

Cutaneous melanomas

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According to the authors, the guidelines contains the most justified principles of diagnostic and therapeutic procedures. They should, however, be interpreted in the context of the individual clinical situation. Recommendations do not always correspond to the current refund rules in force in Poland. In case of doubt, you should be sure of the current refund possibilities of each procedure.

Epidemiology and aetiology

Skin melanomas are malignant neoplasms deriving from neuroendocrine melanocytic cells. Melanoma are relatively rare in Poland — a standardised incidence rate reaches about 5/100,000, which represents 3100 new melanoma cases per year during the last few years (about 1400 men and about 1700 women). However,

Table 1. American ABCD(E) system, which enables the initial identification of a part of melanomas based on a clinical examination without use of any supplementary diagnostic methods**ABCD system**

A — asymmetry (a melanoma in contrast to usually round or ellipsoidal benign changes, is asymmetrical in relation to any axis. Melanoma presents as an uneven change composed of **elevations** called 'islands')

B — borders (irregular and unravelled)

C — colour [the presence of more than one colour (from bright brown to black or steel blue) or the uneven distribution of colour, often with spotted distribution of the pigment. (especially well visible on the dermatoscopy)]

D — diameter (diameter > 5 mm or **dynamics** of the morphological sizes in a tumour)

E — elevation or evolution [elevation of surface over the level of the change surrounding epidermis. Thin melanomas (thickness ≤ 1 mm according to Breslow scale) do not form a palpable node compared to a normal skin surrounding the lesion; increase of the diameter (extension or evolution) of the primary change is more significant than its elevation]

the incidence rate of melanoma is increasing rapidly compared to other neoplasms. A threefold increase of melanoma morbidity has been observed in Poland during the years 1980 to 2010. The median age at diagnosis is similar for both sexes and equals about 50 years. The standardised mortality rate reaches 2.3/100,000 men and 1.5/100,000 women, which represents, during the last years, respectively, about 700 and 630 melanoma related deaths [1, 2].

The influence of the natural ultraviolet radiation (solar rays) and artificial radiation (e.g. tanning beds, solarium), permanent mechanical or chemical irritation, low content of pigment in the skin, and genetic predispositions (e.g. familial atypical mole syndrome; FAMS) constitute risk factors of melanomas.

Skin melanoma has an unique chance to be cured due to its localisation, which enables early identification of the primary site (microstaging I — excisional biopsy of the primary lesion) and of the metastases to the locoregional lymph nodes (microstaging II — sentinel nodes biopsy).

In about 80% of patients, cutaneous melanoma is a limited, local disease, while a loco-regional advanced or metastatic disease is primarily diagnosed in, respectively, 15% and 5% of patients. Progress in the adjuvant and palliative therapy of patients with metastatic melanoma is still unsatisfactory. The five-year overall survival rates reach in early stages of melanoma 70–95% as well as 20–70% and 5–10% in regionally advanced and metastatic disease.

The crucial recommendation is to treat a melanoma patient with a multidisciplinary team formed by specialists experienced in diagnosing and treating melanoma [3, 4].

Diagnosics

Clinical symptoms

Skin melanomas may be suspected in both de novo skin changes and in alterations of pre-existing

moles. There are some attempts to create diagnostic systems based on clinical symptoms (Table 1). The most popular is the American mnemonic, clinical system called ABCD(E), actually used mostly with educational intention because it is useful only in identification of some melanomas, mostly of the superficial spreading melanomas and of the majority of advanced melanomas. However, this system cannot be used as a diagnostic (screening) tool in daily clinical practice. A clinical ABCD(E) system does not permit appropriate qualification of about 50% of melanomas (especially including the early stages of skin melanomas with diameter < 5 mm, nodular melanoma usually without parameter C — heterogeneity of colour and B — irregular border as well as amelanotic melanomas and changes of the hairy skin of the head surface) [1].

Thin melanomas (< 1 mm of thickness according to Breslow scale) are usually identified during the medical examination, whereas very rarely by a patient him/herself or by his/her relatives.

Diagnosics

Medical history should include questions concerning skin condition (information concerning changes of the pre-existing skin moles or the appearance of new moles) and risk factors of cutaneous melanoma (e.g. sunburn, use of tanning beds, melanomas in relatives). We should stress that skin examination is a crucial method of detecting skin melanomas and should be performed by each physician during the ambulatory visit or hospitalisation of any patient. The major rule of the visual inspection is to evaluate the total skin surface in appropriate lighting, also including the hard-to-reach areas (head, feet, interdigital spaces, urogenital, and perianal areas).

Dermatoscopy (dermoscopy) is a recommended tool used in initial diagnostics. Due to dermatoscopy the sensitivity of the diagnostics may be improved by 30%. The simplest dermatoscopic technique (the so-called three-point dermatoscopic scale) is based on clinical suspicion of a skin melanoma in the case when

two of the following three criteria are present: 1) asymmetric distribution of the structures within the change, 2) atypical pigmentation network, and 3) blue-white veil. The sensitivity of this diagnostic method reaches 96.3% and specificity 94.2%. Other methods of dermatoscopic analysis including the dermatoscopic method ABCD, pattern analysis, seven-point scale, Menzies's method, or CASH (colour, architecture, symmetry, homogeneity) algorithm are characterised by similar sensitivity and slightly higher specificity. It should be stressed that the presented dermatoscopic evaluation systems cannot be used to assess lesions placed in 'special locations' including changes of palms and soles of the feet, the hairy skin of the head surface, the skin of the face, mucosa of the mouth, and the external sex organs. In such cases it is necessary to apply dermatoscopic algorithms, dedicated to the character of the skin of each localisation. In the case of atypical mole syndrome it may be useful to collect photographic records of a lesion or of the total skin surface (total body photography) and to compare taken pictures and observed skin lesions in consecutive time sequences. There are some systems that automatically compare dermatoscopic pictures taken in different time sequences; however, they are not commonly used due to their technological limitations.

