed, and in the remaining eight patients, S-100B values were not suitable for response assessment because they were negative

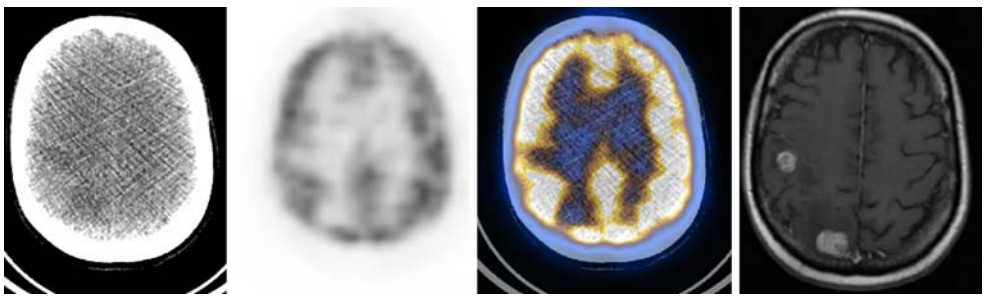

Fig. 4 A 46-year-old female patient (no. 2) with a melanoma resected at the flank 1 year before (Breslow 1.7 mm). After detection of lung and mediastinal metastases in the baseline ^{18}F-FDG-PET (**a**) with an increased S-100B (0.6 μg/l) the patient received temodal chemotherapy. Follow-up ^{18}F-FDG-PET/CT (**b**) showed a partial response with decrease of the size and FDG-uptake in the metastases. Correspondingly S-100B dropped to normal values (0.2 μg/l). The next ^{18}F-FDG-PET/CT (**c**) showed a complete response with disappearance of the metastases and the S-100B remained normal (0.2 μg/l**).** The last ^{18}F-FDG-PET/CT (**d**) showed no extracerebral metastases but raised the suspicion of brain metastases, which was confirmed by an MRI of the brain (Fig. 4). S-100B failed to indicate new distant metastases (0.1 μg/l). The patient received radiotherapy of the brain but died 18 months after the beginning of the chemotherapy and 9 months after the detection of brain metastases

