Radiol Oncol 2001; 35(2): 95-103.

Conventional staging and ^{18}F-FDG-PET staging of malignant melanoma

Lars Jenicke[1], Susanne Klutmann[1], Karl H. Bohuslavizki[1], Karsten Neuber[2], Jürgen Altenhoff[2], Juliane Wedler[2], Ralph Buchert[1], Bruno Nebeling[1], Malte Clausen[1]

[1]Departments of [1]Nuclear Medicine and [2]Dermatology, University Hospital Eppendorf, Hamburg, Germany

Background. *Preliminary reports suggest that PET using ^{18}F-FDG may be a valuable diagnostic tool in patients with advanced malignant melanoma. Therefore, the aim of this study was to compare the findings of ^{18}F-FDG-PET and those of conventional imaging including physical examination for both primary and follow-up staging of patients with malignant melanoma.*

Patients and methods. *Thirty-five patients with histologically proven malignant melanoma underwent 61 PET examinations. After an intravenous injection of 370 MBq ^{18}F-FDG, whole-body images were acquired on an ECAT EXACT 47 (921) with an axial field-of-view of 16.2 cm. Moreover, all patients underwent physical examination and conventional imaging, i.e. ultrasound, CT, and MRI within a two-week interval after ^{18}F-FDG-PET. Based on the findings of both staging procedures, the patients were classified according to UICC.*

Results. *In primary staging or follow-up, 5 out of 35 patients were classified as stage I by conventional staging. Seven out of 35 patients were classified as stage II. The remaining 23 patients were initially classified as stage III. In the follow-up, two out of the latter 23 patients were upstaged to stage IV. However, none of these patients was classified as stage IV in primary staging by conventional diagnostic procedures.*

According to the results of ^{18}F-FDG-PET, 9 out of 35 patients revealed neither evidence for distant metastases nor presence of lymph node metastases in primary staging (stage I/II). However, initially 21 out of 35 patients were suspected for lymph node metastases but no distant metastases (stage III). Moreover, ^{18}F-FDG-PET suspected 5 patients, initially classified as stage IV, for distant metastases. However, in the follow-up, ^{18}F-FDG-PET turned out to be false-positive for distant metastases in one out of the latter 5 patients; therefore, this patient was staged down to stage III.

As compared to conventional diagnostic work-up, ^{18}F-FDG-PET revealed the corresponding tumor stage in 17 out of 35 patients (49 %). However, 14 patients (40 %) were staged up by ^{18}F-FDG-PET and 4 patients (11 %) were staged down by ^{18}F-FDG-PET in primary staging or follow-up investigations. With respect to anatomical localization, the majority of false-negative PET lesions were lymph node metastases close to the skin area.

Conclusions. *Our results underline the added value of ^{18}F-FDG-PET in staging of malignant melanoma. Since further treatment mainly depends on the clinical stage, ^{18}F-FDG-PET might help to select the appropriate treatment protocol for each individual patient.*

Key words: melanoma; neoplasms staging; tomography, emission-computed, ^{18}F-FDG-PET; morphological imaging; treatment strategy

Introduction

Cutaneous malignant melanoma is one of the most common malignancies with a twofold to threefold increasing incidence over the last 40 years.[1] The most important prognostic factor is tumor staging at the time of diagnosis.[2] According to the recommendations of the American Joint Commission on Cancer (AJCC), the clinical stage is divided into four groups. Clinical stages I and II are defined for primary malignant melanomas limited to the site of the origin without any evidence of a tumor spread elsewhere. In case of palpable local lymph node involvement or a disseminated disease, patients are classified as clinical stage III and IV, respectively. At the time of the first presentation, nearly 80 % of all patients are noted in clinical stage I or II with a mean 5-year survival rate of 85 %.[2] However, one third of the latter patients will have clinically undetectable lymph node metastases which, if left untreated, will significantly worsen the survival rate.[3,4] Thus, an accurate tumor staging is a prerequisite for selecting the adequate treatment protocol.