An initial dermatoscopic diagnosis may be verified by use of the confocal reflection microscopy. In some justified cases when an excisional biopsy cannot be performed (e.g. when melanoma is suspected in the area of the extensive congenital moles in small children), it is possible to perform a dermatoscopy-guided biopsy in order to obtain a sample for further histopathological examination.

Histopathologic examination of the whole excised mole is crucial for diagnosing a skin melanoma. Procedures other than excisional biopsy (micrograding I) do not permit an appropriate diagnosis [III, A].

Once a histopathological diagnosis of a skin melanoma has been made a clinical stage tailored therapy should be implemented (*see below*).

The supplementary diagnostic tests used in clinical staging of the melanoma include: essential blood test [peripheral blood morphology, liver enzymes levels, lactate dehydrogenase (LDH) activity], radiologic exam (RTG) of the chest in an anteroposterior and in lateral projection as well as the ultrasonographic exam of the abdomen and of the locoregional lymph nodes. In asymptomatic patients, no other supplementary test should be done, including computed tomography (CT) and positron emission tomography (PET). CT or PET may be considered in patients with diagnosed skin melanoma in clinical stage III (especially if the clinical metastases to the lymph nodes are present) or with isolated metastases to the distant organs. In the case of the clinical metastases to the inguinal lymph nodes it is recommended that CT or magnetic resonance imaging (MRI) of the pelvis and abdomen is performed.

In patients with melanoma metastases from an unknown primary site to the lymph nodes or to the skin, a primary lesion should be searched for carefully (especially on the hairy skin of the head surface and the mucosal membranes) and a detailed medical history taken (e.g. concerning any cosmetic medicine ablation methods applied to any lesion).

Differentiation

The conditions that should be considered in the differential diagnostics of the early and locally advanced skin melanoma are presented in Table 2.

Histopathological diagnosis — excisional biopsy of the skin lesion (microstaging I)

An excisional biopsy of the clinically suspected skin lesion is a method of choice because it allows confirmation of a microscopic diagnosis of melanoma and collection of data concerning the crucial risk factors, crucial for planning a further therapeutic approach (microstaging III, A) [1, 3–5]. There are no indications for prophylactic excision of skin moles that are not suspected of being skin melanoma.

Pathomorphological examination of samples from the excisional biopsy consists of macro and microscopic assessment of all elements that are required or recommended for examination and inclusion in the histopathologic protocol (http://www.pol-pat.pl/pliki/files/standardy_pdf/1.2_czerniak.pdg):

1. Macroscopic assessment
 - a. Size of the excised skin section with the lesion (three dimensions);
 - b. Size of the lesion (two dimensions);
 - c. Pigmentation (homogenous, heterogeneous);
 - d. Border of the lesion (regular, irregular);
 - e. Nodule (present, not present);
 - f. Margins (lateral and deep margin).
2. Microscopic assessment

Microscopic features/characteristics that are required

 - a. Breslow thickness of infiltration (in millimetres) is measured from the top of the granular layer of the epidermis, or if the surface is ulcerated — from the base of the ulcer, to the deepest invasive cell across the broad base of the tumour;
 - b. The presence or absence of ulceration including the whole thickness of the epidermis covering the tumour as well as information about the extent of ulceration, measured either as the diameter or percentage of tumour width;
 - c. The mitotic count per square millimetre of the invasive melanoma (only in a vertical component, in the mitotic high-power fields that equates to 1 mm², so-called hot spots);

Table 2. Clinical differential diagnostics of skin melanoma

Early skin melanoma	<ul style="list-style-type: none"> — Nevus pigmentosus, including junction nevus (naevus melanocyticus junctionalis, marginalis) and compound nevus (naevus melnocycticus compositus) — Blue nevus (naevus coeruleus) — Simple lentigo (lentigo simplex) — Actinic keratosis or solar keratosis — Superficial basal cell carcinoma (carcinoma basocellulare superficiale) — Spitz's naevus — Tattoo
Locally advanced melanoma	<ul style="list-style-type: none"> — Seborrheic keratosis (verruca seborrhoica, keratosis seborrhoica) — Dermatofibroma — Keratoacanthoma — Pigmented basal cell carcinoma (carcinoma basocellulare pigmentosum) — Haemangioma — Venous extravasation — Pyogenic granuloma (granuloma pyogenicum) and teleangiectatic granuloma (granuloma teleangiectaticum) — Pigmented hidrocystoma — Kaposi's sarcoma — Angiomyoneuroma — Other adnexal tumours, especially pigmented — Onychomycosis — Subungual or under cutaneous corn haemangioma

d. Growth phases [horizontal (radial) — intraepidermal, *in situ* with microinvasion and sagittal (vertical), always skin invasion];

e. Presence or absence of microscopic satellite sites (sites composed of melanocytes with diameter > 0.05 mm removed > 0.3 mm and < 2 cm from the invasive component of the primary melanoma tumour — parameter N).

