View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Via Medica Journals

VIA MEDICA
Nuclear Medicine Review 2009
Vol. 12, No. 2, pp. 83–88
Copyright © 2009 Via Medica
ISSN 1506–9680
Review

The role of radiopharmaceuticals in diagnosis of melanoma malignum

Michał Janczak
Department of Nuclear Medicine, Medical University of Lodz

[Received 25 XI 2009; Accepted 1 XII 2009]

Abstract

Melanoma malignum belongs to the group of neoplasms with the highest lethality. Due to the continuous increase of incidence in numerous countries, this malignance has become a serious health problem.

This highly aggressive neoplasm is a source of metastases to most organs and eo ipso of bad prognosis. Early detection of the primary tumour and of metastases creates a chance for optimal therapy.

The methods of nuclear medicine are becoming more popular in diagnostics of melanomas because they offer advantages over traditional methods of anatomic imaging. Functional imaging, based on the use of modern radiopharmaceuticals frequently offers more successful identification and characterization of malignant neoplasms.

Over the last few decades there have been numerous attempts to utilize, in the diagnostics of melanomas, a number of compounds labelled with radioactive nuclides.

An accepted role in diagnosis of melanoma found a technique of lymphoscintigraphic mapping of lymphatic nodes and of detection of the sentinel node. In addition, modern positron emission tomography (PET) with use of ^{18}F-fluorodeoxyglucose has found acceptance in melanoma diagnostics.

The present review refers to information on the presently used and potential new radiopharmaceuticals promising effective melanoma diagnostics.

Key words: melanoma imaging, radiopharmaceuticals

Nuclear Med Rev 2009; 12, 2: 83–88

Correspondence to: Michał Janczak
Department of Nuclear Medicine, Central Clinical Hospital
Medical University of Lodz
ul. Czechosłowacka 8/10, 92–216 Łódź, Poland
Tel: (+48 42) 675 72 71, fax: (+48 42) 679 17 80
e-mail: sandman@csk.umed.lodz.pl

Introduction

Melanoma malignum is an aggressive neoplasm, originating most often in the skin. Less frequent primary foci of melanotic character are mucosa and ocular retina. The process of neoplastic transformation, leading to the development of melanomas, results from genetic predisposition and depends on numerous external factors. Among the indicated principal causes of malignant melanoma is enhanced exposure to solar light and probably artificial sources of ultraviolet light [1–3]. The melanoma is at present a neoplasm with the highest yearly increase in incidence among all malignancies. This increase varies among different populations; however, among Caucasian populations the increase is estimated at 3–7% per year [4].

The aggressiveness of such melanomas is characterized by their ability to form metastases to almost every organ. The most frequent location of earliest metastases is near lymphatic nodes and skin. The next most frequent locations of metasta-ses in internal organs are: brain, lungs, liver, intestines, and kidneys.

Surgical removal of the primary focus in the early phase of the disease often leads to complete cure. However, occurrence of metastases leads to worsening of the prognosis. Mean 5-year survival for patients with metastases in regional lymphatic nodes varies between 20 and 50 per cent [5, 6].

An assessment of how advanced the neoplastic process is plays a dominant role in prognosis and therapy planning. For this purpose there are several classifications used which take account of various morphologic characteristics of the primary focus in the skin, a.o. the depth of skin penetration (Clarks's scale), the thickness of neoplastic infiltration (Breslow scale), and the presence or absence and localization of metastases. The length of survival is determined mostly by localization of metastases and by general advancement of the neoplastic process [7–9].

Among the noninvasive imaging techniques used for the staging of the disease and for the detection of metastases, the role of those belonging to nuclear medicine is increasing steadily. They are free of the numerous inadequacies of traditional morphological imaging techniques such as MRI, CT, and ultrasound. In anatomic imaging there are instances when differentiation of benign and malignant character are almost impossible; the same applies to changes post therapy and relapse of neoplasm. Small metastatic foci, not affecting the morphology of an organ, may be missed [10].

For many years investigators had been trying to find new radiopharmaceuticals with a high affinity to melanoma cells. The accepted role in diagnostics has been granted to lymphoscintigraphic mapping of lymph nodes and detection of the sentinel node. The same position has been granted to PET techniques utilizing ^{18}F-fluorodeoxyglucose as the marker of malignant cells. Many other techniques and tracer compounds tested did not have a sufficiently high uptake by the melanotic cells and/or too slow elimination from the surrounding tissues. The latter feature resulted in a low tumour/non-tumour ratio, which in turn made the procedure useless for the detection of melanoma foci. Further in the text the radiopharmaceuticals presently in use for melanoma diagnostics will be presented. In addition, the methods and radiopharmaceuticals that are only of historic importance and the new substances which may be potentially useful for melanoma diagnostics will be reviewed.