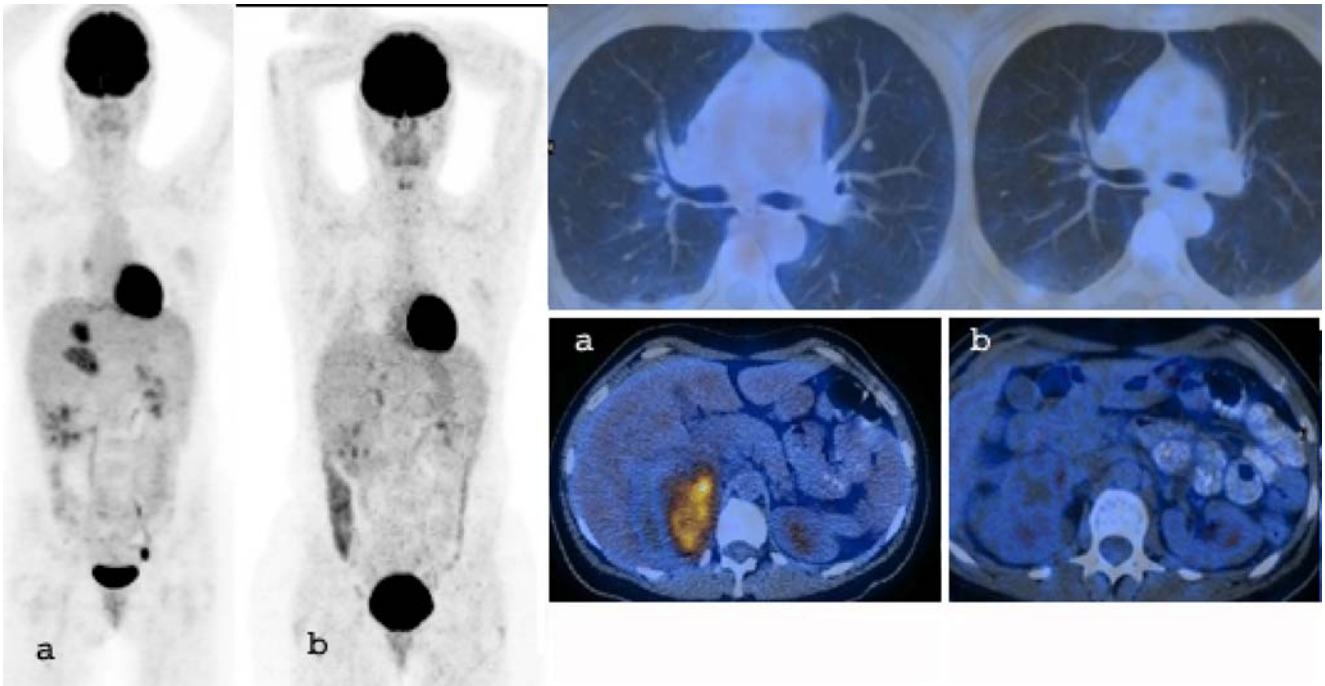

Fig. 5 A 40-year-old female patient (no. 5) with a melanoma resected at the arm 6 years ago (Breslow 6.5 mm). Baseline ^{18}F-FDG-PET/CT (**a**) showing metastases in the lung, liver and a right adrenal metastasis with hematoma. S-100B was clearly pathologic with an value of 1.7 μg/l. The patient was treated with temodal and the first follow-up ^{18}F-FDG-PET/CT (**b**) showed disappearance of the FDG-activity, a resolving hematoma in the adrenal region and disappearance of the metastases in the liver and lung. S-100B dropped to 0.2 μg/l. The patient is alive with persisting complete remission at the 19 months follow-up

at baseline (median 0.1 μg/l, mean 0.08 μg/l; range 0.0–0.2 μg/l) despite the presence of proven distant metastases. So S-100B was suitable for therapy response assessment in 14 patients: median values of 0.6 μg/l (mean 1.7 μg/l; range 0.3 μg/l–12.6 μg/l) before and 0.5 μg/l (1.3 μg/l; 0.1 μg/l–7.3 μg/l) after therapy. Nine of these 14 patients showed response (Fig. 5), and five showed no response. There was no significant difference in the 1-year survival of S-100B-responders (56%) and S-100B non-responders (40%; p=0.77) and no significant correlation with OS (p=0.825) or PFS (p=0.070). There was agreement between S-100B, CT, and PET/CT response assessment in 11 of 14 patients. In three patients (nos. 10, 18, 23), disagreement between imaging and S-100B was observed: the tumormarker showed response and PET/CT showed no response (progression in two cases and stable disease in one case). However, two of these patients started with a relatively low S-100B value before therapy and decreased only moderately but more than 30% (0.6 to 0.4 μg/l and 0.3 to 0.2 μg/l). In the third patient, the decrease of S-100B was more impressive (12.6 to 3.1 μg/l) (Fig. 6). Two of these three patients died after 6 and 11 months, and one lives since 14 months with a high tumor load and brain metastases.

No patient had brain metastases at the beginning of systemic therapy. Eleven patients developed brain metastases during the follow-up period, and brain metastases were first detected in one of the follow-up PET/CT examinations in two and by MRI in nine of 11 patients. We observed seven patients who died for brain metastases, although they had only a low extracerebral tumor load. One patient had only brain metastases and otherwise a complete remission of the extracerebral tumor manifestations 3 months before he died (no. 8). Overall survival after diagnosis of brain metastases was very poor with a median OS of 3 months (range 1 to 4 months). Only one patient was still alive at the end of the follow-up 8 months after diagnosis of a brain metastasis.