f. Peripheral margin (measured from the *in situ* to the invasive component) and in depth;

g. Clinical stage pT;

Recommended elements:

h. Presence and extend of tumour regression;

i. Clark level of invasion (level I, II, III, IV, V);

j. Histopathologic subtype [superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM); arising from a lentigo or in a Hutchinson age spot, nodular melanoma (NM), acral lentiginous melanoma (ALM) — subungual, other types — e.g. desmoplastic];

k. Cell type (epithelioid, fusiform, small, pleomorphic, other);

l. Presence and grading of the lymphocytic infiltration [tumour infiltrating lymphocytes (TILs); evaluated only in a vertical component; absent, moderate — TILs non-brisk, abundant — TILs brisk];

m. Presence or absence of lymph and blood vessel infiltration;

n. Presence or absence of nerve trunk infiltration;

o. Presence of a mole.

An excisional biopsy is a simple surgical procedure and usually may be done in an outpatient clinic. Excision of the suspected skin change is done in local infiltration anaesthesia. The lateral excision margin should include 1–2 mm of healthy skin. The surgical specimen should include not only the whole thickness of the skin but also a superficial layer of the adipose tissue. The fascia should not be excised, and the wound should be closed by a primary suture. The skin should be cut as an ellipse specimen following the lines of relaxed skin tension (Fig. 1). Only the cut of the face lesion should follow the aesthetic lines. Transversal cuts should never be done (on the limb area) because in the case of repeated surgery they give a poor cosmetic effect and are inconsistent with oncological recommendations.

Results of the fine- or core-needle aspiration biopsy or of the incisional (section) or shave biopsy do not deliver reliable data [according to recommendations of the American Joint cancer Committee/Union International Contre le Cancer (AJCC/UICC)] concerning the primary melanoma lesion and therefore should not be used.

If the lesion is extensive and ulcerated, imprint cytology may be performed in order to obtain a sample for cytological examination (a glass slide should be pressed

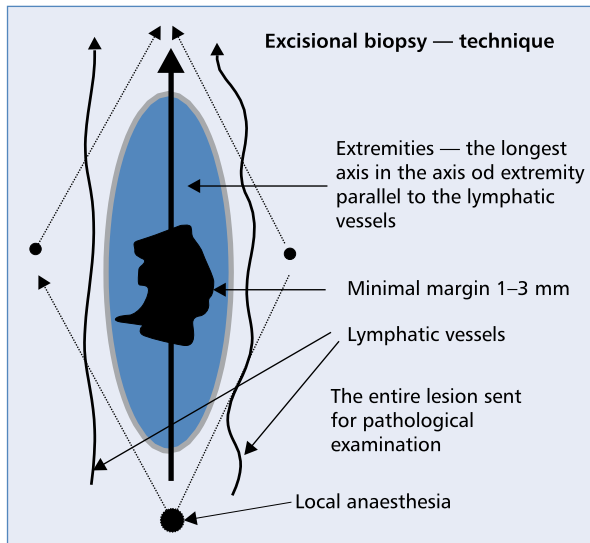


Figure 1. (According to W. Ruka) Recommended direction of the cut during the excisional biopsy. Spindle-shaped excision of the suspected pigmented lesion should be made collaterally to the regional lymph vessel (toward the nearest draining lymph node/lymph vessel confluence), in the majority of cases enabling a primary suture of the wound

onto the tumour surface and then the material should be referred to cytological examination).

It is currently known that some defined subtypes of melanoma are associated with specific mutations (e.g. *KIT* gene mutations — subungual melanoma or mucosa melanomas). In patients with disseminated (primary or secondary) melanoma, testing for *BRAF* gene mutation in the fixed section is obligatory [and may also be reasonable in the case of high risk of relapse of melanoma (clinical stage IIIB, IIIC and IIID)] and for *KIT* and *NRAS* mutation is optional [V, A]. There is no need for repeated sampling of the metastases to detect the presence of molecular disorders. Genetic tests should be performed in referral centres that undergo quality audits. It is not recommended that mutations are tested for in patients with skin melanoma and no metastatic sites [4].

Sentinel node biopsy (microstaging II)

A sentinel node biopsy should be done in patients [II, A] [1, 3, 4, 7, 8]:

- after an excisional biopsy and with histopathological confirmation of skin melanoma but not after a wide local excision of a primary site;
- with Breslow thickness ≥ 1 mm:
 - with (micro-) ulceration on the melanoma surface independently of the thickness of the infiltration [melanoma with primary site that has been classified as pT1b-T4b according to TNM UICC/AJCC 2010 classification]; according to

recommendations of the American Society of Surgical Oncology (SSO), American Society of Clinical Oncology, and the European Society of Medical Oncology (ESMO) a sentinel node biopsy may be considered in melanoma pT1b and thickness from 0.75 mm and coexistence of additional risk factors e.g. mitotic index $\geq 1/\text{mm}^2$ [III, A];

- without clinical symptoms of metastases to the regional lymph nodes or to the distant organs.

A sentinel node biopsy is obligatory to assess the presence of micrometastases in the lymph nodes [6]. During the sentinel node biopsy, a preoperative lymphoscintigraphy and an intraoperative lymphoscintigraphy combined with staining should be done. A sentinel node biopsy should be performed after the excisional biopsy of melanoma, simultaneously with the radical, wide local excision of the scar after the primary excisional biopsy of melanoma. Accessible data do not indicate any negative prognostic impact of performing the sentinel node biopsy six weeks after the excision of the primary melanoma site [III, B]. The accuracy of this method depends on the cooperation of a nuclear medicine specialist, surgeon, and pathologist. A sentinel node biopsy is a diagnostic procedure that is 'minimally invasive' due to low frequency of early and late complications.