Conventional imaging, i.e. computed tomography, magnet resonance imaging, and ultrasound are valuable and well-established diagnostic tools in pretherapeutic staging.[5-8] However, these imaging modalities allow an identification of morphologic changes only, whereas the tumor tissue in normal-sized lymph nodes cannot be detected by definition.[9] Moreover, the morphologically orientated imaging permits a screening of a pre-selected body area only. Since malignant melanomas are known for their aggressive lymphatic and hematogenic spread potency [3,7], one single non-invasive imaging modality with simultaneous imaging of the whole-body would significantly facilitates pretherapeutic management of these patients. Thus, a number of radiotracers have been suggested for this purpose, i.e. ^{67}Ga-citrate [1], ^{123}I-benzamide, ^{123}I-α-methyltyrosine [9], and ^{99m}Tc-labelled antimelanoma-antibodies.[11] A great number of false-negative findings were reported for all of these radiotracers.[9,12] In contrast, initial experiences demonstrated the clinical potency of positron emission tomography (PET) using ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) for the detection of both local and systemic spread of metastatic malignant melanoma.[1,13-22] Within its geometric resolution of about 4-6 mm (FWHM), PET is able to detect tumor tissue independent of morphological changes due to an increased rate of glycolysis in malignant transformed cells. Since the early detection of malignant melanoma metastases increases the patients' survival rate, ^{18}F-FDG-PET might be a valuable diagnostic tool in detecting melanoma metastases.[23,24]

The aim of this study was to compare the findings of ^{18}F-FDG-PET and those of conventional imaging including physical examination for both, the primary and follow-up staging of patients with malignant melanoma.

Patients and methods

Patients

Thirty-five patients (13 female, 22 male) aged from 31 to 81 years with histologically proven malignant melanoma were investigated. The primary tumors were located in the skin area of the head and neck region in 5 patients, of the upper extremities in 4, of the lower extremities in 6, on the chest wall in 3, on the back in 15, and on the abdominal wall in 1 pa-

Received 6 February 2001
Accepted 14 February 2001

Correspondence to: Karl H. Bohuslavizki, MD, PhD, Department of Nuclear Medicine, University Hospital Eppendorf, Martinistr. 52, D-20246 Hamburg, Germany. Phone: +49 40 42803 4047; Fax: +49 40 42803 6775; E-mail: bohu@uke.uni-hamburg.de

tients. The anatomic site of the primary tumor was unknown in one patient.

Clark levels (CL)[25] and classification of the thickness of the primary lesions according to Breslow scheme [26] are listed in Table 1. In short, the following distribution was observed: CL I, no patient; CL II, 1 patient; CL III, 8 patients; CL IV, 18 patients; CL V, 1 pa-

Table 1. Staging of all melanoma patients, according to the findings of conventional imaging and ^{18}F-FDG-PET, respectively. Demographic data, Clark level (CL) and Breslow scheme (BS) are shown in detail as well as a comparison of both staging procedures, respectively. ↑: up-staging by PET; ↓: down-staging by PET; =: staging unchanged, Δ Staging: staging changed by PET with respect to conventional staging, NA: data not available

	Suspicious depth		Conventional staging		PET-staging		
Patient	CL	BS	Primary	Follow-up	Primary	Follow-up	Δ Staging
M/74	IV	0.7	I		III		↑
M/64	NA	3.7	III	III	III	III	=
M/41	III	0.4	III	III	I/II	I/II	↓
F/71	IV	3.3	II		I/II		=
M/48	II	0.5	III		III		=
F/61	IV	>6	III		III		=
F/66	IV/V	8.3	III		III		=
M/81	IV	>4	III		III		=
M/74	IV	1.0	III	III	III	III	=
M/71	NA	>8	III	III	III	IV	↓
M/61	IV	1.2	III		III		=
F/69	III	0.8	I	I	I/II	IV	↑
F/44	III	1.2	I	I	III	III	↑
M/56	IV	4.5	III		I/II		↓
M/59	IV	1.3	II	II	I/II	I/II	=
M/49	IV	2.1	II		IV		↑
M/43	IV	1.9	III		III		=
F/53	III	1.7	III	III	IV	IV	↑
M/63	NA	NA	II		I/II		=
F/79	IV	1.6	III	III, III	III	III, III	=
M/53	IV	3.0	III	III	I/II	I/II	↓
M/45	IV	3.5	III	III	III	IV	↑
M/62	IV	2.6	III	III	III	III	=
M/58	IV	1.1	II	II	III	IV	↑
M/81	NA	NA	II		I/II		=
F/55	III	NA	III	III	I/II	I/II	↓
F/46	IV	1.9	III	III, III	III	III, III	=
F/66	II/III	0.6	I		III		↑
F/60	IV	1.4	III	III, IV, IV	IV	III, IV, IV	↑
F/47	III	1.0	I		III		↑
M/31	IV	2.1	III	IV	III	IV	=
M/66	II/IV	1.9	II	IV	IV	IV	↑
M/43	III	1.6	III	III, III	III	III, III	=
F/52	V	7.0	III		IV		↑
M/57	III	0.4	III	III	III	IV	↑