Discussion

Our data show that ^{18}F-FDG-PET/CT and CT imaging alone are effective tools for chemotherapy response assessment in stage IV melanoma patients. Imaging is superior to serial S-100B measurement for assessing overall survival.

Despite other data supporting the value of serum S-100B as a clinical marker for monitoring therapy response of metastatic melanoma during systemic therapies, a clear drawback of this tumormarker is the fact that it has a false negative rate in one third of patients with metastases [7, 28, 29]. In the present study, 36% patients failed to show elevated S-100B values despite the presence of proven distant metastases. This is in keeping with a previous study

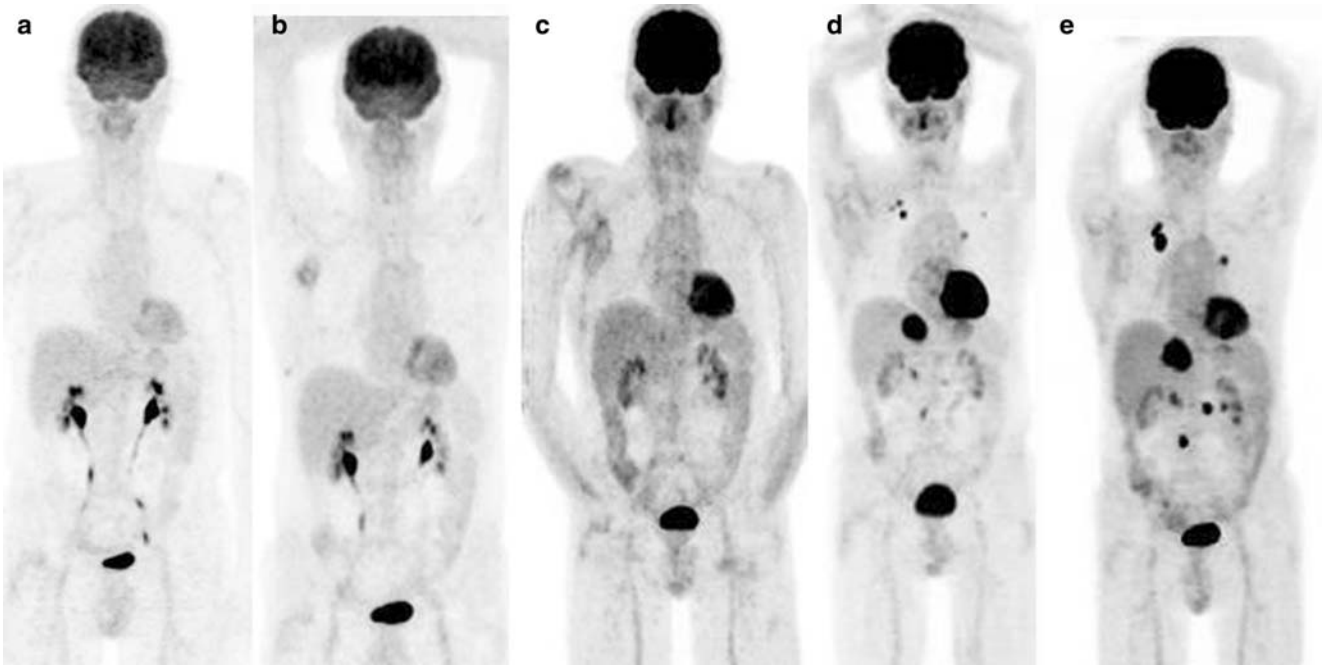

Fig. 6 A 66-year-old male patient (no. 23) after resection of a lumbar melanoma (Breslow 1.4). First ^{18}F-FDG-PET/CT (**a**) shows no metastases. Second ^{18}F-FDG-PET/CT (**b**) demonstrates lymph node metastases in the right axilla which were resected. Third ^{18}F-FDG-PET/CT (**c**) with postoperative changes in the right axilla without metastases. Fourth ^{18}F-FDG-PET/CT (**d**) shows lung and liver metastases with a corresponding S-100B value of 12.6 μg/l. A systemic combination therapy with dacarbazine and thalidomide was started but the fifth ^{18}F-FDG-PET/CT (**e**) shows progression of the metastases regarding size and FDG-activity. S-100B pretended a response with a decrease to 3.1 μg/l. Brain metastases were detected with MRI and radiation therapy of the brain as well as change to a second-line chemotherapy was performed. The patient died 3 months after the last ^{18}F-FDG-PET/CT