Nuclear medicine techniques used at present for the diagnostics of melanomas

Lymphoscintigraphy — detection of the sentinel lymph node

In the diagnostics of melanomas, a common acceptance has been obtained by lymphoscintigraphic detection of the sentinel lymph node.

For this purpose a number of colloidal substances labelled with radionuclides have gained common acceptance. At present the method is a commonly accepted standard in the diagnostics (staging) of melanomas [11–13].

The lymphatic route is the principal way of spread of melanomas from their original focus. The neoplastic cells progressing via the lymphatic vessels are stopped in the first node on the way; this node is called a sentinel lymph node. The absence of metastases in the latter, when screened by a histopathologist, indicates that the spread of the melanotic cells through a lymphatic route has not yet taken place. Such an observation also suggests with high probability that distant organs are free of metastases. According to commonly accepted standards, a negative result of sentinel node ana-lysis for the presence of melanotic cells is an accepted basis for resignation from elective lymphadenectomy dissection. However, the presence of metastases in regional lymph nodes is found in approximately 20% of patients with primary focus of melanoma only. In the remaining 80 per cent of patients, elective lymph node dissection would lead to substantial disorder and post-surgical complications while providing no therapeutic gain [12, 13].

At the beginning of lymph node mapping, the sentinel node can be detected by intracutaneous injection of a dye close to the tumour (isosulfan blue, patent blue). This method detects the sentinel node in 80% of cases [12]. Lymphoscintigraphy with a radioactive colloid, combined with pre- and intrasurgery scintigraphy by means of a manual gamma-ray detector increases the detection rate of the sentinel node to 95 per cent. The colloidal compounds used at present (albumin, sulphur-, tin-, antimonium trisulphide colloid, and albumin nanocolloid) are labelled with ^{99m}Tc [12, 13]. After injection of a radiocolloid, the regional lymph nodes may be imaged using a stationary gamma camera and localized intra surgically by using a manual gamma-ray detector.

The most difficult localization of the sentinel node by the above method is encountered in patients with the primary melanoma focus in the region of the head or neck. This small region contains numerous clusters of lymph nodes located at small distances. The injected colloid tracer moves rapidly from the site of injection and labels numerous lymph nodes. Detection of sentinel nodes in this area is also made difficult by the close proximity of the original primary focus of melanoma.

Good results were obtained by Mar and her colleagues by using the above method in the region of the head and neck and applying a hybrid SPECT-CT camera for detection while injecting a sulphur colloid labelled with ^{99m}Tc [14].

^{18}F-FDG PET

^{18}F-FDG, i.e. ^{18}F-fluoro-2-deoxy-D-glucose is widely used at present for oncological, cardiological, and neurological purposes. This analogue of glucose is preferentially taken up by cells with high metabolic activity, of which the neoplastic cells form the most frequent subject of interest. The majority of melanomas belong to this category. Initial clinical tests made in the 1990s with ^{18}F–FDG and PET provided results that promised success when using this method for detection of melanomas and their metastases [15].

The ^{18}F-FDG-PET imaging has certain limitations. The radiopharmaceutical is not specific for melanomas. Apart from the foci of various neoplasms it is taken up by muscles, inflammatory foci, and the central nervous system [16]. Access — at least in several countries — to PET is more limited than it is to SPECT imaging.

Pfannenberg and co-workers compared results of imaging using ^{18}F-FDG PET/CT and using whole body magnetic resonance imaging (MRI). While comparing results of melanoma foci detection, in which 64 patients were studied, the accuracy of PET/CT was 86.7%, of the MRI 78.8%, and the ^{18}F-FDG PET alone yielded 74.3% accuracy. The PET/CT imaging when compared with MRI was more sensitive where metastases to skin, subcutaneous tissue, and lungs were concerned. The MRI, on the other hand, demonstrated better accuracy when tumours of the brain, liver, and bone marrow were considered. Staging of the disease was most accurate in patients with advanced melanomas when a combination of ^{18}F-FDG PET/CT and MRI imaging of several organs like the brain and liver was applied [17]. Some studies of patients with melanomas in the early stages demonstrated a low effectiveness of ^{18}F-FDG PET in the assessment of melanoma spread. Wagner and co-workers assessed the sensitivity of metastases detection to the regional lymph nodes using ^{18}F-FDG PET as the tool. The sensitivity was low (21%) indicating that this mode of imaging is not a good alternative to commonly used techniques of detection of sentinel nodes and their histopathological evaluation [18].