All detected lymph nodes should undergo pathophysiological assessment. If the metastatic deposits are macroscopically visible it is enough to exam only one section while in all other cases serial sections of the lymph node at every 2–4 mm should be done. A histopathological report describing this material should include the number of lymph nodes found, the number of lymph nodes with metastases, the size and localisation of the biggest metastatic site, the presence or absence of the extracapsular spreading, and vascular invasion. Immunohistochemical exam with use of specific markers (e.g. HMB45, Melan-A) may visualise tiny conglomerates of the neoplastic cells.

The results of the prospective study Multicentre Selective Lymphadenectomy Trial 1 (MSLT-1) suggest that a sentinel node biopsy melanoma helps to identify patients with high risk of metastases, helps to assess the clinical stage of the disease, ensures excellent local disease control, and enables qualification of patients to clinical trials with the use of homogenous criteria [7]. In the MSLT-1 trial in the whole analysed population of patients who underwent sentinel node biopsy, no disease-free survival time and no overall survival time improvement was proven, compared to the whole study population. However, in a subgroup of patients with present metastases to lymph nodes the overall 10-year survival rate was significantly better in patients in whom an immediate lymphadenectomy had been performed in the case of a positive sentinel node, compared to patients who had received this therapy later for clinically overt metastases (62.1% vs. 41.5%; $p = 0.006$) [7].

If the histopathological assessment affirms the presence of melanoma metastases to sentinel nodes, a radical lymphadenectomy may be considered (so-called completion lymph node dissection, CLND) because the melanoma metastases to other lymph nodes are detected by routine histopathological methods in about 20–30% of patients [9] (especially when micrometastasis size exceeds 1 mm). An alternative option is an observation with use of ultrasonographic monitoring of the regional lymphatic system every 4–6 months. The results of two published randomised studies [10, 11] did not prove any survival benefit in patients who had CLND due to a positive sentinel node biopsy. However, an improvement in regional lymphatic basin control was achieved. Crucial prognostic value of the sentinel node biopsy was also confirmed in these studies.

Actually, there are ongoing clinical studies evaluating if the adjuvant lymphadenectomy may be limited in some patients (sub-micrometastases to the sentinel lymph node with diameter < 0.1 mm or placed subcapsular and with diameter < 0.04 mm) with no negative impact on the melanoma reoccurrence rate [12].

Staging and risk factors

Identification of the clinical and pathomorphological risk factors aims to understand the biology of the neoplasm and to plan a tailored therapy for a given patient, which considers relapse risk factors and overall survival probability.

Risk (prognostic) factors

The primary melanoma lesion

The most important risk factors in patients with skin melanomas without metastases are thickness (Breslow) and presence of micro(ulceration) of the primary site. An important prognostic value of mitotic index and microsatellitosis as part of parameter N has recently been proven. These factors are included in TNM system version 8 (Table 3) [4–6, 13].

Metastases to the regional lymph nodes (clinical stage III)

The presence of metastases in the regional lymph nodes is the most important prognostic factor in patients with skin melanomas. In the case of the presence of metastases, the number of involved regional lymph nodes constitutes the principal risk factor. The type of metastases also influences the risk; patients with micrometastases have better prognosis (neoplastic sites detected during the microscopic exam in the clinically not enlarged and not palpable lymph nodes — excised during the sentinel node biopsy) than patients with

macrometastases (foci of neoplasm diagnosed during the microscopic exam in a clinically enlarged and palpable lymph node). Extracapsular infiltration of the neoplastic cells constitutes an additional negative risk factor in patients with metastases to the lymph nodes.

Metastases to the distant organs (clinical stage IV)

Localisation of metastases and LDH activity are the major prognostic factors in patients with extranodal metastases.

Clinical staging — classification

The actual clinical and pathological stage classification system of skin melanoma according to TNM was revised in 2010 and 2017, and formulated based on the multifactor analysis of data of 38,000 patients (Table 3) [13] [II, A].

Treatment

Surgery is a treatment by choice in patients with melanoma [I, A]. After performing an excisional biopsy of the suspected pigmented lesion and making a diagnosis of melanoma, we should consider a wide scar excision with appropriate margins and a sentinel node biopsy. In the case of detecting a metastasis in clinically palpable regional lymph nodes by fine-needle biopsy, lymphadenectomy of the regional lymph nodes should be performed. Lymphadenectomy should be considered if a sentinel node biopsy confirms metastases. Actually, adjuvant therapy after surgery is used only in special situations, and in patients with metastatic disease it should be tailored to the clinical situation. The essential and obligatory recommendation is to refer patients to a multidisciplinary team of specialists experienced in diagnostics and treating melanomas.

Surgical treatment

Primary site

Radical therapy of the primary site of melanoma includes a radical wide excision of the scar after the excisional biopsy of the primary site.

Based on the results of six multicentre, randomised trials it was decided to derogate from extended excisions of the primary melanoma site (with margin ≥ 3 cm) in favour of narrower margins of healthy tissues. There are following actual recommended margins of radical therapy of the primary melanoma lesion (excision of the scar after excisional biopsy of the primary site): melanoma in situ — margin 5 mm, melanoma with tumour depth ≤ 2 mm — margin 1 cm, melanoma with tumour depth > 2 mm — margin 2 cm (Table 4) [II, A].

