Piotr Rutkowski[1], Piotr J. Wysocki[2], Anna Nasierowska-Guttmejer[3], Jacek Fijuth[4], Ewa Kalinka-Warzocha[5], Tomasz Świtaj[1], Arkadiusz Jeziorski[4], Milena Szacht[1], Wojciech Zegarski[6], Wojciech M. Wysocki[7], Lidia Rudnicka[8], Witold Owczarek[9], Maciej Krzakowski[1]

[1]The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw
[2]West Pomeranian Oncology Centre, Szczecin
[3]Central Clinical Hospital of Ministry of the Interior, Warsaw
[4]Medical University, Lodz
[5]Regional Cancer Centre, Lodz
[6]*Collegium Medicum,* Bydgoszcz, Nicolaus Copernicus University, Oncology Centre, Bydgoszcz
[7]The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Division in Krakow
[8]Medical University, Warsaw
[9]Military Institute of Medicine, Warsaw

Cutaneous melanoma — diagnostic and therapeutic guidelines in 2016

Address for correspondence:

Prof. Piotr Rutkowski
Centrum Onkologii — Instytut
im. Marii Skłodowskiej-Curie w Warszawie
Klinika Nowotworów Tkanek Miękkich,
Kości i Czerniaków
ul. Roentgena 5, 02–781 Warszawa
e-mail: piotr.rutkowski@coi.pl

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ABSTRACT

Dermoscopy is currently the standard method for clinical differential diagnosis of cutaneous melanoma and for qualifying a lesion for excisional biopsy. Full-thickness excisional biopsy of suspicious melanomatous skin lesions likely to be diagnosed as early melanomas is crucial in establishing diagnosis and defining prognostic factors. Early diagnosis and surgical removal of cutaneous melanoma not only improves patients' prognosis, but it is also associated with an approximately 90% likelihood of cure. The next steps in the therapeutic management of cutaneous melanoma following excisional biopsy are radical scar excision with adequate margins and sentinel lymph node biopsy. Radical lymph node dissection is recommended in cases of regional lymph node metastases. High-risk patients (lymph node involvement and/or ulcerated primary lesion) should be advised to participate in prospective clinical trials on adjuvant therapy. Melanoma patients with distant metastases are still characterised by poor outcomes. In patients with metastatic disease, testing for the presence of *BRAF* gene mutation is mandatory. Patients with metastatic disease should be considered for participation in clinical trials. Long-term survival is confined to a selected group of patients undergoing resection of isolated metastatic lesions. In systemic (mainly first-line) therapy of patients with *BRAF* V600 mutation BRAF inhibitor — vemurafenib or dabrafenib (preferentially in combination with MEK inhibitor) — may be employed. Immunotherapy with anti-PD-1 antibodies (nivolumab or pembrolizumab), and eventually ipilimumab (anti-CTLA4 antibody), could be used regardless of mutational status.

Key words: cutaneous melanoma, diagnosis, therapy

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Introduction

Melanomas are malignant skin neoplasms derived from neuroectodermal melanomatous cells. In Poland melanoma is a relatively rare cancer with a standardised morbidity rate accounting for approximately 4.9/100,000, which corresponds to 3100 new cases yearly in recent years (ca. 1400 in male and 1700 in female patients). Nevertheless, melanomas are characterised by one of the most dynamically growing levels of incidence. Between 1980 and 2010 the number of new cases in Poland increased up to three fold. The median age of patients at diagnosis is similar regardless of gender, accounting for ca. 50 years. Standardised mortality rates reach ca. 2.3/100,000 in male and 1.5/100,000 in female patients, which corresponds, respectively, to 700 and 630 deaths due to melanoma in recent years [1, 2].

Table 1. Clinical picture of melanomas — ABCDE system

ABCDE system
A asymmetry — melanoma is asymmetrical according to each axis of the lesion, unlike benign moles, which are usually round or oval, additionally presenting irregular shape with protrusions called islands
B borders — uneven and notched
C colour — variety of colours (from different shades of brown to black, steely) with uneven pigment distribution, frequently with spot deposits (especially visible in dermatoscopy)
D diameter — higher than 5 mm or dynamics of morphological changes in the tumour
E elevation or evolution — elevation of surface above the level of surrounding epidermis. Thin melanomas (thickness ≤ 1 mm according to Breslow scale) make it impossible to palpate protuberance compared to normal skin surrounding the lesion; more important than elevation of primary lesion is extension or evolution

The most important factors of increased melanoma risk include: long exposure to natural (sunlight) and artificial (e.g. sunbed, solarium) ultraviolet radiation, continuous mechanical or chemical irritancy, low skin pigmentation, and genetic predisposition, e.g. familial atypical mole syndrome (FAMS).

Feasible early identification of primary lesion according to localisation (microstaging I — excisional biopsy of primary lesion) and metastases to regional lymph nodes (microstaging II — sentinel lymph node biopsy) give the unique opportunity to cure the patients with melanoma.

In ca. 90% of patients melanoma is a localized lesion at diagnosis, whereas regional and metastatic stages of primary lesion are noticed only in ca. 10% and < 5% of patients, respectively. In recent years there has been an advance observed in systemic treatment of patients with metastatic melanoma; nevertheless, survival rates in this group of patients are still unsatisfactory. Five-year survival rates in early stages of melanoma are 60–95% and either 20–70% or 5–10% in regional and metastatic stages, respectively.

The aim of the presented publication is to summarise the current guidelines regarding diagnosis and therapy of melanoma, established based on evidence and experts experiences, which are widely accepted and need to be disseminated*. A basic and obligatory rule should be treatment of patients within multidisciplinary teams, the members of which are experienced in the diagnosis and treatment of melanoma [3, 4].

Symptoms and diagnosis

Clinical symptoms

Skin melanoma could be suspected in case of either the appearance of *de novo* changes or nevus pigmentosus (thickening, changes of surface, colour, or borders as well as appearance of itching and/or bleeding). Clinical symptoms are sometimes grouped in systems that are intended to make diagnosis easier (Table 1). Basic system is the clinical ABCDE system, currently used mainly for didactic purposes, as it allows identification of the majority of advanced melanomas. Nevertheless, it could not be used as (screening) a diagnostic tool in clinical practice. The clinical ABCDE system does not allow proper qualification of ca. 50% of melanomas, among them particularly early lesions (< 5 mm), nodule melanomas (which usually do not show colour heterogeneity and irregularity of borders), as well as amelanotic melanomas, and lesions within the hairy part of head skin [1].

Thin melanomas (< 1 mm thickness according the Breslow scale) are mostly indicated accidentally during physical examination, but very rarely by patients or family member.

Diagnosis

Anamnesis should consider questions about skin conditions (e.g. information about changes within previously existing nevi on the skin or appearance of new nevi) as well as factors increasing the risk of skin melanoma mortality (e.g. sun burn, solarium use, positive family history regarding melanoma).

The most important element making early diagnosis of melanoma possible is skin examination, which could be performed by every physician during ambulatory visit as well as hospitalisation. Evaluation of the whole body in good light with consideration of difficult-to-visualise skin surfaces is the rule (head, feet, inter-digital spaces, genital and anus region).