Radiopharmaceuticals on the market, which were tested for effectiveness in melanoma diagnostics

Gallium-67 citrate

First attempts to use ^{67}Ga-citrate for the imaging of melanomas indicated high specificity but low sensitivity — in the order of 50 per cent. In the eighties, the use of larger activities of ^{67}Ga combined with modern scintigraphic imaging, mostly SPECT, yielded

a higher sensitivity of detection [19–21]. Kirkwood and his team, using an activity of ^{67}Ga citrate of 370 MBq, obtained mean sensitivity of detection of 90% and specificity of 99% when studying metastases to lymph nodes and soft tissues in a group of 67 patients. A higher percentage of false negative cases were found when metastases were looked for in internal organs (sensitivity of detection in the thorax reached only 68%). Where the brain was concerned, the same method did not visualize any of the four metastasis which were detected using other methods [20].

Present studies indicate better diagnostic efficacy of newer imaging methods when compared with ^{67}Ga citrate scintigraphy. Thus, Murata and his co-workers in their studies (1991–2001) of 44 patients with diagnosed melanomas were able to find the initial focus only in 25 per cent of cases [22]. The Kalif team compared the effectiveness of gallium-67 scintigraphy with PET tomography using ^{18}F-FDG (121 patients). This study demonstrated a higher effectiveness when compared with ^{67}Ga citrate SPECT scintigraphy. The former method also detected important melanoma foci which changed staging in the initial stadium of the disease and required correction of the therapy. Apart from diagnostic efficacy, there were other reasons for avoidance of this radiopharmaceutical: the long duration of the procedure (i.e. planar scintigraphy and SPECT after several days since administration of ^{67}Ga citrate) and the necessity to use high activities of the radiopharmaceutical [19].

^{99m}Tc-Sestamibi

Methoxyisobutyl isonitrile labelled with ^{99m}Tc (^{99m}Tc-MIBI), originally synthesized for heart perfusion studies, has also been tested for its affinity to several carcinomas. The sensitivity of mammary, pulmonary, and brain neoplasm detection varies between 60 and 85 per cent [23–29]. There have also been attempts to use the compound for the imaging of melanomas [30–34]. Soler and co-workers studied the diagnostic efficacy of ^{99m}Tc-MIBI in a group of 30 patients after resection of dermal melanomas. The sensitivity of detection of metastases of the regional lymph nodes reached a surprisingly high value — 94%. There was only one false negative result (1 out of 16 investigated and histologically verified cases) [33]. Alonso and co-workers studied a group of 81 patients with resected primary focus of melanoma, and they also obtained a very high sensitivity of metastases detection with ^{99m}Tc-MIBI — 92%. Planar scintigraphy revealed 68 from 74 melanoma foci. Most of them were localized in skin (n = 16) and regional (n = 23) or distant lymph nodes (n = 10). The metastases to internal organs were less numerous (brain: n = 6, lungs: n = 8, bones: n = 4, breast: n = 1) [34]. According to this author's opinion, the relative high fraction of false negative results was due, at least partially, to the poor resolution of the SPECT camera. This was also the reason for resignation of the use of scintigraphy for the assessment of the sentinel node by means of ^{99m}Tc-MIBI. Histopathology of the resected node was diagnostically more accurate [30, 32].

^{123}I-iodoamphetamine (^{123}I-IMP)

N-isopropyl-p-^{123}I-iodoamphetamine is a lipophilic derivative used for brain scintigraphic investigation. Holman et al. discovered the uptake of ^{123}I-IMP by melanocytes actively synthesizing melanin [10]. Murata with his team, while analyzing 44 patients with diagnosed melanomas, over 10 years, succeeded to image the primary melanoma tumour by using ^{123}I-IMP in ~91% [22].

Kato and co-workers applied ^{123}I-IMP for ocular melanoma diagnostics by using SPECT imaging. This method gave better results than ^{18}F-FDG PET, which was characterized by a high percentage of false negative results [35].

^{123}I-IMP scintigraphy is difficult when melanoma is looked for in brain, lungs, or liver due to the high physiological uptake of the radiopharmaceutical in these organs [36].

Otsuka et al. demonstrated that detection of metastases to the skeleton with IMP scintigraphy gave better results when compared with conventional skeletal scintigraphy (with ^{99m}Tc-HMDP as the radiopharmaceutical) [37].

Attempts to find a radiopharmaceutical with specific affinity to melanoma cells

Alpha-methyltyrosine labelled with ^{123}I

Tyrosine as a precursor in melanin synthesis may form an interesting tracer for diagnostics of melanoma. In the 1980s, experiments on cellular lines *in vitro* were promising [38, 39]. However, the investigations of Boni et al. later gave discouraging results. There was accumulation of alpha-methyltyrosine (AMT) in melanoma cells of the M19 line (in culture), but studies in several patients (SPECT) demonstrated a sensitivity of 37% when verified by the presence of melatonic cells by ^{18}F-FDG PET. In planar images, the melanoma foci were not detected. Due to its low sensitivity, the tests with ^{123}I-AMT were discontinued [40].