Table 3. Clinical staging classification according to TNM AJCC/UICC from the year 2017

A. TNM system categories

Parameter T	Breslow thickness [mm]	(Micro-)ulceration
<i>pTis (in situ)</i>		
T1	≤ 1.0	
T1a	< 0.8	Without ulceration
T1b	< 0.8 0.8–1.0	With or without ulceration
T2	> 1.0–2.00	Unknown or undetermined
T2a		a) Without ulceration
T2b		b) With ulceration
T3	> 2.0–4.0	Unknown or undetermined
T3a		a) Without ulceration
T3b		b) With ulceration
T4	> 4.0	Unknown or undetermined
T4a		a) Without ulceration
T4b		b) With ulceration
Parameter N	Number of the regional lymph nodes with metastases	Presence of an in-transit metastasis, satellite sites and/or microsatellite***
Nx	The status of the regional lymph nodes cannot be assessed	No
N0	0	No
N1	One lymph node with metastatic transformation or presence of in-transit metastases satellite and/or microsatellite foci without involvement of the lymph nodes	
N1a	Metastasis to one lymph node detected by sentinel biopsy (micrometastasis*)	No
N1b	Metastasis to one lymph node assessed by clinical exam (macrometastasis**)	No
N1c	No metastases to regional lymph nodes	Yes
N2		
N2a	Micrometastases to 2 or 3 lymph nodes	No
N2b	Metastases to 2 or 3 lymph nodes, at least one clinically involved	No
N2c	Metastasis to 1 lymph node (assessed by sentinel lymph node biopsy or clinically)	Yes
N3	≥ 4 lymph nodes or a conglomerate of lymph nodes or in-transit/satellite changes with coexisting metastases to at least lymph nodes	
N3a	Micrometastases to at least 4 lymph nodes	No
N3b	Metastases to at least 4 lymph nodes and at least one as clinically overt or conglomerate of lymph nodes	No
N3c	Metastases to 2 or more lymph nodes and/or conglomerate of lymph nodes	Yes
Parameter M	Localisation of the metastases	Serum LDH activity
M0	Without distant metastases	
M1a	Skin, subcutaneous tissue or non-regional lymph nodes	
M1a(0)		Normal
M1a(1)		Increased

→

Table 3 cd. Clinical staging classification according to TNM AJCC/UICC from the year 2017

M1b	Lungs ± localisations M1a	
M1b(0)		Normal
M1b(1)		Increased
M1c	Other than above mentioned visceral organs with exclusion of central nervous system and ± localisations M1a and M1b	
M1c(0)		Normal
M1c(1)		Increased
M1d	Metastases to the central nervous system ± localisations M1a, M1b or M1c	
M1d(0)		Normal
M1d(1)		Increased

*Micrometastasis to the lymph node — detected by the microscopic exam of the clinically asymptomatic (not enlarged) lymph node, after performing the sentinel node biopsy; **macrometastasis to the lymph node — confirmed by the microscopic exam of the clinically palpable lymph node (enlarged) after a therapeutic lymphadenectomy; ***micro-/satellitosis — neoplastic infiltration or nodules (macro or microscopic) removed up to 2 cm from the primary site of the skin melanoma to the level of the nearest regional lymph confluence/drainage; LDH — lactate dehydrogenase

B. Clinical stages

Clinical stages*				Pathological stages**		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a T1b	N0 N0	M0 M0
IB	T1b T2a	N0 N0	M0 M0	T2a	N0	M0
IIA	T2b T3a	N0 N0	M0 M0	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0	T4b	N0	M0
III***	Any T	N1 N2 N3	M0			
				IIIA	T1a/b–T2a	N1a N2a M0 M0
				IIIB	T0 T1a/b–T2a T2b/T3a	N1b/N1c N1b/c or N2b N1a–N2b M0 M0
				IIIC	T0 T1a–T3a T3b/T4a T4b	N2b, N2c, N3b or N3c N2c or N3a/b/c Any N ≥ N1 N1a–N2c M0 M0 M0
				IIID	T4b	N3a/b/c M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

*Clinical staging includes micrograding of the primary site and a clinical/radiological assessment of presence of metastases. Consequently, clinical staging may be applied only after complete excision of the primary site of the skin melanoma (excisional biopsy) and evaluation of the regional lymph nodes and distant organs for the presence of metastases; **pathologic grading/staging includes micrograding of the primary site and a pathological assessment of the regional lymph nodes: after a sentinel lymph node biopsy or after a radical lymphadenectomy (except from stage 0 and IA in which no procedure is applied to the regional lymph nodes); ***clinical staging does not include any subgroups of stage III

Table 4. Summary of the recommendations of the National Comprehensive Cancer Network (NCCN) v. 3.2016, European Organisation for Research and Treatment of Cancer (EORTC), and the European Society of Medical Oncology (ESMO) concerning the final margin of the radical excision of the primary melanoma site depending on the Breslow thickness

Melanoma thickness (Breslow)	Recommended clinical margin
In situ	0.5 cm
≤ 2.0 mm	1 cm
> 2.0 mm	2 cm

Applying margins wider than 2 cm decreases the local reoccurrence rate but does not improve long-term survival. The scar after an excisional biopsy of a melanoma ≤ 2 mm should be removed without superficial fascia. These rules cannot be applied for melanomas located on the face, where no fascia are present and the excision margin may be narrower. In the case of the subungual localisation of melanomas, a distant phalanx should be amputated.