Dermoscopy (dermatoscopy) or videodermoscopy is a recommended evaluation, performed during initial diagnosis. Dermoscopy gives the possibility to improve diagnostic sensitivity by ca. 30%. The most simple

*The meeting of the experts and the authors of the presented publication took place on October 23, 2015 in Warsaw. The presented guidelines reflect the statements of the authors regarding evidence-based diagnostic and therapeutic management, but they should be interpreted within the context of the individual clinical situation.

dermatoscopy technique, e.g. three-item dermatoscopic scale, is based on clinical suspicion of melanoma in cases with two out of three of the following criteria: 1) asymmetric distribution of structures within the lesion, 2) atypical pigment net, and 3) blue-white veil. The sensitivity of this method is up to 96.3%, and its specificity is up to 94.2%. Other methods of dermoscopic analysis, including dermoscopic ABCD method, pattern analysis, 7-item scale, Menzies' method, or CASH (*colour*, *architecture*, *symmetry*, *homogeneity*) algorithm, are characterised by comparable sensitivity with slightly higher specificity. It should be underlined that those dermoscopic analysis systems are not used in the assessment of the lesions in "specific localisations", among them lesions of palmar skin and feet, hairy part of head skin, facial skin, or mouth of genital mucosa. In such cases it is indispensable to use dermoscopic algorithms, established separately for skin specificity in each localisation. In case of numerous atypical nevi a good, available-for-all practice is to collect the photography documentation of lesions or whole skin surface and to compare all pictures and observed skin lesions in subsequent time points. Self-measurement of observed lesions with a ruler should be recommended to the patients at regular (e.g. every 3 months) time intervals — this method allows simple objectification of possible increases in lesion size. In questionable cases when excisional biopsy is not possible (e.g. with suspicion of melanoma within expansive congenital nevi in small children or on facial skin), recommended evaluation is by confocal laser scanning microscopy of the skin.

The main test during diagnosis of skin melanomas is histological evaluation of whole dissected nevus lesion. Any other type of procedure, other than excisional biopsy (e.g. microstaging I) does not ensure appropriate diagnosis.

After histological diagnosis of skin melanoma, treatment according to the staging of skin cancer should be initiated (see below).

Laboratory tests, which are performed during the diagnostic process in order to assess the stage of primary lesion, include: basic blood analyses [blood count, liver tests, lactate dehydrogenase (LDH) activity level], X-ray picture (RTG) of chest (in posterior-anterior and lateral projections), and ultrasound (USG) evaluation of abdomen and possibly regional lymph nodes. In asymptomatic cases other tests are not needed [among them computed tomography (CT) and positron emission tomography (PET-CT)]. CT or PET-CT should be considered in patients with diagnosis of skin melanoma in stage III (particularly with presence of clinical manifestations of metastases in lymph nodes) or isolated metastases to distant organs. In case of clinical metastases to inguinal lymph nodes, CT or magnetic resonance imaging (MRI) of the pelvis is indicated.

In patients with melanoma metastases in lymph nodes or skin with unknown primary lesion, a careful searching for a potential primary lesion is mandatory (particularly on the hairy part of head skin and mucosa) and careful taking of medical history (e.g. in the direction of potential previous electrocoagulated changes).

Differential diagnosis

Table 2 presents the conditions that should be considered during differential diagnosis of early, as well as advanced, skin melanoma.

Histological diagnosis — excisional biopsy of melanomatous skin lesion (microstaging I)

Excisional biopsy of melanomatous skin lesion is the management of choice, as it allows us to confirm microscopic diagnosis of melanoma and obtain information about major risk factors, and it is used during planning of the next steps of management (micrograding) [1, 3–5]. There are no indications for "prophylactic" excision of lesions that are not suspected of skin melanoma.

Histological evaluation of tissue sample from excisional biopsy includes macro- and microscopic evaluation with obligatory and conditional assessed features included in pathological report (http://www.pol-pat.pl/pliki/files/standardy_pdf/1.2_czerniak.pdf):

I. Macroscopic evaluation
   a. size of dissected skin fragment together with lesion (3 dimensions);
   b. lesion size (2 dimensions);
   c. colour (uniform, not uniform);
   d. lesion border (regular, irregular);
   e. nodule (present, absent);
   f. margin (lateral, in-depth).

II. Microscopic evaluation
   Microscopic features assessed obligatory:
   a. thickness of infiltration according to the Breslow scale in millimetres measured since epidermal granular layer or fundus of the ulceration until the deepest infiltrated cluster of melanocytes;
   b. presence or absence of ulceration including whole thickness of epidermis covering the tumour and assessing its extent based on diameter or percentage of affected tumour area;
   c. number of figures of mitoses calculated per 1 mm^2 in the field of highest mitotic activity;
   d. growth phase [horizontal (radial)] — intraepidermal, *in situ* with microinvasion and vertical, always invasive skin);
   e. surgical margins, the nearest peripheral (since *in situ* and invasive component) and in-depth;
   f. pT staging.

Table 2. Clinical differential diagnosis of skin melanoma

Early melanoma	• Naevus pigmentosus, naevus melanocyticus junctionalis, marginalis, naevus melanocyticus compositus • Atypical naevus • Naevus coeruleus • Lentigo simplex • Pigmented actinic keratoses • Carcinoma basocellulare superficiale • Spitz' naevus • Extramammary Paget's disease • Tattoo
Developed melanoma (locally advanced)	• Verruca seborrhoica, keratosis seborrhoica • Dermatofibroma • Keratoacanthoma • Carcinoma basocellulare pigmentosum • Haemangioma • Venous extravasation • Granuloma pyogenicum, teleangiectaticum • Pigmentosus ebaceous cyst • Sarcoma Kaposi • Glomus tumour • Other appendicular tumours, particularly pigmentosus • Onychomycosis • Subungual or subcorneal hematoma

Histologic features assessed conditionally:

g. regression grade;
h. infiltration depth according to the Clark scale (levels I, II, III, IV, V);
- histological subtype [superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM) developing within lentigo simplex or Hutchinson senile freckle, nodular melanoma (NM), acral lentiginous melanoma (ALM) in distal parts of limbs, and other types, e.g. desmoplastic];

i. presence or absence of lymphatic or blood vessels;
j. presence or absence of microscopic satellite lesions (lesions consisting of melanocytes of diameter exceeding 0.05 mm at a distance of between 0.3 mm and 2 cm from invasive component of primary melanoma lesion — N feature);
k. type of cell (epithelioid, fusiform, small, pleomorphic, other);
l. presence and intensity of lymphocytic infiltration [tumour infiltrating lymphocytes (TIL)], assessed only in vertical component; TILs non-brisk and TILs brisk;
m. presence or absence of neural trunk infiltrations;
n. presence of nevus.

Excisional biopsy is a technically simple surgical procedure and is usually possible in an outpatient setting. Excision of melanomatous skin lesion is made in local infiltration anaesthesia with a lateral margin of unchanged skin of 1–2 mm. Operational preparations include whole thickness skin as well as superficial layer of fat tissue, although the fascia is not dissected and the wound is connected with primary suture. The skin cut should be aligned with the long axis of the body (Fig. 1); only within face skin should the cut should be made according to aesthetic lines. Transverse cuts should never be made (in limb/extremities location), which in the case of reoperation gives a very bad cosmetic effect, and from an oncological point of view is wrong.

The results of fine needle or thick needle aspiration biopsy and incisional biopsy (excision or *shave biopsy*) did not provide reliable information about the primary melanoma lesion according to the requirement of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) system, and those methods should not be used.

In cases of expansive and ulcerative lesions it could be possible to take material for imprint cytology, e.g. pressing a microscopic slide into the tumour surface and sending material obtained in this way for cytological assessment.