where 15 of 41 patients (37%) showed a false-negative S-100B before therapy of metastases [16].

FDG-PET/CT is increasingly used for therapy assessment of different tumors [30]. Current data regarding therapy assessment of melanoma patients with PET or PET/CT are limited to case reports showing the effect of limb perfusion therapy and one study comparing change of PET/CT findings to change of S-100B values in a mixed population of stage III and stage IV melanoma patients during different therapies (surgery or chemotherapy) [16, 17]. To our knowledge, this is the first study comparing S-100B, FDG-PET/CT, and CT alone for therapy response assessment by using outcome data.

In many clinical trials, CT remains the imaging modality of choice for therapy assessment in patients with stage IV melanoma. The big advantage of PET/CT is that this method provides the combination of metabolic and morphologic information. A recently published study compared FDG-PET/CT imaging for N- and M-staging of 250 consecutive melanoma patients with PET alone and CT alone showed the accuracy of PET/CT for M-staging was significantly higher than that of PET alone and CT alone (98% vs. 93% and 84%) [5]. We share the experience that PET/CT is clearly superior to CT alone in the staging situation. Our data in the present study showed complete agreement in differentiating chemotherapy responders and non-responders between CT alone and PET/CT. This contradicts the results in therapy response assessment in other tumors, especially lymphoma [31] where it has been shown that metabolic changes precede morphologic changes qualifying PET for effective therapy response assessment very early after initiation of the systemic therapy. Our results should be confirmed with a larger number of patients because they could have an important impact on costs: if CT is a prognostic parameter which is as strong as the more expensive and less available PET/(CT) in stage IV melanoma patients, a significant reduction of imaging costs can be made. In support of the PET/CT, we also want to state that we still use PET/CT for therapy response assessment because it provides very clear and convincing images, normally easy to interpret and to demonstrate in interdisciplinary meetings, thus enjoying a high acceptance rate by the referring dermatologists and oncologists in our hospital. Criteria for therapy response assessment are under debate especially since combined modalities like PET/CT are being more frequently used. The simplest method for therapy assessment is a visual analysis comparing the baseline and post-therapy scans. Another approach is the use of semiquantitative measurements such as SUV max or average SUV [32]. This approach takes a little more time if multiple lesions are present but is highly reproducible and superior to visual

analysis in specific tumors such as recently shown in lymphoma patients [33]. More sophisticated and time-consuming measurements like total lesion glycolysis (TLG) promise to be more exactly to determine the tumor burden because size and FDG-uptake of all lesions are assessed. In recently published papers, the TLG approach failed to show superiority compared with the simpler SUV measurements [7, 32]. With this paper, we tried to establish combined therapy response assessment criteria which take morphologic (CT part) and metabolic (PET part) changes in account. We think specific PET/CT therapy response criteria should be evaluated and established for every specific type of tumor in the future in a way it has been initiated for therapy assessment in lymphoma [34].

Clinically apparent brain metastases develop in about 18–46% of patients with stage IV disease, and the prevalence is even much higher in autopsy series of patients dying from melanoma [35]. One important drawback of PET/(CT) is the poor sensitivity of approximately 60% in detecting brain metastases due to the high physiological uptake in the normal brain [26]. MRI is clearly the imaging gold standard in the detection of metastases. In our population, brain metastases were first detected by PET/CT in two and by MRI or CCT in nine of 11 patients. Detecting and staging for brain metastases in melanoma patients is important for choosing individual therapy which can consist of surgery, radiotherapy, or chemotherapy or combinations of these strategies [35, 36]. Our data support the importance of identifying brain metastases because it seems to be a critical cause of early death and thus an important prognostic factor [37]. These findings confirm the suspicion that current chemotherapy is not as able to treat intracerebral as extracerebral tumors.