Radioimmunoscintigraphy

Radioimmunoscintigraphy utilizes monoclonal antibodies (mAb) or their fragments (Fab), labelled with radioactive nuclide, having a specific affinity to antigens present on neoplastic cells [10, 41–43]. In the 1900s there were numerous tests utilizing antibodies labelled with ^{99m}Tc (9.2.27, 255-28 S, NR-ML-05) and with ^{111}In (96.5, ZME-018).

The results obtained in many laboratories indicated a high specificity (93–100%) but were disappointing where sensitivity was concerned (49–74%). Blend and co-workers, while experimenting with Fab fragments of a monoclonal antibody NR-ML-05 labelled with ^{99m}Tc, were able to reach a sensitivity of 86%. These authors estimated the stadium of melanoma, and obtained correct results in 24 out of 26 cases; 4 neoplastic changes were found, the presence of which was not anticipated, and 2 cases were misdiagnosed as false negative [41].

Another laboratory of S.B. Sergiev used a ^{99m}Tc labelled fragment Fab2 of the antibody 255-28 S for detection of ocular melanomas. The sensitivity and specificity of the method reached 79 and 100%, respectively [43].

Wider use of radioimmunoscintigraphy in the diagnostics of melanomas is hampered by several problems. Preparation of monoclonal antibodies is very expensive and the same applies to derived radiopharmaceuticals. Secondly, for ethical reasons, mouse cells are used for in vitro preparation of antibodies with the result that antibodies are nonhuman, which may lead to an undesired reaction of patient's immunological system. There is a possible solution for the last problem by using chimeric and "humanized" antibodies. Finally yet importantly, monoclonal antibodies are large

molecules which migrate slowly in the tissues, leading to high background after introduction of such a radiopharmaceutical into the system.

Melanotropin analogues (alpha-MSH)

Melanoma cells have a high affinity to melanotropic hormone (alpha-melanocyte stimulating hormone). The hormone stimulating melanocytes acts on the cell via a melanocortin receptor of type 1 (MC1R), which, in the melanoma tissue, is over-expressed. Numerous investigators directed their attention to the possible use of MSH, connected to metal chelators, in the diagnostics of melanomas. An MSH conjugate labelled with ^{111}In and linked with metal chelator DTPA (diethylenetriaminepentaacetic acid) demonstrated promising results for melanoma imaging. However, there was a nonspecific uptake by some organs, e.g. the liver, which often acts as a recipient for melanoma metastases [44, 45].

The ^{99m}Tc labelled (Arg^{11})-CCMSH and ^{111}In labelled conjugate of MSH derivative with metal chelator DOTA (^{111}In-DOTA--Re(Arg^{11})-CCMSH) possessed a high affinity to experimental melanoma tumours. The tumour/non-tumour ratios obtained were very high for the majority of organs — with the exclusion of the kidneys, which accumulated the tracer to high concentrations [46].

Another compound investigated by Froidevaux and co-workers, an ^{111}In labelled derivative of alpha-MSH containing eight amino acids in the molecule and coupled to DOTA (^{111}In-DOTA-MSH$_{oct}$), also displayed a high accumulation in the kidneys [44]. Other modifications of the structure with utilization for coupling to DOTA, a C-end peptide, led to a new compound, DOTA-NAPamide, with still higher affinity to MC1R receptor and reduced retention in the kidneys. Utilizing a ^{68}Ga positron emitting isotope for labelling, DOTA--NAPamide gives the chance to image the melanoma by PET [45].

A team led by L. Wei utilized a ^{68}Ga labelled cyclic derivative, DOTA-Re(Arg^{11})CCMSH, in PET imaging of experimental tumours in animals [47]. The possibility to complex the DOTA-MSH derivation with numerous radioactive cations, both 2- and 3-valid, as well as strong specific binding of the complex with neoplastic cells, also creates the chance to utilize these compounds in melanoma therapy [44, 45].

Iodinated aminoalkyl benzamide derivatives

In the last few years there have been intensified investigations aimed at finding a specific radiopharmaceutical for the diagnostics of melanomas. Several compounds from the group of N-alkylated benzamide derivatives labelled with radioactive iodine nuclides (^{123}I, ^{131}I) were found that could be classified as potentially useful [48–52]. A general formula of compounds from this group is presented in Figure 1.

Preliminary investigations of several compounds yielded hope that some of them might be useful for the evaluation of regional lymph nodes, and for the detection of metastases in patients with removed primary focus of the neoplasm.