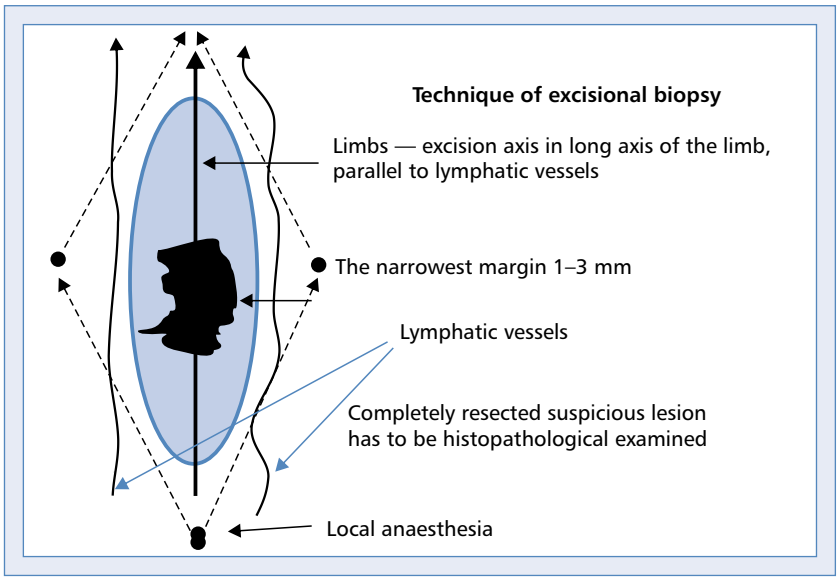

Figure 1. The correct cut axis at excisional biopsy. A spindle-shaped excision of the suspicious melanomatous skin in parallel to the nearest lymphatic vessels (in the direction of the nearest lymphatic drainage); in the majority of cases enables direct suture

It is currently known that some melanoma subtypes are connected with specific genes mutations (like *KIT* gene mutations in melanomas of distal parts of limbs/subungual or mucosal). In patients with generalised (primary or secondary) melanoma eligible for systemic treatment it is mandatory to assess mutation of the *BRAF* gene in embedded material [and also could be justified in situation of very high risk of recurrence (stage IIIC)] and optionally *KIT* and *NRAS* mutations. There is no need to additionally collect material from metastatic lesions in order to verify the presence of molecular changes. Genetic assessment should be performed in centres with validated procedures. Mutation analyses in patients with primary melanoma without metastases are not recommended [4].

Sentinel lymph node biopsy (microstaging II)

The following patients are eligible for sentinel lymph node biopsy [1, 3, 4]:

— after excisional biopsy with diagnosis of skin melanoma confirmed in histological evaluation, but without wide excision of primary lesion;
— with primary tumour thickness according to the Breslow scale ≥ 1.0 mm;
— with (micro-) ulceration on the surface of the melanoma regardless of the thickness of infiltration or mitotic index ≥ 1/mm^2 (melanoma with primary lesion classified as pT1b–T4b category according to TNM UICC/AJCC 2010 classification; based on data from the Society of Surgical Oncology (SSO), American Society of Surgical Oncology (ASSO), and European Society of Medical Oncology (ESMO), sentinel lymph node biopsy could be abandoned in pT1b melanomas with a thickness of 0.75 mm (nevertheless, it should be considered after recognition of ulceration of primary lesion);
— without clinical features of metastases in regional lymph nodes and distant organs.

Sentinel lymph node biopsy is currently an essential method of assessment of micrometastases in lymph nodes [6]. In 1999 the World Health Organisation (WHO) stated that sentinel lymph node biopsy should be the standard of care in patients with skin melanomas without clinical symptoms of metastases in regional lymph nodes [4, 6–8]. During the sentinel lymph node biopsy procedure preoperative lymphoscintigraphy and intraoperative lymphoscintigraphy should be employed together with dyeing. Sentinel lymph node biopsy should be also performed after excisional biopsy of melanoma, concomitantly with radical scar excision after excisional melanoma biopsy. Available data do not indicate any negative influence on the prognosis of sentinel lymph node biopsy performed six weeks after excision of the primary lesion. The accuracy of the method depends upon cooperation between the nuclear medicine specialist, surgeon, and pathologist. Sentinel lymph node biopsy is a "minimally invasive" diagnostic method, taking into account low frequency of early and late postoperative complications.

All found lymph nodes should undergo histological evaluation. It is enough to take one excision from lymph nodes containing macroscopically visible metastatic deposits, whereas in the remaining cases the series of lymph node specimens, each 3–4 mm, should be taken if possible. The pathological report describing this material

should contain the number of found lymph nodes, the number of lymph nodes with metastases, the size and localisation of the largest metastatic focus, the presence (or absence) of crossing of the lymph node capsule, and vessel involvement. Small clusters of neoplastic cells could be visualised with immunohistochemical assay using specific markers (e.g. HMB45, Melan-A).

The results of the prospective Multicentre Selective Lymphadenectomy Trial-1 (MSLT-1) indicate that sentinel lymph node biopsy in melanoma patients allows assessment of the group with high risk of cancer dissemination, helps to appropriately assess the disease stage, ensures excellent regional control, and makes possible qualification of patients to clinical trials according to unified criteria [7]. The MSLT-1 study did not show an improvement of time to disease recurrence and overall survival (OS) time in the whole group of patients who underwent sentinel lymph node biopsy as compared with the group with observation alone. However, in the subgroup of patients with metastases in lymph nodes 10-year survival rates were significantly higher in patients with immediate lymphadenectomy in cases of metastases in sentinel lymph node as compared with the patients who underwent such therapy later, due to indication of clinically apparent metastases (62.1% vs. 41.5%; p = 0.006) [7].

After indicating in histological evaluation the metastases of melanoma in sentinel lymph nodes, radical lymphadenectomy should be done because, based on routine histological methods, melanoma metastases in other lymph nodes (non-sentinel lymph node) are noticed in 20–30% of patients [9].

Recently clinical trials have been conducted assessing the possibility of limitation of supplementary lymphadenectomy in some patients (submicrometastases in sentinel lymph node of diameter of < 0.1 mm or in subcapsular location with diameter of up to 0.4 mm) without concomitantly negative influence on melanoma recurrence [10].

Staging and risk factors

The aim of identification of clinical and pathological prognostic factors is to understand the cancer biology and assist planning appropriate management for particular patients, with consideration to the risk of disease recurrence and the probability of survival after treatment.

Risk factors

Primary melanoma lesion

The most important risk factors in patients with skin melanoma without metastases are the thickness (according Breslow) and presence of (micro-)ulceration of the primary lesion. Currently the assessment of mitoses number has also been found to have a significant risk importance in cases of "thin" melanomas with a thickness ≤ 1 mm (pT1). These factors were used to define the TNM system (Table 3) [4–6].

Metastases in regional lymph nodes (stage III)

The presence of metastases in regional lymph nodes is the most important factor determining the risk in skin melanoma patients. In case of metastases presence the most important factor is the number of affected regional lymph nodes. The type of metastasis is also important — prognosis in patients with micrometastases (cancer focuses found during microscopic evaluation are not enlarged and clinically non-palpable lymph node, taken during sentinel lymph node biopsy) is better as compared with macrometastases (cancer focuses revealed during macroscopic evaluation of enlarged and clinically palpable lymph node). An additional important factor adversely influencing the prognosis of patients in the group with metastases in lymph nodes is crossing of the lymph node capsule by infiltration of melanoma cells.