tient, and 1 patient in each of the following levels: CL II/III, CL III/IV, and CL IV/V. Five patients presented with thin lesions (0.75 mm or less), 21 intermediate lesions (0.76-3.99 mm), and 6 patients thick lesion (4 mm or more). Clark levels and Breslow scheme were not available in four and three patients, respectively, due to the localization of the primary tumor and initial resection.

For the primary staging (n = 35) or follow-up study (n = 26), all patients underwent conventional staging consisting of physical examination as well as of morphological imaging, i.e. chest x-ray, CT scans of the chest, brain and abdomen or MRI. A total of 61 ^{18}F-FDG-PET examinations were performed on these patients. According to the criteria of the UICC [27], (Table 2), the patients were staged both conventionally and by the findings of ^{18}F-FDG-PET, and both results were compared. All tumor-suspicious findings were evaluated by histopathology as a golden standard.

PET scanning

The patients fastened for at least 12 hours prior to PET-scanning in order to minimize blood insulin levels and glucose utilization of normal tissue.[28] Whole-body emission images were acquired without attenuation correction 60 min after i.v. injection of 370 MBq ^{18}F-FDG using an ECAT EXACT 47 (921) scanner (Siemens/CTI, Knoxville, TN, USA) with an axial field-of-view of 16.2 cm.

Table 2. Staging of the cutaneous malignant melanoma according to the criteria of the UICC from 1997

Tumour stage	T	N	M
Stage I	PT1, pT2	N0	M0
Stage II	PT3	N0	M0
Stage III	PT4	N0	M0
	Any pT	N1, N2	M0
Stage IV	Any pT	Any N	M1

Patients were laid in the PET gantry feet first with both arms folded over the abdomen. Images were acquired for 4 min per bed position covering the feet up to the middle of the femurs. Then, the patients were repositioned in the gantry head first, and the second set of images was acquired from the brain down to the waist. Prior to the third acquisition set from the waist down to the lower extremities, the patients were asked to empty the bladder in order to decrease urine activity. Emission data were reconstructed by filtered back projection using a Hanning filter with a cut-off frequency of 0.4 of the Nyquist frequency. PET images were printed on transparency film (Helios 810, Sterling) using a linear gray scale with the highest activity displayed in black. Images were displayed with an upper threshold of five times of the mean activity in the lung. Standardized documentation included both 20 transversal and 20 coronal slices, and maximum-intensity-projections (MIPs) in the anterior, left lateral, right-anterior-oblique, and left-anterior-oblique view as published previously.[29]

Two independent nuclear medicine physicians, blinded to the results of conventional staging, interpreted PET images visually.

Results

Conventional staging

The results of conventional diagnostic procedures are listed in detail in Table 1. According to the results of conventional imaging and clinical examination, 5 out of 35 patients were classified as stage I in primary staging or follow-up, and 7 out of 35 patients as stage II in primary staging. One out of these 7 patients was initially classified as stage II but was then staged up to stage IV at the first follow-up. The remaining 23 patients were initially classified as stage III. In the follow-up investigations, 13 out of these 23 patients remained stage III, whereas two patients were

upstaged to stage IV. However, none of the patients was classified as stage IV in primary staging by conventional diagnostic procedures.

^{18}F-FDG-PET staging

Results of ^{18}F-FDG-PET are listed in detail in Table 1 as well. According to the results of ^{18}F-FDG-PET, nine out of 35 patients had neither evidence of distant metastases nor presence of lymph node metastases at primary staging. These patients were initially classified as stage I to II since ^{18}F-FDG-PET allows in principle no differentiation between pT1, pT2 or pT3. In further follow-up staging, this initial tumor stage was changed in one patient to stage IV malignant melanoma. In primary staging, 21 out of 35 patients were suspected for lymph node metastases, but not for distant metastases; therefore, these patients were classified as stage III by ^{18}F-FDG-PET. In the follow-up investigations, this initial stage was changed in five patients due to distant metastases seen by ^{18}F-FDG-PET. These patients were classified as stage IV. As far as primary staging is concerned, ^{18}F-FDG-PET suspected five patients for distant metastases, classifying these patients as initial stage IV. However, in the follow-up, ^{18}F-FDG-PET turned out to be false-positive for distant metastases in one out of the latter patients; therefore, this patient was staged down to stage III.