Regional lymph nodes

Patients with melanoma with metastases to the regional lymph nodes are a heterogeneous group of patients considering the prognosis (five-year survival range: 15–70%). Prospective clinical trials did not confirm any benefit of performing an elective lymphadenectomy in patients without clinical signs of melanoma metastases to the lymph nodes. Currently, lymphadenectomy is recommended only in melanoma patients with confirmed metastases in sentinel lymph nodes (microstaging II) or when metastases are diagnosed by fine-needle biopsy (in special situations — surgical biopsy) of enlarged and clinically suspected lymph nodes [1, 3, 7, 14].

Therapeutic lymphadenectomy

Qualification of patients for lymphadenectomy should be based on a clinical exam, laboratory test (including LDH serum level), and at least conventional chest radiogram and abdomen ultrasound. If the metastases to distant organs are suspected a patient should have computed tomography or PET-CT (especially of the pelvis when metastases to the iliac and obturator lymph nodes are suspected) and MRI. Imaging exam of the central nervous system should be performed in the case of occurrence of clinical symptoms.

The extent of the therapeutic lymphadenectomy in skin melanoma is as follows [III, C]:

- in the axilla all lymph nodes should be removed according to the anatomic definition [three groups of lymph nodes and the surrounding fascia: lower

compartment — pectoral (anterior) and subscapular (lateral) lymph nodes, central compartment — central axillary lymph nodes, upper compartment — infraclavicular (deltopectoral) and apical lymph nodes];

- in the groin we should remove the lymph nodes of the inguinal-femoral lymph nodes located below the inguinal ligament in the femoral triangle together with the femoral fascia, iliac lymph nodes placed along the external iliac vessels (optionally also internal and common), as well as the lymph nodes of the obturator fossa (in the case of metastases diagnosed in the sentinel nodes the lymphadenectomy should be restricted to inguinal lymph nodes,
- in the cervical lymphatic confluence modified procedures may be applied. These procedures must be maximally radical. Usually the jugular structures that contain superficial lymph nodes (anterior and posterior) and profound in one piece, limited from behind by profound jugular fascia and frontally by the platysma muscle.

Sometimes it is necessary to perform lymphadenectomy in the popliteal or ulnar fossa.

Local reoccurrence and *in-transit* metastases

Terms: satellitosis (micro- or macroscopic), local reoccurrence and *in-transit* metastases form a kind of continuity and represent different forms of one pathologic phenomenon. Usually a local reoccurrence (often even after a very wide excision of the primary site) represents spreading of melanomas through the regional lymphatic vessels (microsatellites become macrosatellites), which then may transform into *in-transit* metastases. That is why in the majority of cases the above-mentioned forms of relapse of melanoma are analysed together and have similar prognosis (10-year survival about 20–30%). Surgery is an essential method to treat a local relapse and *in-transit* metastases. Therapy should be individualised and should consider the number of metastases, their size, localisation, and clinical course [III, B]. In case of *in-transit* metastases surgical therapy includes excision of the countable changes (< 10) with a microscopic melanoma infiltration-free margin (it may be macroscopically narrow). In the case of a single relapse lesion another sentinel lymph node biopsy may be considered. In case of *in-transit* dissemination of melanoma limb amputation is not recommended. In case of multiple/non-resectable lesions one of the local therapeutic methods should be considered (ablation, radiotherapy, cryotherapy), intratumoural immunotherapy (talimogene laherparepvec-T-VEC, PV-10 or interleukin-2) or local immunotherapy (imiquimod is not registered for this indication) and electrochemotherapy [III, B]. In the case of extensive, multiple, lesions located on the limb an hyperthermic isolated limb perfusion chemotherapy is a method of choice [HILP], mostly with use of mel-

phalan. This method may be used only by experienced and trained centres. If HILP is contraindicated systemic therapy should be administered [1, 4, 5, 14–16].

Adjuvant therapy

Actually, there are no recommendations concerning the routine use of systemic adjuvant therapy in clinical practice in patients after radical surgery of a primary lesion with lymphadenectomy. Adjuvant radiotherapy may be considered only in some, well-determined situations. Results of some recently published clinical studies indicate an improvement of survival rates after both adjuvant immunotherapy with use of immune checkpoint inhibitors and combined therapy with BRAF and MEK inhibitors [I, B].

High doses of interferon α -2b (INF α -2b) has been registered based on the positive result of one of three clinical studies by the Eastern Cooperative Oncology Group (ECOG) -ECOG 1684 — in the United States of America and in the European Community, to treat patients with melanoma in clinical stage IIB–III. Low dose INF α -2b has been registered in Europe for patients with clinical stage II melanoma [17, 18]. The registration was based on the significant prolongation of the overall survival during the seven-year observation time. These results have not been proven during a longer observation time (12 years). The results of the studies showed a repeatable (10 from 17 studies) improvement in the disease-free survival rates. The recent meta-analysis showed a significant decrease by 17–18% of the relative disease relapse risk after the administration of the adjuvant therapy with use of INF α -2b. The clinical evidence concerning overall survival rates is weaker and is based mostly on the results of meta-analyses. The overall five-year survival benefit for the whole group of patients reaches about 3–5%. The use of adjuvant therapy with INF α -2b in patients with intermediate and high relapse risk melanomas should be individualised due to its controversial clinical value and toxicity [II, B]. The result of meta-analyses shows that an adjuvant therapy with INF α -2b may be beneficial in patients with ulcerated primary melanoma lesion, especially with coexistent micrometastases (to the sentinel node but with absence of metastases to the clinically enlarged lymph nodes) [I, B] [19, 20].