Metastases in distant organs (stage IV)

The most important prognostic factors in patients with distant metastases are localisation of metastases and LDH serum level.

Staging classification

The current system of clinical and pathological staging of skin melanoma according to TNBM classification comes back from a revision presented in 2010 and was developed by AJCC based on multivariate analysis of data from over 38,000 patients (Table 3) [6].

Management principles

Surgical treatment is the therapy of choice in patients with melanoma. After excisional biopsy of suspicious nevi lesions and diagnosis of melanoma a decision regarding possible wider dissection of the scar with appropriate margins and sentinel lymph node biopsy should be made. In cases of either metastases in sentinel lymph node or confirmation of metastases in clinically palpable lymph nodes using fine needle aspiration biopsy, a lymphadenectomy of lymph nodes from lymphatic drainage should be done. Currently, in selected patients after surgery, an adjuvant treatment is used, whilst in patients with metastatic disease the management should be individualised according to the clinical situation. Management within a multidisciplinary team, the members of which are experienced in diagnosis and treatment of melanoma, should be a fundamental and mandatory principle.

Table 3. 2010 TNM AJCC/UICC melanoma staging

A. TNM categories

T classification	Thickness of infiltration [mm]	(Micro-)ulceration/mitoses
pTis (*in situ*)		
T1	≤ 1.0	a: without ulceration + mitotic index < 1/mm^2 b: with ulceration or mitotic index ≥ 1/mm^2
T2	1.01–2.00	a: without ulceration b: with ulceration
T3	2.01–4.0	a: without ulceration b: with ulceration
T4	> 4.0	a: without ulceration b: with ulceration
N classification	**Number of lymph nodes with metastases**	**Metastatic type**
N0	0	
N1	1	a: micrometastasis* b: macrometastasis**
N2	2–3	a: micrometastasis* b: macrometastasis** c: in-transit metastases/satellitosis without metastases in lymph nodes
N3	4 or more lymph nodes or lymphatic packet or in-transit metastases/satellite lesions with concomitant metastases in lymph nodes	
M classification	**Location of metastases**	**LDH serum level**
M0	Without distant metastases	
M1a	Skin, under skin tissue, or other lymph nodes outside of regional lymphatic drainage	Normal
M1b	Lung	Normal
M1c	Visceral organs other than mentioned above Any location	Normal Increased

Definitions:

*Micrometastasis in lymph node — detected in microscopic evaluation of clinically asymptomatic lymph node (not enlarged) after sentinel lymph node biopsy

**Macrometastasis in lymph node — detected in microscopic evaluation of palpable lymph node (enlarged) after therapeutic lymphadenectomy

Satellitosis — cancer infiltration or nodules (macro- or microscopic) located up to 2 cm from primary skin melanoma lesion

In-transit — metastases in the skin or under skin tissue at a distance of more than 2 cm from primary skin melanoma lesion until the level of the nearest regional lymphatic drainage

LDH — lactate dehydrogenase

B. Staging categories

Clinical staging*				Pathology grading**		
	T	**N**	**M**	**T**	**N**	**M**
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0

Table 3. 2010 TNM AJCC/UICC melanoma staging (continued)

Clinical staging*				Pathology grading**			
	T	N	M		T	N	M
III***	Any T	N1	M0				
		N2					
		N3					
				IIIA	T1–4a	N1a	M0
					T1–4a	N2a	M0
				IIIB	T1–4b	N1a	M0
					T1–4b	N2a	M0
					T1–4a	N1b	M0
					T1–4a	N2b	M0
					T1–4a	N2c	M0
				IIIC	T1–4b	N1b	M0
					T1–4b	N2b	M0
					T1–4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	Any M1		Any T	Any N	Any M1

*Clinical staging including microstaging of primary lesion and clinical/radiological assessment of the presence of metastases, so as a rule it could be used only after complete resection of primary skin melanoma lesion (excisional biopsy) and assessment of possible metastases in local/regional lymph nodes as well as distinct organs

**Pathology grading includes microstaging of primary lesion and pathological assessment of lymph nodes of regional lymphatic drainage: after sentinel lymph node biopsy or after radical lymphadenectomy (excluding stages 0 and IA, in which operations within lymph nodes of regional lymphatic drainage are not performed)

***In clinical staging there is no subgroup in stage III

Surgical treatment

Primary lesion

Radical treatment of the primary melanoma lesion is based on radical scar dissection after excisional biopsy of the primary lesion.

Based on the results from six multicentre randomised clinical trials, excision of the primary melanoma lesion with narrower margins of healthy tissues was introduced instead of extensive resections (e.g. with a margin of ≥ 3 cm). The following margins are recommended during radical treatment of primary melanoma lesion (excision of scar after excisional biopsy of primary lesion): melanoma *in situ* — margins 5 mm, melanoma of thickness ≤ 2 mm — margins 1 cm, melanoma with thickness > 2 mm — margins 2 cm (Table 4) [4, 5, 11]. Using of margins narrower than 2 cm decreases the local recurrence rate but without any influence on long-term survival. The scar after excisional biopsy of melanoma with thickness ≤ 2 mm should be removed without superficial fascia, but in cases of scar after biopsy of melanoma with more thick infiltration, fascia excision seems to be a good lower margin. These principles are not used in the case of face localisation of the melanoma, in which case there is a lack of fascia and the excision margins could be narrower. In cases of subungual location of melanoma amputation of distant phalange should be performed.

Table 4. Summary of the guidelines of the *National Comprehensive Cancer Network* (NCCN) v. 3.2015, *European Organisation for Research and Treatment of Cancer* (EORTC) and *European Society of Medical Oncology* (ESMO) according to final margin of radical excision of primary skin melanoma depending on its thickness according to Breslow scale

Thickness of melanoma (Breslow)	Recommended clinical margin
In situ	0.5 cm
≤ 2.0 mm	1 cm
> 2.0 mm	2 cm

Regional lymph nodes

Patients with skin melanomas with metastases in regional lymph nodes show high levels of heterogeneity according prognosis (five-year survival rates — 13–69%). In prospective clinical trials it was not confirmed that elective lymphadenectomy is beneficial in patients without clinical symptoms of metastases in lymph nodes. Currently lymphadenectomy in skin melanoma patients is performed only in cases with confirmed metastases in sentinel lymph nodes within non-clinically suspicious lymphatic drainages (microstaging II) or in cases with confirmed metastases based on histological evaluation of specimens taken during fine needle biopsy (in specific cases — surgical biopsy) from enlarged and clinically suspicious lymph nodes [1, 3, 7, 11].

Curative lymphadenectomy

Qualification to lymphadenectomy should be based on clinical evaluation in order to exclude distant

metastases (at least conventional chest radiography and ultrasound examination of the abdomen should be performed). In case of suspicions of metastases to distant organs the patient should be qualified to more specific examinations like CT or PET-CT (especially imaging of the pelvis in patients with suspected metastases to iliac and obturator lymph nodes) and MRI. Brain imaging techniques are used only when signs and symptoms occur.