IBZA

The most thorough investigations were concentrated on N-(2-diethylaminoethyl)-4-iodobenzamide (IBZA). Michelot and coworkers studied, under clinical conditions, ^{123}I-IBZA as a potential marker of melanoma foci and obtained sensitivity and specificity of 81 and 100%, respectively [51].

W. Brandau and his team imaged melanotic foci using the same compound and confirmed presence of melanotic foci in all suspected localizations [48]. In both studies, however, there was intensive cumulation of the compound in the liver, which made detection of metastases in the abdominal cavity very difficult. The long imaging time after injection of IBZA (18–24 h) was also unfavourable, resulting from slow elimination of the radiopharmaceutical from the body [52]. On the other hand, satisfying results were obtained in diagnostics of ocular melanomas by SPECT 4 hours after administration. Everaert and his co-workers detected ocular melanomas in 9 out of 10 patients with clinically and radiologically confirmed neoplasm. One false negative case was seen in a patient with a small, hypochromatic focus. At the same time, the authors diagnosed as truly negative 4 cases in patients with ocular pathology of other origin. Therefore, the specificity reached 100% [49]. Similar results with another derivative of IBZA (iodine atom at the 2-position of the benzene ring) were obtained by I. Sillaire Houtmann (sensitivity 78%, specificity 95) [53].

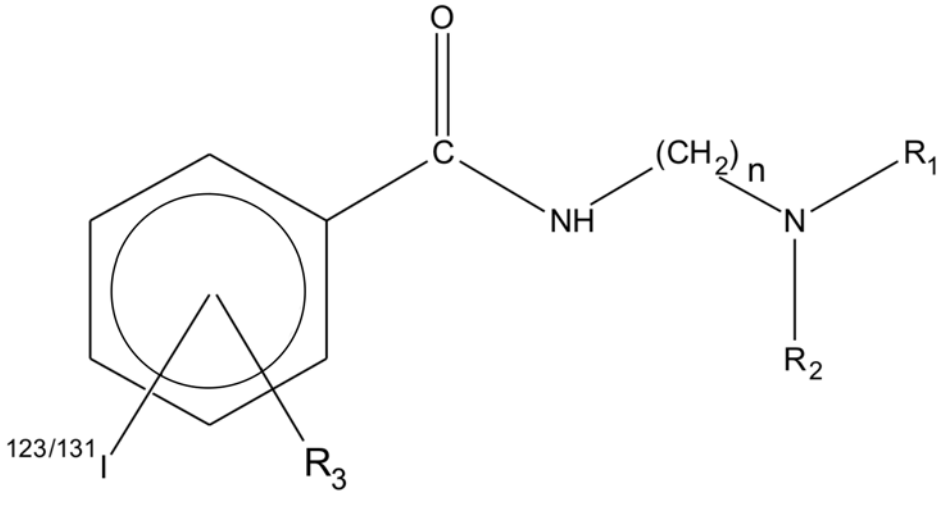

Figure 1. General structure of aminoalkyl benzamide derivatives.

IBZM

IBZM, i.e. 2-hydroxy-3-iodo-6-metoxy-N-[(1-ethyl-2-pyrodinyl)methyl] benzamide is a commercially available radiopharmaceutical from the group of benzamides used in neuropsychiatry (Parkinson's disease, schizophrenia), which is utilized due to its affinity to dopamine 2 and probably dopamine 3 receptors.

IBZM, labelled with radioiodine, was studied to ascertain if it could be useful in the diagnostics of melanomas. However, the maximum tumour/non-tumour ratio did not exceed 2.6 and was similar to that seen by Brandau for ^{123}I-IBZA . Intensive cumulation of the compound in liver was similarly inconvenient [50].

IMBA

N-(2-diethylaminoethyl)-3-iodo-4-metoxybenzamide — IMBA was synthesized while seeking a modified structure of IBZA that would improve the pharmacokinetic properties of the potential radiopharmaceutical by being faster excreted from the organism (> 90% via urinary tract). IMBA also has less affinity to erythrocytes and proteins of the serum and negligible binding by structures of the brain.

Nicholl and co-workers demonstrated in preliminary studies on a few patients that ^{123}I-IMBA is characterized by high tumour/ /non-tumour ratios in as little as 4 hours after injection [54]. Studies by Edreira and co-workers confirmed specific and high accumulation of IMBA in melanotic tissue and a high tumour/non-tumour ratio due to fast clearance of the compound from the body (in animals) via the urinary tract (whole body retention 19.7 $\pm$ 7.1% at 6 h after administration and 4 $\pm$ 2.4% at 24 hours after administration) [55]. High tumour/non-tumour ratios (153 $\pm$ 39 for blood, 176 $\pm$ 26 for intestines, 270 $\pm$ 107 for kidneys, and 448 $\pm$ 82 for muscles) were obtained in animal models studied in the Department of Nuclear Medicine of the Medical University of Lodz. This give rise to a degree of optimism when applying IMBA as a new and specific radiopharmaceutical for the diagnostics of melanomas in humans [56].