Comparison of conventional diagnostic work-up and ^{18}F-FDG-PET

As compared to the conventional diagnostic work-up, ^{18}F-FDG-PET revealed the corresponding tumor stage in 17 out of 35 patients (49 %), whereas 14 patients (40 %) were staged up by ^{18}F-FDG-PET and 4 patients (11 %) were staged down by ^{18}F-FDG-PET at primary staging or follow-up investigations.

Discussion

Initial studies assessed the clinical utility of ^{18}F-FDG-PET for the detection of metastatic malignant melanoma. Gritters and coworkers[3] studied 12 patients with a total of 52 biopsy- or CT-diagnosed melanoma lesions. All patients underwent additional ^{18}F-FDG-PET. Their initial data demonstrated the potential role of ^{18}F-FDG-PET for the detection of metastatic malignant melanoma, especially in untreated extrathoracic lesions. Steinert and coworkers[21] examined 33 patients with the primary diagnosis or known relapse of malignant melanoma. In their patients, ^{18}F-FDG-PET showed a sensitivity of 92 % for the detection of malignant melanoma lesions. Moreover, the specificity was 77 % without further clinical information and 100 % with clinical information. Corresponding findings were demonstrated by Holder and coworkers[16] who recommended ^{18}F-FDG-PET as a primary strategy imaging modality in the staging of melanoma patients.

In this study, a total of 35 patients with malignant melanoma underwent 61 ^{18}F-FDG-PET examinations. In nine of these patients, initial tumor staging revealed a stage I/II disease with no evidence of lymph node metastases or distant metastatic spread. However, in four of these nine patients, morphological imaging and physical examination revealed lymph node metastases and, due to the findings of conventional imaging, these patients were classified as stage III. Thus, ^{18}F-FDG-PET initially led to down-stage these patients. However, in the great majority of the patients, a stage III malignant melanoma was detected both by conventional diagnostic procedures and by ^{18}F-FDG-PET. Thus, 23 and 21 patients were initially classified as stage III melanoma by conventional diagnostic procedures and by ^{18}F-FDG-PET, respectively. However, a detailed comparison of primary staging by ^{18}F-FDG-PET and by conventional imaging showed that only 13 out of 21 pa-

tients, classified as stage III by ^{18}F-FDG-PET, were staged equivalently also by conventional imaging. Yet, in 8 of these patients, conventional imaging and physical examination were false-negative concerning the detection of lymph node metastases. In these 8 patients, ^{18}F-FDG-PET required an up staging. Moreover, ^{18}F-FDG-PET was not able to detect the presence of lymph node metastases only in 4 of 23 patients initially classified as a stage III malignant melanoma by conventional diagnostics. In six of these 23 patients, ^{18}F-FDG-PET not only detected lymph node metastases, but was also suspicious of distant metastatic spread. These patients were therefore classified by ^{18}F-FDG-PET as stage IV. In all patients but one mentioned before, ^{18}F-FDG-PET was true-positive concerning the presence of distant metastases at primary staging.

Comparing the results of both staging methods, it is remarkable that none of the patients was initially classified as stage IV by conventional staging at primary staging. In contrast, ^{18}F-FDG-PET showed suspicious-suspicious tracer accumulations, which aroused suspicion of stage IV. The histological evaluation of the detected lesions confirmed the stage IV in all these patients but one. Thus, concerning the detection of distant metastases at primary staging, ^{18}F-FDG-PET was true-positive in a total of 4 out of 35 patients.

With regard to the findings of conventional diagnostic work-up and those of ^{18}F-FDG-PET, corresponding results were seen in about half of the patients investigated. In 11 % of all patients, conventional diagnostic work-up staged-up the patients comparably to ^{18}F-FDG-PET.