The following explains the scope of lymphadenectomy in patients with skin melanomas:

— in axillary lymphatic drainage all lymph nodes should be dissected according to anatomical definition (three groups of lymph nodes together with surrounding fascia: lower level — paramammary and subscapular lymph nodes, middle level — central axillary lymph nodes, upper level — lymph nodes of axillary and subclavian veins);
— in inguinal lymphatic drainage the lymph nodes of inguinofemoral region, located below the inguinal ligament in the femoral triangle should be dissected, together with respective femoral fascia, iliac lymph nodes located along with iliac vessels, and lymph nodes of the obturator foramen [in case of small (with size of up to 1 mm) metastases in sentinel lymph nodes lymphadenectomy could be limited to only inguinal lymph nodes];
— in jugular lymphatic drainage the modified operations that meet the criterion of maximal completeness could be performed; however, usually cervical structures containing superficial (anterior and posterior) and profound lymph nodes are dissected in one block, between deep cervical from behind and platysma muscle from the front.

Sometimes it is necessary to perform lymphadenectomy within popliteal and cubital fossa.

Local recurrence and in-transit metastases

The terms "satellitosis" (micro- and macroscopic), local recurrence, and in-transit metastases comprise some consistency and describe different patterns of the same pathological phenomenon. Usually the state that is labelled as local recurrence (commonly even after very wide dissection of primary lesion) reflects spreading of melanomas along surrounding lymphatic vessels (microsatellites become macrosatellites), and then they could transform into in-transit metastases. For this reason, in the majority of reviews mentioned above, forms of skin melanoma recurrences are analysed together and show similar prognosis (10-year survival rates — 20–30%). Surgery is the main method of local treatment of local recurrence and *in-transit* metastases. It should be individualised and depends on the number, size, and location of lesions as well as the clinical course. In the case of in-transit metastases surgical management includes dissection of countable lesions (< 10) with microscopic margin without melanoma infiltration (macroscopically it could be narrow). With every next cascade of in-transit metastases dissemination, after recent dissection (e.g. before one month), the validity of subsequent local excision should be carefully considered. In the case of single recurrent lesions sentinel lymph node re-biopsy could be considered, providing there has been an adequately long time since primary operation and sentinel lymph node biopsy (12 months minimally, > 24 months optimally). Amputations should not be performed in cases of disseminated in-transit skin melanomas. In patients with multiple/non resective lesions local treatment modalities should be considered (laser ablation, radiotherapy, cryotherapy), intra-tumour (PV-10 or interleukin-2), or local immunotherapy (imiquimode not registered in this indication), and electrochemotherapy (ECT). In case of expansive, multiple lesions localised mainly on the limbs hyperthermic isolated limb perfusion (HILP), most frequently in combination with melphalan, is the preferred method, which can be used only in adequately equipped and experienced medical centres; lack of possibility of HILP use is an indication for systemic treatment [1, 4, 5, 11, 12].

Adjuvant therapy

In current clinical practice there are no indications in patients after radical operation of the primary lesion and lymphadenectomy to routine use of systemic adjuvant therapy (chemotherapy or immunotherapy), and radiotherapy should be considered only in selected patients.

Only interferon (IFN) alfa-2b in high doses has been registered in the United States (US) and the European Union (EU) for the treatment of melanomas with stage IIB–III based on the ECOG 1684 study, one of three Eastern Cooperative Oncology Group (ECOG) clinical trials, whilst IFN alfa-2b in low doses was registered in the EU for patients with stage II melanoma [13, 14]. This decision was based on significant prolongation of OS during ca. seven years of observation, which was also confirmed after an even longer follow-up (12 years). The results of clinical trials consistently (10 out of 17 analysed studies) show improvement of relapse-free survival; however, recently published meta-analyses indicate a decrease in relative risk (RR) of disease relapse by 17–18% ($p < 0.0001$) after adjuvant treatment with IFN. The evidence for overall survival improvement is significantly weaker, mainly derived from meta-analysis, and translates into an increased five-years survival rate in the whole patient population by ca. 3–5%. Taking into consideration the controversy around adjuvant IFN alfa-2b treatment of melanoma patients in moderate and high relapse risk groups, as well as its toxicity, use

of this therapeutic method should be individualised. The results of meta-analysis showed that the benefits from adjuvant INF treatment are noticed mainly in patients with ulcerated primary lesions, particularly in the subgroup of patients with micrometastases (in sentinel lymph node), but not with macrometastases in clinically enlarged lymph nodes [15]. Ipilimumab is registered in the US for adjuvant treatment of patients after lymphadenectomy due to metastases to regional lymph nodes, for whom, in randomised clinical trials, significant improvement of relapse-free survival was noted together with high toxicity of the therapy.

Other methods, such as immunotherapy (e.g. interleukin-2), vaccines, or cytotoxic drugs, have no applicability in adjuvant treatment after surgery.

Adjuvant radiotherapy is possible in selected patients after surgical operation of high-risk melanomas — dosing regimens include hypofractionation with 3–8 Gy/fraction or conventional fractionation depending on the location of the lesion. The indications for adjuvant radiotherapy after primary lesion dissection could be as follows: desmoplastic melanoma dissected with narrow surgical margins (especially after dissection of locally recurrent lesion), presence of satellite lesions, enhanced neurotropism, or head-and-neck localisation (radiotherapy as monotherapy could be used in cases of extensive lesion LMM-type), and state after dissection of locally recurrent lesion. In patients after lymphadenectomy due to metastases to regional lymph nodes indications for adjuvant radiotherapy could be as follow: extracapsular infiltration of lymph node, involvement of four or more lymph nodes (stage IIIC), diameter of metastasis > 3 cm, metastases in cervical lymph nodes (from two metastatic lymph nodes or with the minimal size of the metastasis 2 cm), and recurrence after resection [16, 17]. The results of one already completed randomised clinical trial assessing the value of adjuvant radiotherapy (48 Gy in 20 fractions) after lymphadenectomy in patients with high relapse risk confirmed an improvement in local control after irradiation, with no impact on overall survival and with concomitant increase of delayed locoregional complications.

Treatment of patients with generalised disease

The results of treatment of patients with stage IV skin melanomas are not satisfying — median survival is ca. 6–12 months (longer with recent new therapies), and 10% of patients live for five years.

Significantly important prognostic factors in patients with stage IV melanomas include performance status (PS), LDH serum level, and localisation of metastatic lesions. In patients with stage IV melanoma, qualified to surgery or systemic treatment disease intensity, should be assessed using imaging techniques or PET-CT (only isolated metastatic lesions which are qualified for resection) [1].

Dissection should be always considered in secondary lesions in skin, soft tissues, and lymph nodes (better prognosis); similar management is recommended in the case of isolated metastases in parenchymal organs. When dissection of the lesions is impossible, further management depends on the presence of metastases in the central nervous system (CNS), which is an indication for primary consideration of either surgical operation or whole CNS irradiation in order to delay the occurrence of haemorrhage or neurological symptoms (final therapeutic decision is based on localisation and number of lesions). Radiotherapy is also used in palliative care in patients with metastases in soft tissues (ulceration and pain) as well as bones (pain).

Since the effectiveness of classical cytotoxic drugs is low, progress in the treatment of generalised melanoma is connected to non-specific immunotherapy using monoclonal antibodies anti-CTLA4 or anti-PD-1, inhibiting mechanisms of systemic immunosuppression in order to induction anticancer immune response (T-cell activation), as well as targeted therapy using serine/threonine protein kinase inhibitors. Nevertheless, patients with generalised melanoma should be considered for enrolment into prospective clinical trials.