Conclusions

Malignant melanomas belong to the group of most aggressive neoplasms. Appropriate staging of melanomas should improve the treatment process. Due to its high capacity for metastatic spread, the tumour requires accurate assessment of the spread before and after the therapy. Nuclear medicine techniques are being improved and offer potential progress in diagnostics and perhaps treatment. Lymphoscintigraphy of the sentinel node and positron emission tomography (^{18}F-FDG) already have an appropriate position in clinical practice. Further improvement should be expected from combining functional with anatomic imaging in image fusing (PET/CT, SPECT/CT). Numerous compounds labelled with radionuclides have been tested for the diagnostics of melanomas. Some of these products did not find a permanent place in clinical practice, others (melanotropin analogues, radioimmunoscintigraphic tracers, and particularly the aminoalkyl benzamide derivatives seem to offer potential use in classical scintigraphic techniques (planar, SPECT). Those that seem to be specific for melanotic cells may offer an alternative by more common application of the PET technique. However, in spite of its usefulness and better resolution, PET technology is still not a commonly available technique, particularly in less affluent countries. However, new radiopharmaceuticals specific for melanomas may offer better than usual capacity for further PET diagnostics. In addition, new compounds may enable the detection of melanotic foci in numerous organs in which ^{18}F-FDG is not possible due to the physiologically high accumulation of fluorodeoxyglucose, an important case being the detection of melanoma metastases in the brain.

Acknowledgements

The author would like to thank Professors Jacek Kuśmierek and Julian Liniecki for their valuable comments and assistance during the preparation of this article.

References

1. Diepgen TL, Mahler V. The epidemiology of skin cancer. Br J Dermatol 2002; 146 (suppl 61): 1–6.
2. Kricker A, Armstrong BK, Goumas C et al. Ambient UV, personal sun exposure and risk of multiple primary melanomas. Cancer Causes Control 2007; 18: 295–304.
3. Swerdlow AJ, English JS, MacKie RM et al. Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. BMJ 1988; 297: 647–650.
4. de VE, Coebergh JW. Cutaneous malignant melanoma in Europe. Eur J Cancer 2004; 40: 2355–2366.
5. Kalkman E, Baxter G. Melanoma. Clin Radiol 2004; 59: 313–326.
6. de la Monte SM, Moore GW, Hutchins GM. Patterned distribution of metastases from malignant melanoma in humans. Cancer Res 1983; 43: 3427–3433.
7. Balch CM, Sober AJ, Soong SJ, Gershenwald JE. The new melanoma staging system. Semin Cutan Med Surg 2003; 22: 42–54.
8. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970; 172: 902––908.
9. Clark WH, Jr., From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 1969; 29: 705–727.
10. Ak I, Stokkel MP, Bergman W, Pauwels EK. Cutaneous malignant melanoma: clinical aspects, imaging modalities and treatment. Eur J Nucl Med. 2000; 27: 447–458.
11. Berman CG, Choi J, Hersh MR, Clark RA. Melanoma lymphoscintigraphy and lymphatic mapping. Semin Nucl Med 2000; 30: 49–55.
12. Morton DL, Chan AD. The concept of sentinel node localization: how it started. Semin Nucl Med 2000; 30: 4–10.
13. Statius Muller MG, van Leeuwen PA, Borgstein PJ, Pijpers R, Meijer S. The sentinel node procedure in cutaneous melanoma: an overview of 6 years' experience. Eur J Nucl Med 1999; 26 (4 supl): S20–S25.
14. Mar MV, Miller SA, Kim EE, Macapinlac HA. Evaluation and localization of lymphatic drainage and sentinel lymph nodes in patients with head and neck melanomas by hybrid SPECT/CT lymphoscintigraphic imaging. J Nucl Med Technol 2007; 35: 10–16.
15. Cobben DC, Koopal S, Tiebosch AT et al. New diagnostic techniques in staging in the surgical treatment of cutaneous malignant melanoma. Eur J Surg Oncol 2002; 28: 692–700.
16. Strobel K, Dummer R, Husarik DB, Perez LM, Hany TF, Steinert HC. High-risk melanoma: accuracy of FDG PET/CT with added CT morphologic information for detection of metastases. Radiology 2007; 244: 566–574.
17. Pfannenberg C, Aschoff P, Schanz S et al. Prospective comparison of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma. Eur J Cancer 2007; 43: 557–564.