Ipilimumab is registered in the United States for adjuvant therapy of patients after lymphadenectomy of involved regional lymph nodes. Randomised clinical trials [21] showed a significant improvement of disease-free survival and overall survival but with high toxicity of ipilimumab therapy [II, B] [22].

A randomise clinical trial showed that patients with melanoma in clinical stage IIIB, IIIC, and IV, after lymphadenectomy, who received nivolumab, had by 10% improved one-year disease-free survival and lower toxicity compared to ipilimumab therapy [I, B].

Adjuvant therapy with dabrafenib and trametinib in patients with present *BRAF* gene mutation, clinical stage III, high-risk melanoma resulted in improvement of disease-free survival and overall survival compared to placebo [23]. These results suggest that all patients with melanoma in clinical stage II–IV should undergo a detailed, multidisciplinary examination.

Other methods of immunotherapy (e.g. interleukin-2), vaccines, or cytotoxic drugs have no clinical value in the adjuvant, postoperative therapy of melanomas.

In some individual cases, after the surgical therapy of high-risk melanomas, an adjuvant radiotherapy (RT) may be applied. A dosing schedule includes, depending on the localisation of the melanoma lesion — hypofractionation, 3–8 Gy per fraction or conventional fractioning. Indications for adjuvant radiotherapy after the primary tumour excision include: diagnosis of desmoplastic melanoma excised with narrow margins, presence of ‘positive’ surgical margins (especially after excision of the local recurrence), presence of satellite foci, significant neurotropism, or head and neck region localisation (solo RT may be used for extensive LMM lesions). In the case of excision of local recurrence and lymphadenectomy due to metastases to the regional lymph nodes, indications for adjuvant RT are: presence of extracapsular node infiltrations, involvement of ≥ 4 lymph nodes (clinical stage IIIC), diameter of a metastasis > 3 cm, detection of metastases to cervical lymph nodes (from two metastatic lymph nodes or when a metastasis measures at least 2 cm), and recurrence after prior resection [24, 25]. The results of the only completed randomised clinical trial assessing the value of adjuvant RT (48 Gy in 20 fractions) after lymphadenectomy in the case of high-relapse-risk melanoma, confirmed the improvement of local control in patients receiving radiation. RT had no impact on overall survival rate and resulted in a higher ratio of locoregional complications and deterioration of patients’ quality of life. These results suggest that use of adjuvant RT should be limited [II, C]. No adjuvant RT should be applied after CLND.

Therapy of patients with advanced disease

The results of treatment of skin melanomas in clinical stage IV are still unsatisfactory. The median overall survival time exceeds 12 months (and is significantly higher for new therapies) but about 20% of patient survive for five years.

The significant prognostic factors in patients with melanoma in clinical stage IV are: performance status, LDH activity, and localisation of the metastatic lesions. In the case of qualification of a patient with clinical stage IV melanoma for surgery or systemic therapy, disease should be staged by imaging exams or PET-CT (only in the case of isolated metastatic foci qualified for resection) [1].

In the case of secondary changes to the skin, soft tissues, and non-regional lymph nodes (M1a, better prognosis), it is always recommended to consider excision. A similar approach should be applied for isolated (not necessarily single) metastases to the visceral organs. In the case of unresectable lesions, the choice of therapeutic approach depends on the presence of metastases to the central nervous system (CNS). If the metastases to the CNS are present neurosurgical treatment and/or radiotherapy of the central nervous system (usually stereotactic or radiosurgery) should be considered as a first-line therapy (the decision depends on the location and number of lesions) in order to delay the occurrence of bleeding or neurological disorders. Radiotherapy of the central nervous system may be a part of combined therapy during immunotherapy (preferred) and during BRAF protein molecularly targeted therapy. RT is also used in palliative therapy in patients with metastases to soft tissues (ulceration, pain) and to bones (pain).

The advance in therapy of advanced melanoma, considering the low efficacy of cytotoxic agents, results from the use of nonspecific immunotherapy with use of monoclonal antibodies anti-CTLA4 or anti-PD1, which inhibit the systemic mechanisms of immunosuppression in order to induce an antineoplastic response (activation of lymphocytes T) as well as from the use of molecularly targeted therapies with use of serine-threonine kinases inhibitors. Patients with advanced melanoma should still be referred and screened to prospective clinical trials.

Dacarbazine is the only registered cytotoxic drug for advanced melanoma. Its efficacy is limited (objective response rate — 15% of patients, median duration of response four months) [1, 3]. The only registered scheme of dacarbazine therapy is a five-consecutive-day schedule with a daily dose of 200 mg/m²; an alternative schedule of administering a higher dose of a drug (850–1000 mg/m² every three weeks) has formally not been accepted; however, this alternative is considered useful in clinical practice. Paclitaxel in monotherapy or in combination with dacarbazine does not improve the duration of the response to the second-line therapy. Randomised trials in patients did not confirm higher efficacy of a polychemotherapy schedule including dacarbazine combined with cisplatin, vinca core alkaloids (e.g. vinblastine) and nitrosamine derivatives (e.g. carmustine) and tamoxifen. Use of biochemotherapy (chemotherapy combined with interleukin-2 and INF α -2b) does not improve melanoma patients' overall survival rates compared to chemotherapy. The results of clinical studies indicate that interleukin-2 in monotherapy or combined with IFN α -2b slightly improves the overall response rate with no influence on the overall survival rate. The toxicity of this therapy is significant. Currently the use of chemotherapy should be limited

to lifesaving situations after failure of the molecularly targeted therapies or immunotherapy [I, A].