Dacarbazine is the only registered cytotoxic drug for the treatment of metastatic melanoma, but its effectiveness is limited [objective response rate (ORR) — 15% of patients, median response duration time — 4 months] [1, 3]. The only possible regimen with dacarbazine, based on registered indications, includes administration of the drug for five consecutive days in a daily dose of 200 mg/m^2. The possibility of one-day administration of a higher dose of the drug (850–1000 mg/m2 every three weeks) was not formally approved, although this treatment method is very useful in clinical practice. Paclitaxel used as a monotherapy or in combination with carboplatin in second-line treatment does not give long-lasting disease control. Randomised clinical trials did not confirmed higher effectiveness of multidrug schedules with dacarbazine in combination with cisplatin, vinca alkaloids (e.g. vinblastine), and nitrosourea derivatives (e.g. carmustine) as well tamoxifen. Biochemotherapy (chemotherapy in combination with interleukin-2 and IFN alfa-2b) did not improve the survival as compared to chemotherapy alone. The results of scarce clinical studies indicate that interleukin-2 in monotherapy or in combination with IFN alfa-2b only slightly increases the response rate with no impact on OS; however, side effects are markedly more intensive. Currently, chemotherapy should be limited to salvage treatment after failure of targeted therapy or immunotherapy.

Immunotherapy

Ipilimumab was registered for the treatment of patients with metastatic melanoma, and compared to peptide vaccine gp100 in second-line treatment showed a significant increase of OS median (with difference of ca. 3.5 months) with no significant influence on progression-free survival (PFS) [18, 19]. Kinetics and duration time of responses for ipilimumab are distinct from classical chemotherapy, and the benefits from the therapy are apparent after 3–4 months, which limits its use in patients with minimally symptomatic metastatic melanoma, good PS, and slow clinical course of disease, as well as (according to safety profile) no concomitant autoimmune diseases. As objective responses occur late during treatment, conclusive assessment of the efficacy of ipilimumab therapy should be made 12 weeks after treatment initiation, particularly taking into consideration the possibility of paradoxical progression during the early period of therapy connected with infiltration of the tumour by immunocompetent cells. Employment of the criteria of immunological response is recommended in order to objectify imaging assessment of response to ipilimumab treatment [18–20]. Currently there are no known predictive factors for ipilimumab treatment. It is recommended that ipilimumab be administered in a dose of 3 mg/kg of body weight intravenously every three weeks, until a total of four doses.

The objective response rate after ipilimumab treatment is very small (ca. 10% of patients), and only a limited number of patients (20–25%) are expected to have long-term benefit from treatment, but they have survival of many years (the longest observations reach 10 years). Side effects including autoimmune reactions are problematic during ipilimumab therapy (3–4 grade adverse events are observed in ca. 20–25% of patients). The most common immune adverse reactions include skin changes, diarrhoea, hepatotoxicity, and endocrinopathy (among them hypopituitarism and hypothyroidism). Occurrence of such symptoms in patients treated with ipilimumab should lead to referral of the patient to a medical centre with appropriate experience in the treatment of immunotherapy complications. If the intensity of clinical symptoms makes patient transportation impossible, therapy with corticosteroids should be introduced immediately [dexamethasone (or equivalent) 1–2 mg/kg daily] and further therapy should be conducted in cooperation with a reference centre. There are available appropriate algorithms [19] that should be rigidly used from the time of the first clinical symptoms suggesting immune toxicity.

Ipilimumab treatment should be conducted only in medical centres with tertiary reference, which could ensure the possibility of complex diagnostic and therapeutic management. Treatment in centres with no comprehensive management options is not justified.

Current skin melanoma treatment is connected with blockade of checkpoints within immune system PD-1/PD-L1 in monotherapy (nivolumab 3 mg/kg every two weeks or pembrolizumab in the dose of 2 mg/kg every three weeks) [21–23] or in combination with monoclonal antibodies anti-CTLA-4 (combination not registered in the EU) [24]. In a clinical setting these drugs in monotherapy or in combination with ipilimumab showed long-lasting clinical benefit in some patients with advanced melanomas as well as high response rates (up to 50%), with a one-year survival rate of 70–80%. Two-year survival rates for pembrolizumab-treated patients account for ca. 50–60%, with acceptable toxicity (< 15% of grade 3/4 adverse events, e.g. significantly lower than during ipilimumab treatment), although side effects of highest intensity still involve immune adverse events. Clinical studies have confirmed its higher effectiveness in relation to OS and PFS as compare to ipilimumab in first-line therapy, as well chemotherapy after failure of previous treatment [23]. The results of nivolumab treatment are similar [21, 22]. In a recently published clinical study comparing the efficacy of nivolumab monotherapy, and ipilimumab monotherapy with a combination of both drugs, nivolumab showed better effectiveness than ipilimumab (median PFS 6.9 vs. 2.9 months, respectively), but the combined therapy was found to be the most effective, with a median PFS of 11.5 months. Combination therapy was the best option in case of PD-L1 expression in tumour cells below 5%. If PD-L1 expression exceeded 5%, the results of treatment with nivolumab in monotherapy or in combination with ipilimumab were comparable, although to date there have been no OS data presented [24]. Considering the toxicity, serious adverse events were most frequent in patients treated with combination (grade 3/4), and they were observed in 55% of patients, in 16% of patients treated with nivolumab, and in 27% of patients receiving ipilimumab in monotherapy.

In light of the presented data ipilimumab should no longer be a basic immunotherapy in patients with advanced melanomas (giving worse results compared to monoclonal antibodies anti-PD-1), but it should be initiated with monoclonal antibodies anti-PD-1 (pembrolizumab or nivolumab) in monotherapy; in combination with anti-CTLA-4 needs to be explored in further clinical trials.

Targeted therapy

Approximately 75% of skin melanoma cases harbour mutations of MAP kinase (MAPK) involved in RAS/RAF/MEK/ERK pathway. Mutation of BRAF kinase coding gene is the predominant mechanism leading to RAS/RAF/MAPK pathway over-reactivity in skin melanoma; however, somatic mutations of *BRAF* gene are observed in only 50–70% of skin melanomas that develop in places with no long-lasting sunlight exposure.

The results of a phase III pivotal trial with vemurafenib in first-line treatment of patients with *BRAF* V600 mutation, published in 2011, revealed 48% of responses in patients treated with BRAF inhibitor compares with 5% receiving dacarbazine, as well as significant improvement of progression-free survival (PFS) (difference of ca. five months) and overall survival (OS) (difference of ca. three months) [25]. Vemurafenib was approved for the treatment of patients with advanced melanomas with *BRAF* mutation (in Polish centres there is available validated test for this mutation assessment). Despite treatment resistance occurring in the majority of patients (median PFS is 6–7 months), the results of phase II–III clinical trials showed median OS in patients with metastatic melanoma of ca. 13–16 months, which significantly exceeds the previously observed survival in this group of patients. Vemurafenib is characterised by significant skin toxicity (hypersensitivity on ultraviolet [UV] rays), hepatotoxicity typical for kinase inhibitors, and leads to secondary malignancies (keratoacanthoma/skin cancer in nearly 20% of treated patients). Secondary malignancies could develop just a few weeks after initiation of therapy with vemurafenib. This diagnosis is an indication for local treatment, but cessation of vemurafenib is not required. Adverse events relatively often lead to vemurafenib dose reduction. In 2012 the effectiveness of dabrafenib, another BRAF inhibitor, was confirmed — this drug is characterised by an effectiveness comparable with vemurafenib but different toxicity profile, e.g. lower skin toxicity. Median PFS for dabrafenib was 6.7 months vs. 2.9 months for dacarbazine, and median OS in dabrafenib-treated patients reported in 2013 was 18.2 months [26]. Currently both drugs are available in Poland within therapeutic drug programs for first-line treatment of patients with advanced melanoma with confirmed *BRAF* mutation. Phase III clinical trial results confirmed also the effectiveness of trametinib, an MEK inhibitor, in the treatment of patients with metastatic melanoma with *BRAF* mutation [27]. The effectiveness of MEK inhibitors was observed also in patients with *NRAS* mutations [28]. The results of recent clinical trials (COMBI-d, COMBI-v and coBRIM) showed that in patients with metastatic melanoma with *BRAF* mutation using a combination including BRAF and MEK inhibitor (dabrafenib with trametinib or vemurafenib with cobimetinib) gives better effects than monotherapy, without increased toxicity [29–31]. Median survival using the aforementioned drugs has prolonged to ca. 20–25 months, with a median PFS of ca. 12 months.