Surprisingly, in the patients in whom ^{18}F-FDG-PET was not able to detect the presence of lymph node metastases, it is remarkable that most of these lesions were found in the inguinal area close to the skin. Thus, the skin might be problematic for the detection of malignant melanoma metastases by ^{18}F-FDG-PET. One potential cause of false-negative results is the fact that ^{18}F-FDG is excreted via the urine. Thus, suspicious lesions of the skin, predominantly on the lower extremities and in the inguinal area, might be interpreted as contaminations. Moreover, it is also known that the patients treated with interferon alpha and interleukin-2 exhibit cutaneous inflammatory infiltrations at the injection site[24] which may be difficult to be differentiated from a metastastic spread. The limited impact of ^{18}F-FDG-PET for the detection of metastases close to the skin might be explained for physiological and technological reasons. First, suspicious lesions located within the regions of high physiological ^{18}F-FDG uptake, i.e. the brain or the kidneys, might not be identified by ^{18}F-FDG-PET imaging. Second, the detection of small lesions with diameters of less than 5 mm might be limited by geometrical resolution of ^{18}F-FDG-PET. Moreover, PET-images in this study were reconstructed by filtered back-projection. As a consequence, melanoma metastases in borderline areas, i.e. the skin, can hardly be differentiated from non-malignant tissue. This problem might be overcome by time-consuming iterative reconstruction algorithms. With these limitations in mind, whole-body ^{18}F-FDG-PET is a suitable imaging modality in order to prove suspicious lesions in malignant melanoma. However, for the exclusion of skin metastases, an accurate and careful physical examination by a dermatologist is still indispensable in daily clinical patient management.

Any diagnostic test should, in principle, not only be judged with respect to its statistic data, but rather in the light of its effect on a treatment strategy. The therapeutic approach in malignant melanoma mainly depends on the extent of the disease. In clinical stages I and II, the excision of the primary malignancy has always been the golden standard. In the last few years, elective lymphadenectomy

was abandoned because its additional value in improving the patients' survival rate was demonstrated only in retrospective[30,31] but not in randomized prospective studies of patients.[31] If patients present with regional lymph node metastases (stage III), the therapeutic approach includes therapeutic lymphadenectomy. However, 10-year-survival-rate decreases from 97 % in patients staged pT1N0M0 to 19 % in patients staged N1 or N2 and M0 melanoma.[32] The primary treatment goal in patients with M1 malignant melanoma (stage IV) is the reduction of tumoral masses in order to prolong the patients' life expectancy as well as to improve the quality of life.[33] In principle, there are three therapeutic options: surgery, external radiotherapy, and chemotherapy. In case of isolated metastases, surgical operative treatment has appeared to be helpful in the prolongation of patients life expectancy. In most studies, life prolongation was demonstrated only in cases of total resection of all tumoral masses.[34] Thus, a 10-year-survival-rate was expected to be as low as 3 % in the patients with advanced malignant melanoma.[32] Unfortunately, there is no well-established, standardized systemic treatment protocol for managing the patients with distant metastases. The treatment strategy itself is still under clinical investigation and the subject of several patients studies. It is now evident that the patients with stage IV malignant melanoma benefit from an aggressive chemotherapy consisting of the application of interleukin-2 and interferon alpha. These authors report 5-year-survival-rate of up to 10 %.[24,35]

In addition to sensitivity and specificity of high-resolution ultrasonography of 70 % and 90 %,[36] respectively, even the patients with advanced malignant melanoma may benefit from the detection of metastases by ^{18}F-FDG-PET due to several reasons. First, patients' survival rate decreases with an increasing number of involved lymph node regions.[37] Second, the prognosis of patients is better with an early detection of metastases and with less suspicious masses at the time of detection.[37] Third, in the detection of lung metastases ^{18}F-FDG-PET has been proven superior as compared to conventional, well-established computed tomography.[38,39] And last, ^{18}F-FDG-PET offers the advantage to image the whole body in one single procedure which is especially important since in malignant melanoma often unexpected, aberrant metastatic spread is found. Thus, ^{18}F-FDG-PET has already been suggested as a tool for staging malignant melanomas.[21]

Conclusion

Our results underline the added value of ^{18}F-FDG-PET in the staging of malignant melanomas. Since further treatment mainly depends on the clinical stage, ^{18}F-FDG-PET might help to select the appropriate treatment protocol for each individual patient. However, for the exclusion of metastases, physical examination by a dermatologist and conventional imaging are indispensable.