18. Wagner JD, Schauwecker D, Davidson D et al. Inefficacy of F-18 fluorodeoxy-D-glucose-positron emission tomography scans for initial evaluation in early-stage cutaneous melanoma. Cancer 2005; 104: 570–579.
19. Kalff V, Hicks RJ, Ware RE, Greer B, Binns DS, Hogg A. Evaluation of high-risk melanoma: comparison of [18F]FDG PET and high-dose ^{67}Ga SPET. Eur J Nucl Med Mol Imaging 2002; 29: 506–515.
20. Kirkwood JM, Myers JE, Vlock DR et al. Tomographic gallium-67 citrate scanning. Useful new surveillance for metastatic melanoma. Ann Surg 1983; 198: 102–107.
21. Kagan R, Witt T, Bines S, Mesleh G, Economou S. Gallium-67 scanning for malignant melanoma. Cancer 1988; 61: 272–274.
22. Murata K, Suzuki K, Ayakawa Y, Higashi N, Paul Lin PJ. Comparison of I-123 IMP and Ga-67 citrate scintigraphy of malignant melanoma. Clin Nucl Med 2003; 28: 704–708.
23. Baillet G, Albuquerque L, Chen Q, Poisson M, Delattre JY. Evaluation of single-photon emission tomography imaging of supratentorial brain gliomas with technetium-99m sestamibi. Eur J Nucl Med 1994; 21: 1061–1066.
24. Bom HS, Kim YC, Song HC, Min JJ, Kim JY, Park KO. Technetium-99m-MIBI uptake in small cell lung cancer. J Nucl Med. 1998; 39: 91–94.
25. Danielsson R, Bone B, Agren B, Svensson L, Aspelin P. Comparison of planar and SPECT scintimammography with 99mTc-sestamibi in the diagnosis of breast carcinoma. Acta Radiol 1999; 40: 176–180.
26. Kim SJ, Kim IJ, Bae YT, Kim YK, Kim DS. Comparison of early and delayed quantified indices of double-phase (99m)Tc MIBI scintimammography in the detection of primary breast cancer. Acta Radiol 2005; 46: 148–154.
27. Tiling R, Tatsch K, Sommer H et al. Technetium-99m-sestamibi scintimammography for the detection of breast carcinoma: comparison between planar and SPECT imaging. J Nucl Med 1998; 39: 849–856.
28. Nosotti M, Santambrogio L, Gasparini M, Baisi A, Bellaviti N, Rosso L. Role of (99m)tc-hexakis-2-methoxy-isobutylisonitrile in the diagnosis and staging of lung cancer. Chest 2002; 122: 1361–1364.
29. Sygitowicz M, Lass P, Lyczak P, Stepien-Kocmiel E, Taraszewska M, Bandurski T. [Tc-99m-MIBI and Tc-99m-HMPAO accumulation in primary and metastatic brain tumors assessed by brain SPECT]. Neurol Neurochir Pol 1998; 32: 1099–1106.
30. Alonso O, Martinez M, Delgado L et al. Comparison of 99mTc-MIBI scintigraphy and sentinel node biopsy in the detection of occult lymph node metastases from cutaneous melanoma. Eur J Dermatol 2003; 13: 449–454.
31. Augusseau-Caillot A, Soler C, Teyssier F et al. Interest of PS100 assay when (99m)Tc sestamibi scintigraphy failed to identify lymph node metastases of melanoma. Eur J Dermatol 2001; 11: 432–435.
32. Alonso O, Martinez M, Delgado L et al. Staging of regional lymph nodes in melanoma patients by means of 99mTc-MIBI scintigraphy. J Nucl Med 2003; 44: 1561–1565.
33. Soler C, Perrot JL, Thiffet O et al. The role of technetium-99m sestamibi single photon emission tomography in the follow-up of malignant melanoma and the detection of lymph node metastases. Eur J Nucl Med 1997; 24: 1522–1525.
34. Alonso O, Martinez M, Mut F et al. Detection of recurrent malignant melanoma with 99mTc-MIBI scintigraphy. Melanoma Res 1998; 8: 355–360.
35. Kato K, Kubota T, Ikeda M et al. Low efficacy of 18F-FDG PET for detection of uveal malignant melanoma compared with 123I-IMP SPECT. J Nucl Med 2006; 47: 404–409.
36. Endo M, Kondo S, Iida K, Jimbow K. Successful scintigraphic visualization of metastatic lesions of a hard palate melanoma with N-isopropyl-p-[123I]-iodoamphetamine. Int J Dermatol 2003; 42: 320–321.
37. Otsuka N, Sone T, Morita K, Fukunaga M. I-123 iodoamphetamine scintigraphic detection of bone metastases from malignant melanoma. Clin Nucl Med 1996; 21: 847–850.