The above-mentioned drugs are beneficial also in patients with stable and/or asymptomatic brain metastases, which to-date have comprised the disease's location unavailable for systemic treatment of metastatic melanoma. Patients with melanoma with *BRAF* mutation with asymptomatic brain metastases could be first of all qualified to BRAF inhibitor treatment.

Since BRAF inhibitors (+ MEK inhibitors) produce a quick response and disease control in the majority of patients with advanced melanoma with *BRAF* mutation, with limited time of response duration connected to resistance mechanisms, they should be considered as the treatment of choice in patients with clinical symptoms of cancer and/or large tumour mass. Particular benefits are observed in patients with high LDH serum levels. There is no definitive evidence regarding immunotherapy sequence and targeted therapy in patients with melanoma with *BRAF* mutation, although the activity of BRAF inhibitors is preserved also after immunotherapy and, conversely, immunotherapy (anti-PD-1) after inhibitors. In rare cases of melanoma patients with *KIT* mutations activity of KIT kinase activity was observed [32].

Post-treatment observation

The frequency and type of tests, as well as the duration of observation, should be based on individual disease recurrence risk (depending on baseline disease stage); however, the possibility of recurrence more than 10 years after primary treatment should be remembered [33, 34] (Table 5). The risk of recurrence is the highest during the first three years after treatment, so recommended algorithms of follow-up evaluations suggest especially intense control during this period, mainly in order to detect possible locoregional relapse, which could be treated surgically. Assessment of scars after excision of the primary lesion and lymphadenectomy is the base of post-treatment observation. Special care is needed for evaluation of regional lymphatic drainage (possible in-transit dissemination). Apart from palpation USG could be another method for the assessment of regional lymph nodes. Since quite a large portion of locoregional recurrences could be diagnosed by patients (more than 60%), their awareness of self-control of the area after dissected primary melanoma as well as regional lymphatic drainage should be raised. There are some presumptions that less intense control schemes have no negative impact on the survival of patients with melanoma of lower stages.

Imaging tests are not justified during observation of patients with melanoma in stages IA–IIA; they could be considered during the first 2–3 years (e.g. CT scans) in asymptomatic patients with melanoma of higher stages IIB–IIIC (taking into consideration new effective drugs recently available for patients with metastatic melanoma, as earlier data indicated minimal risk of ≤ 2 months regarding expected survival prolongation with use of extended imaging evaluations). In patients with clinical symptoms suggesting distant metastases (liver enzyme elevation, bone pain, neurological symptoms, cough, and asthaenia) more specific imaging evaluations (e.g. CT, MRI, bone scan) should be performed.

Table 5. Recommended follow-up evaluations in patients with skin melanoma

	Test	Frequency
Early melanomas after excision of primary lesion without metastases in lymph nodes (stages IA–IB)	Medical history and physical examination, particularly whole skin surface and regional lymph nodes and area of scar after melanoma excision Chest X-ray (RTG) — optionally Other tests [e.g. ultrasonography (USG), computed tomography (CT)] in case of suspicious signs and symptoms USG of regional lymph nodes, when sentinel lymph node biopsy not done in melanomas ≥ pT1b No indications for any other additional tests but physical examination on patients after excision of melanoma pT1a Need to educate the patient regarding self-control	Every 6–12 months during first 5 years, then yearly (control is possible outside specialised centre)
Locally advanced melanomas after excision of primary lesion without metastases in lymph nodes (stages IIA–IIC)	Medical history and physical examination, particularly whole skin surface and regional lymph nodes and area of scar after melanoma excision Chest X-ray, abdominal USG Blood count and biochemistry (liver enzymes and lactate dehydrogenase serum level) — optionally Other tests (e.g. CT) in case of suspected signs and symptoms USG of regional lymph nodes, when sentinel lymph node biopsy not done in melanomas ≥ pT1b In patients with melanomas IIB–IIC CT could be performed every 6–12 months, and brain MRI optionally once per year (during first 2–3 years) Need to educate the patient regarding self-control In IIC melanoma more intense follow-up evaluations could be used (as stage III)	Every 3–6 months during first 2–3 years, then every 6–12 months until 5 years, and then yearly after 5 years
After excision of metastases in local lymph nodes or local recurrence/satellite lesion/in-transit metastasis (stages IIIA–IIIC)	Medical history and physical examination, particularly whole skin surface and regional lymph nodes and area of scar after melanoma excision Chest X-ray Blood count and biochemistry (liver enzymes and lactate dehydrogenase serum level) USG of abdomen and alternatively area of excised regional lymph nodes Considering high risk of recurrence, CT scans should be performed every 6–12 months and optionally brain MRI optionally once per year (during first 2–3 years) in stage IIIC Need to educate the patient regarding self-control	Every 3 months during first 2 years, every 3–6 months during subsequent 3 years, and yearly after 5 years
After treatment of distant metastases (stage IV)	Imaging tests according to location of measurable metastatic lesions Lactate dehydrogenase serum level	Follow-up visit schedule individualised for every patient

During follow-up whole skin evaluation is mandatory (as regards statistically higher possibility of development of second, independent melanoma lesion or other skin cancer).

Summary

Excisional biopsy of atypical and suspicious melanomatous skin changes, which could be an early melanoma, is of crucial importance for diagnosis and establishing the most important risk factors (microstaging I). It is widely believed that earlier diagnosis and excision of melanomas not only improves the prognosis, but also give a possibility of cure for nearly 90% of patients. Usual pigment moles with size up to 2 cm in the transverse axis could be removed in an outpatient setting within a so-called excisional biopsy. Additional management steps include the qualification of patients to radical excision of scar after excisional biopsy with appropriate margins and sentinel lymph node biopsy. Radical lymphadenectomy is the management of choice in the case of metastases in regional lymph nodes. It is recommended that the patients with skin melanomas of high recurrence risk be included in prospective clinical trials with adjuvant therapy. Figures 2 and 3 present the algorithm for diagnosis and therapy in cutaneous melanoma patients.