References

1. Macfarlane DJ, Sondak V, Johnson T, Wahl RL. Prospective evaluation of 2-[^{18}F]-2-deoxy-D-glucose positron emission tomography in staging of regional lymph nodes in patients with cutaneous malignant melanoma. *J Clin Oncol* 1998; **16:** 1770-6.

2. Sober AJ, Koh HK. Melanoma and other pigmented skin lesions. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci, A.S, Kasper DL, editors. *Harrison's principles of internal medicine*. 13 ed. New Yoork: McGraw-Hill, Inc; 1994. p. 1867-71.

3. Gritters LS, Francis IR, Zasadny KR, Wahl RL. Initial assessment of positron emission tomography using 2-fluorine-18-fluoro-2-deoxy-D-glucose in the imaging of malignant melanoma. *J Nucl Med* 1993; **34:** 1420-7.

4. Zartman GM, Thomas MR, Robinson WA. Metastatic disease in patients with newly diagnosed malignant melanoma. *N Nucl Med* 1987; **35:** 163-4.

5. Ginaldi S, Wallace S, Shalen P, Luna M, Handel S. Cranial computed tomography of malignant melanoma. *AJR* 1981; **136:** 145-9.

6. Shirkhoda A, Albin J. Malignant melanoma: correlating abdominal and pelvic CT with clinical staging. *Radiology* 1987; **165:** 75-8.

7. Silverman PM, Heaston DK, Korobkin M, Seigler HF. Computed tomography in the detection of abdominal metastases from malignant melanoma. *Invest Radiol* 1984; **19:** 309-12.

8. Patten RM, Shuman WP, Teefey S. Metastases from malignant melanoma to the axial skeleton: a CT study of frequency and appearance. *AJR* 1990; **155:** 109-12.

9. Steinert H, Boni R, Huch-Boni RA, Capaul R, von Schulthess GK, Westera G. ^{123}I-alpha-methyltyrosine scintigraphy in malignant melanoma. *Nuklearmedizin* 1997; **36:** 36-41.

10. Bekerman C, Hoffer PB, Bitran JD. The role of Gallium-67 in the clinical evaluation of cancer. *Sem Nucl Med* 1985; **15:** 72-103.

11. Bockisch A, Oehr P, Biltz H, Hotze A, Kreysel HW, Biersack HJ. The clinical value of radioimmunodetection (RID) using antimelanoma antibodies. *Tumordiag und Ther* 1991; **12:** 112-6.

12. Boni R, Steinert H, Huch Boni R, Von Schulthess GK, Meyer J, Dummer R, et al. Radioiodine-labelled alpha-methyl-tyrosine in malignant melanoma: cell culture studies and results in patients. *Br J Dermatol* 1997; **137:** 96-100.

13. Damian DL, Fulham MJ, Thompson E, Thompson JF. Positron emission tomography in the detection and management of metastatic melanoma. *Melanoma Res* 1996; **6:** 325-9.

14. Boni R. Whole-body positron emission tomography: an accurate staging modality for metastatic melanoma. *Arch Dermatol* 1996; **132:** 833-4.

15. Hsueh EC, Gupta RK, Glass EC, Yee R, Qi K, Morton DL. Positron emission tomography plus serum TA90 immune complex assay for detection of occult metastatic melanoma. *J Am Coll Surg* 1998; **187:** 191-7.

16. Holder WD Jr, White RL Jr, Zuger JH, Easton EJ Jr, Greene FL. Effectiveness of positron emission tomography for the detection of melanoma metastases. *Ann Surg* 1998; **227:** 764-71.

17. Engel H, Steinert H, Buck A, Berthold T, Huch Boni RA, von Schulthess GK. Whole-body PET: physiological and artifactual fluorodeoxyglucose accumulations. *J Nucl Med* 1996; **37:** 441-6.

18. Kern KA. [14C]deoxyglucose uptake and imaging in malignant melanoma. *J Surg Res* 1991; **50:** 643-7.

19. Rinne D, Baum RP, Hor G, Kaufmann R. Primary staging and follow-up of high risk melanoma patients with whole- body ^{18}F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. *Cancer* 1998; **82:** 1664-71.