38. Bubeck B, Eisenhut M, Heimke U, zum WK. Melanoma affine radiopharmaceuticals I. A comparative study of 131I-labeled quinoline and tyrosine derivatives. Eur J Nucl Med 1981; 6: 227–233.
39. Kloster G, Bockslaff H. L-3-123I-alpha-methyltyrosine for melanoma detection: a comparative evaluation. Int J Nucl Med Biol. 1982; 9: 259–269.
40. Boni R, Steinert H, Huch BR et al. Radioiodine-labelled alpha-methyltyrosine in malignant melanoma: cell culture studies and results in patients. Br J Dermatol. 1997;137: 96–100.
41. Blend MJ, Hyun H, Patel B, Sullivan K, Salk D. Radioimmunoscintigraphy in patients with early stage cutaneous malignant melanoma. J Nucl Med 1996; 37: 252–257.
42. Halpern SE, Dillman RO, Witztum KF et al. Radioimmunodetection of melanoma utilizing In-111 96.5 monoclonal antibody: a preliminary report. Radiology 1985; 155: 493–499.
43. Sergieva SB, Virtcheva-Genkova A. Radioimmunoscintigraphy in patients with ocular melanoma. Clin Nucl Med 1997; 22: 25–29.
44. Froidevaux S, Calame-Christe M, Tanner H, Sumanovski L, Eberle AN. A novel DOTA-alpha-melanocyte-stimulating hormone analog for metastatic melanoma diagnosis. J Nucl Med 2002; 43: 1699–1706.
45. Froidevaux S, Calame-Christe M, Schuhmacher J et al. A gallium-labeled DOTA-alpha-melanocyte- stimulating hormone analog for PET imaging of melanoma metastases. J Nucl Med 2004; 45: 116–123.
46. Miao Y, Benwell K, Quinn TP. 99mTc- and 111In-labeled alpha-melanocyte-stimulating hormone peptides as imaging probes for primary and pulmonary metastatic melanoma detection. J Nucl Med 2007; 48: 73–80.
47. Wei L, Miao Y, Gallazzi F et al. Gallium-68-labeled DOTA-rhenium-cyclized alpha-melanocyte-stimulating hormone analog for imaging of malignant melanoma. Nucl Med Biol 2007; 34: 945–953.
48. Brandau W, Kirchner B, Bartenstein P, Sciuk J, Kamanabrou D, Schober O. N-(2-diethylaminoethyl)-4-[123I]iodobenzamide as a tracer for the detection of malignant melanoma: simple synthesis, improved labelling technique and first clinical results. Eur J Nucl Med 1993; 20: 238–243.
49. Everaert H, Bossuyt A, Flamen P, Mertens J, Franken PR. Visualizing ocular melanoma using iodine-123-N-(2-diethylaminoethyl)4-iodobenzamide SPECT. J Nucl Med 1997; 38: 870–873.
50. Maffioli L, Mascheroni L, Mongioj V et al. Scintigraphic detection of melanoma metastases with a radiolabeled benzamide ([iodine-123]-(S)-IBZM). J Nucl Med 1994; 35: 1741–1747.
51. Michelot JM, Moreau MF, Veyre AJ et al. Phase II scintigraphic clinical trial of malignant melanoma and metastases with iodine-123-N-(2-diethylaminoethyl 4-iodobenzamide). J Nucl Med 1993; 34: 1260–1266.
52. Moreau MF, Michelot J, Papon J et al. Synthesis, radiolabeling, and preliminary evaluation in mice of some (N-diethylaminoethyl)-4-iodobenzamide derivatives as melanoma imaging agents. Nucl Med Biol 1995; 22: 737–747.
53. Sillaire-Houtmann I, Bonafous J, Veyre A et al. [Phase 2 clinical study of 123I-N-(2-diethylaminoethyl)-2-iodobenzamide in the diagnostic of primary and metastatic ocular melanoma]. J Fr Ophtalmol 2004; 27: 34–39.
54. Nicholl C, Mohammed A, Hull WE, Bubeck B, Eisenhut M. Pharmacokinetics of iodine-123-IMBA for melanoma imaging. J Nucl Med. 1997;38(1):127–133.
55. Edreira MM, Pozzi OR. Iodide benzamides for the in-vivo detection of melanoma and metastases. Melanoma Res 2006; 16: 37–43.
56. Janczak M, Kapuscinski J, Olasik EM, Rozalski M, Plachcinska A, Kusmierek J. Biodistribution of two (131)I-IMBA preparations, differently labelled, in mice with experimental B16 melanoma tumours. Nucl Med Rev Cent East Eur 2008; 11: 48–52.