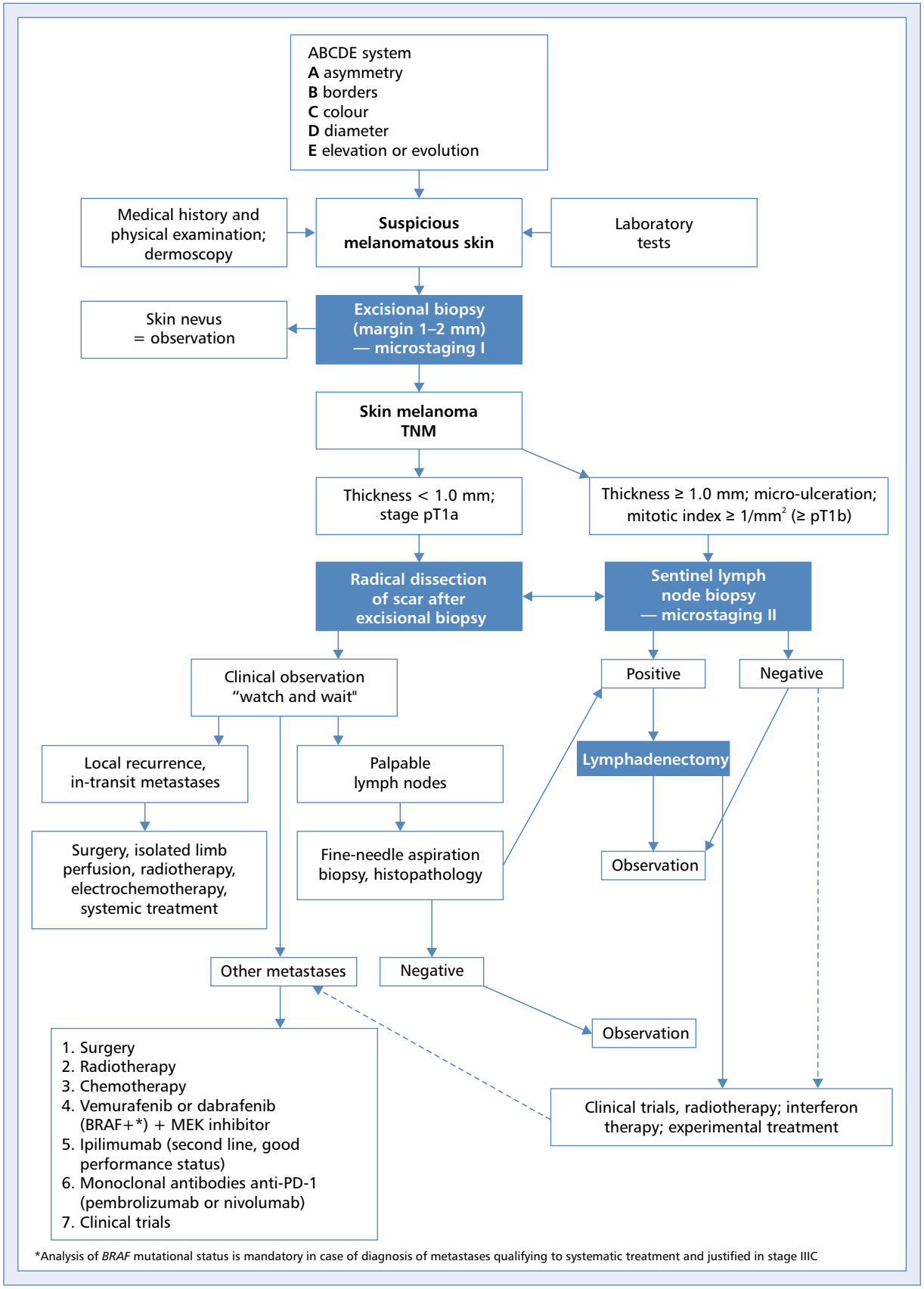

Figure 2. Algorithm for diagnosis and therapy in cutaneous melanoma

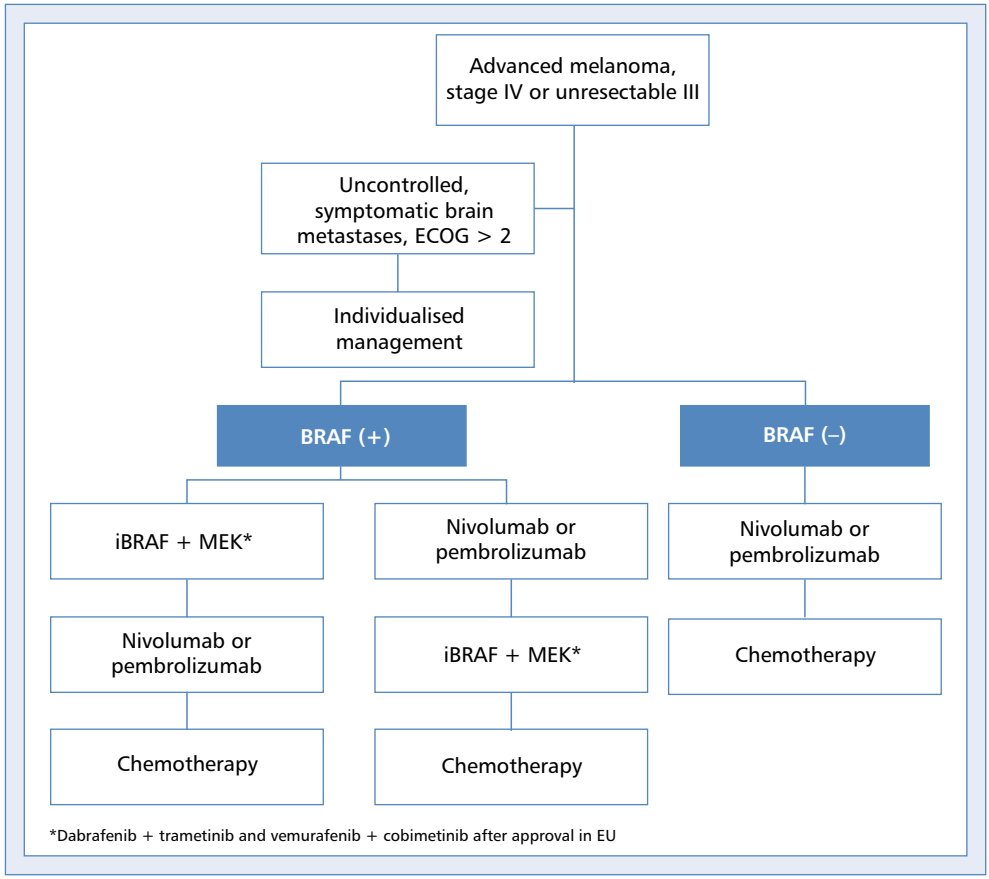

Figure 3. Proposed algorithm of systemic treatment in patients with advanced melanomas in stage IV or unresectable III. iBRAF — BRAF inhibitor; iMEK — MEK inhibitor

The presence of distant metastases is still connected with poor prognosis. In patients with generalised disease, treatment within clinical trials seems to be the best means of management. In patients with metastatic melanoma or with high risk of recurrence (IIIC) assessment of mutation of *BRAF* gene is recommended. Long-term survival is observed mainly in patients who have undergone resection of single metastatic lesions. Systemic treatment — mainly first line — of patients with *BRAF* V600 mutation include BRAF inhibitors (preferably in combination with MEK inhibitor) and immunotherapy with anti-PD-1 antibodies (nivolumab or pembrolizumab), eventually ipilimumab (anti-CTLA4 antibody), regardless of mutational status. The sequence of treatment (particularly with *BRAF* mutation) is not yet established; use of combination treatment with BRAF and MEK inhibitors is connected with high response rate (app. 70%) and rapid disease symptoms relief, and then treatment with monoclonal antibodies anti-PD-1 gives lower response rates, but in the majority of patients they are durable.

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