20. Paquet P, Hustinx R, Rigo P, Pierard GE. Malignant melanoma staging using whole-body positron emission tomography. *Melanoma Res* 1998; **8:** 59-62.

21. Steinert HC, Huch Boni RA, Buck A, Boni R, Berthold T, Marincek B, et al. Malignant melanoma: staging with whole-body positron emission tomography and 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1995; **195:** 705-9.

22. Reske SN, Bares R, Büll U, Guhlmann A, Moser E, Wannenmacher MF. Clinical value of positron emission tomography (PET) in oncologic questions: results of an interdisciplinary consensus conference. *Nuklearmedizin* 1996; **35:** 42-52.

23. Reintgen DR, Balch CM, Kirkwood J, Ross M. Recent advances in the care of the patient with malignant melanoma. *Ann Surg* 1997; **225:** 1-14.

24. Richards JM, Gale D, Mehta N, Lestingi T. Combination of chemotherapy with interleukin-2 and interferon alfa for the treatment of metastatic melanoma. *J Clin Oncol* 1999; **17:** 651-7.

25. Clark WHJ, From L, Bernandino E, Mihm M. The histogenesis and biologic behaviour of primary malignant melanomas of the skin. *Cancer* 1969; 29: 705-26.

26. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970; **172:** 902-8.

27. UICC. *TNM classification of malignant tumors*. 5 ed. New York: John Wiley & Sons; 1997.

28. Minn H, Leskinen-Kallio S, Lindholm P, Bergman J, Ruotsalainen U, Teras M, et al. (18-F)fluorodeoxyglucose uptake in tumors: kinetic vs. stady-state methods with reference to plasma insulin. *J Comput Assist Tomogr* 1993; **17:** 115-23.

29. Bleckmann C, Buchert R, Schulte U, Lorenzen J, Bohuslavizki KH, Mester J, et al. Onko-PET: lesion detection by computer display versus standardized documentation on film. *Nuklearmedizin* 1999; **38:** 56-60.

30. Kaufmann R. Operative Therapie des primären Melanoms. *Onkologe* 1996; **2:** 449-52.

31. Balch CM, Milton GW, Cascinelli N, Sim HF. Elective lymph node dissection: pros and cons. In: Balch CM, Houghton AN, Milton GW, Sober AJ, Soong SJ, editors. *Cutaneous melanoma*. Philadelphia: Lippincott, J. B.; 1992. p. 345-66.

32. Häffner AC, Garbe C, Büttner P, Orfanos CE, Rassner G, Burg G. The prognosis of primary and metastasizing melanoma. An evaluation of the TNM classificationin 2495 patients and proposals for their revision. *Br J Cancer* 1992; **66:** 856-61.

33. Garbe C. Malignes Melanom. In: Seeber S, Schütte J, editors. *Therapiekonzepte Onkologie*. 3 ed. Berlin: Springer; 1998. p. 799-829.

34. Göhl J, Meyer T, Haas C, Altendorf Hofman A, Hohenberger W. Ist die chirurgsche Therapie von Fernmetastasen maligner Melanome sinnvoll? *Langenbecks Arch Chir Suppl Kongressbd* 1996; **113:** 122-6.

35. Hoffmann R, Müller I, Neuber K, Lassmann S, Buer J, Probst M, et al. Risk and outcome in metastatic malignant melanoma patients receiving DTIC, cisplatin, BCNU and tamoxifen followed by immuntherapy with interleukin 2 and interferon alpha2a. *Br J Cancer* 1998; **78:** 1076-1080.

36. Blessing C, Feine U, Geiger L, Carl M, Rassner G, Fierlbeck G. Positron emission tomography and ultrasonography. A comparative retrospective study assessing the diagnostic validity in lymph node metastases of malignant melanoma. *Arch Dermatol* 1995; **131:** 1394-8.

37. Hoh CK, Hawkins RA, Glaspy JA, Dahlbom M, Tse NY, Hoffman EJ, et al. Cancer detection with whole-body PET using 2-[^{18}F]fluoro-2-deoxy-D-glucose. *J Comput Assist Tomogr* 1993; **17:** 582-9.

38. Hoh CK, Schiepers C, Seltzer MA, Gambhir SS, Silverman DH, Czernin J, et al. PET in oncology: will it replace the other modalities? *Semin Nucl Med* 1997; **27:** 94-106.