Our study has several limitations. This is a retrospective study which may lead to a selection bias. The number of patients is limited, a reason why the statistical calculations should be interpreted carefully. S-100B measurements were not available in all the patients. The patients received different types of chemotherapy before the first response assessment scan was performed. In non-responders or patients with severe side-effects, therapy was changed to second- or third-line drugs, which by their nature are not as effective as first line drugs. In some patients with brain metastases irradiation of the brain and/or surgery was performed. In some patients—if downstaging was reached by systemic therapy—surgery of viable tumor rests was performed. We evaluated only the first PET/CT scan during therapy because this was available in all the patients and the most consistent measurement. We have chosen the time-point after three cycles of chemotherapy and not an earlier timepoint for different reasons: PET scans for therapy response assessment are only reimbursed in Switzerland with an interval of 60 days or more; in our experience, the response of melanoma lesions takes more time than in other tumors like lymphoma. While PET/CT and S-100B measurements were performed synchronously at fixed time points during treatment, CT or MR imaging of the brain was performed only if there was a suspicion for brain metastases because of unclear PET/CT findings or neurological symptoms. Autopsy was not performed in all the patients so the exact causes of death are not known, and histopathological proof is obviously not available for all metastases.

In conclusion, our results suggest that ^{18}F-FDG-PET/CT or CT alone are equally accurate tools to differentiate short-term responders and non-responders and can be used in clinical trials for chemotherapy response assessment in stage IV melanoma patients. PET/CT showed no superiority to CT alone, but imaging tools were clearly superior to tumor-marker S-100B therapy response assessment. Additional brain MRI is mandatory because many patients die due to brain metastases despite a low extracerebral tumor load.

References

1. Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol. 2003;4:748–59.
2. Barth A, Wanek LA, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. J Am Coll Surg. 1995;181:193–201.
3. Schadendorf D. Is there a standard for the palliative treatment of melanoma. Onkologie 2002;25:74–6.
4. Serrone L, Hersey P. The chemoresistance of human malignant melanoma: an update. Melanoma Res. 1999;9:51–8.
5. Reinhardt MJ, Joe AY, Jaeger U, et al. Diagnostic performance of whole body dual modality 18F-FDG PET/CT imaging for N- and M-staging of malignant melanoma: experience with 250 consecutive patients. J Clin Oncol. 2006;24:1178–87.
6. Strobel K, Dummer R, Husarik DB, Perez Lago M, Hany TF, Steinert HC. High-risk melanoma: accuracy of FDG PET/CT with added CT morphologic information for detection of metastases. Radiology 2007;244:566–74.
7. Strobel K, Skalsky J, Kalff V, et al. Tumour assessment in advanced melanoma: value of FDG-PET/CT in patients with elevated serum S-100B. Eur J Nucl Med Mol Imaging. 2007;34:1366–75.
8. Dalrymple-Hay MJ, Rome PD, Kennedy C, Fulham M, McCaughan BC. Pulmonary metastatic melanoma–the survival benefit associated with positron emission tomography scanning. Eur J Cardiothorac Surg. 2002;21:611–4, discussion 614–615.
9. Juweid ME, Cheson BD. Role of positron emission tomography in lymphoma. J Clin Oncol. 2005;23:4577–80.
10. Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. N Engl J Med. 2006;354:496–507.
11. Jerusalem G, Hustinx R, Beguin Y, Fillet G. Evaluation of therapy for lymphoma. Semin Nucl Med. 2005;35:186–96.
12. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol. 2006;24:4692–8.
13. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the

oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007;8:797–805.
14. Hoekstra CJ, Stroobants SG, Smit EF, et al. Prognostic relevance of response evaluation using [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. J Clin Oncol. 2005;23:8362–70.
15. Dose Schwarz J, Bader M, Jenicke L, Hemminger G, Janicke F, Avril N. Early prediction of response to chemotherapy in metastatic breast cancer using sequential 18F-FDG PET. J Nucl Med. 2005;46:1144–50.
16. Strobel K, Skalsky J, Steinert HC, et al. S-100B and FDG-PET/CT in therapy response assessment of melanoma patients. Dermatology 2007;215:192–201.
17. Ryan ER, Hill AD, Skehan SJ. FDG PET/CT demonstrates the effectiveness of isolated limb infusion for malignant melanoma. Clin Nucl Med. 2006;31:707–8.
18. Abraha HD, Fuller LC, Du Vivier AW, Higgins EM, Sherwood RA. Serum S-100 protein: a potentially useful prognostic marker in cutaneous melanoma. Br J Dermatol. 1997;137:381–5.
19. Andres R, Mayordomo JI, Zaballos P, et al. Prognostic value of serum S-100B in malignant melanoma. Tumori 2004;90:607–10.
20. Banfalvi T, Gilde K, Boldizsar M, Kremmer T, Otto S. Serum levels of S-100 protein and 5-S-cysteinyldopa as markers of melanoma progression. Pathol Oncol Res. 1999;5:218–22.
21. Domingo-Domenech J, Molina R, Castel T, et al. Serum protein s-100 predicts clinical outcome in patients with melanoma treated with adjuvant interferon—comparison with tyrosinase rt-PCR. Oncology 2005;68:341–9.
22. Guo HB, Stoffel-Wagner B, Bierwirth T, Mezger J, Klingmuller D. Clinical significance of serum S100 in metastatic malignant melanoma. Eur J Cancer. 1995;31A:1898–902.
23. Hamberg AP, Korse CM, Bonfrer JM, de Gast GC. Serum S100B is suitable for prediction and monitoring of response to chemo-immunotherapy in metastatic malignant melanoma. Melanoma Res. 2003;13:45–9.
24. Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. J Nucl Med. 2006;47:885–95.
25. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
26. Rohren EM, Provenzale JM, Barboriak DP, Coleman RE. Screening for cerebral metastases with FDG PET in patients undergoing whole-body staging of non-central nervous system malignancy. Radiology 2003;226:181–7.
27. Holtas S, Cronqvist S. Cranial computed tomography of patients with malignant melanoma. Neuroradiology 1981;22:123–7.
28. Henze G, Dummer R, Joller-Jemelka HI, Boni R, Burg G. Serum S100–a marker for disease monitoring in metastatic melanoma. Dermatology 1997;194:208–12.
29. Hauschild A, Engel G, Brenner W, et al. Predictive value of serum S100B for monitoring patients with metastatic melanoma during chemotherapy and/or immunotherapy. Br J Dermatol. 1999;140:1065–71.
30. Weber WA, Figlin R. Monitoring cancer treatment with PET/CT: does it make a difference. J Nucl Med. 2007;48(Suppl 1):36S–44S.
31. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006;107:52–9.
32. de Geus-Oei LF, van der Heijden HF, Visser EP, et al. Chemotherapy response evaluation with 18F-FDG PET in patients with non-small cell lung cancer. J Nucl Med. 2007;48:1592–8.
33. Lin C, Itti E, Haioun C, et al. Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. J Nucl Med. 2007;48:1626–32.
34. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25:571–8.
35. Majer M, Jensen RL, Shrieve DC, et al. Biochemotherapy of metastatic melanoma in patients with or without recently diagnosed brain metastases. Cancer 2007;110:1329–37.
36. Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol. 2004;22:1293–300.
37. Budman DR, Camacho E, Wittes RE. The current causes of death in patients with malignant melanoma. Eur J Cancer. 1978;14:327–30.