Immunotherapy

Ipilimumab has been registered in the therapy of patients with advanced melanomas and resulted in-compared to peptide vaccine gp100 in a second-line therapy — significantly higher overall survival rates (a difference of about 3.5 months) with no impact on the disease-free progression time [26, 27]. Kinetics and time of response duration on ipilimumab therapy are different than for classical chemotherapy. The benefit of therapy is observed only after 3–4 months of therapy, which limits its application to patients with advanced melanoma with minimal symptoms, good performance status, and low disease course as well as (considering the safety profile) to patients with no autoimmune diseases. Due to late objective response occurrence, a reliable evaluation of the efficacy of ipilimumab therapy should be done after 12 weeks of treatment. Moreover, in the early phase of the therapy a phenomenon of paradoxical progression due to infiltration of the tumours by the immunocompetent cells may occur. The immunological response criteria should be applied in order to get objective imaging examination evaluation of the ipilimumab efficacy [26–28]. Currently there are no known predictive factors of response to ipilimumab. A recommended dosing schedule is 3 mg/kg of body weight, administered every three weeks up to four doses [I, A].

The objective overall response rate to ipilimumab therapy is low (about 10%), and long-term benefits are observed in a limited number of patients (20–25%); however, they are characterised by long-lasting responses (the longest observation reaches 10 years). Adverse events related to autoimmunological reactions constitute a major problem of ipilimumab therapy (grade 3–4 adverse events occur in about 20–25% of patients). The most common immunological adverse events include: skin changes, diarrhoea, hepatotoxicity, and endocrinopathies (including insufficiency of pituitary and thyroid gland). Occurrence of these syndromes in a patient treated with ipilimumab should result in an urgent referral of this patient to a medical centre experienced in treating complications of immunotherapy. In the case of intensified symptoms that disenable transportation, corticosteroids should be immediately administered [dexamethasone (or equivalent) 1–2 mg/kg of body weight], and further therapy should be applied in collaboration with/with assistance of a referral centre. The appropriate algorithms of proceeding are accessible [27] and should be rigorously implemented from the moment of the occurrence of first symptoms suggesting immunological toxicity.

Ipilimumab therapy should be applied only in tertiary referral centres that provide holistic diagnostic and therapeutic proceedings. It is not recommended to start this therapy in inexperienced centres with limited therapeutic options.

Currently, immunotherapy in skin melanomas is mostly related to the usage of immune control checkpoints PD-1 in monotherapy (nivolumab 3 mg/kg of body weight every two weeks or pembrolizumab 2 mg/kg of body weight every three weeks) [29–31] [I, A] or in combination with anti-CTLA-4 antibodies [32] [I, B]. These agents have been proven in clinical practice, in monotherapy or in combination with ipilimumab, to give long-lasting clinical benefit in some patient with advanced melanomas and significant response rates (reaching 50%) and one-year survival rates of 70–80%. The use of nivolumab or pembrolizumab results in two-year survival rates of 50–60% (median survival exceeds two years, three-year survival rate reaches about 45%), with acceptable toxicity (about 15% in grade 3/4, which is significantly less than for ipilimumab); however, the most severe symptom also results from autoimmune toxicity. Clinical studies confirmed a higher efficacy of pembrolizumab concerning the overall survival and disease-free survival time compared to ipilimumab in first-line therapy, and compared to chemotherapy after failure of prior therapy [29–31]. In recently published results of a clinical trial which compared efficacy of nivolumab in monotherapy, ipilimumab in monotherapy, and a combination of both drugs, nivolumab revealed to be more effective than ipilimumab (the median disease-free survival time reached respectively 6.9 vs. 2.9 months); however, the combination of both drugs had the highest efficacy (the median disease-free survival was 11.5 months). The combination therapy was the best option in the case of low PD-L1 expression in the neoplastic tissue (< 5%). In the case of high PD-L1 expression (> 5%) the results of nivolumab therapy in monotherapy or in combination with ipilimumab were comparable, and similarly overall survival results [32]. The results of combined ipilimumab and nivolumab therapy were also better when a *BRAF* gene mutation was present; however, in the whole group of patients [33] the improvement in three-years survival rates in the combination therapy arm compared to monotherapy with nivolumab reached only 6%: 58% vs. 52%, respectively. The adverse events in Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4 were significantly more frequent in the combined therapy arm (56.55%) compared to 19% in nivolumab and 27% in the ipilimumab arm.

In the clinical study a therapy with anti PD-L1 antibody, pembrolizumab, was maximally continued for two years. In the group of 104 patients who accomplished the two-year therapy period, 102 persons (98%) are still alive

while the nine-month disease progression-free survival rate reached 91% (which means that in the majority of patients disease control is maintained even when the active therapy had been stopped) [II, B] [34].

In light of the presented results of the clinical studies, ipilimumab should not constitute an essential type of immunotherapy in patients with advanced melanomas because it is less efficient than anti PD-L1 antibodies and has a worse safety profile. The therapy should be started from anti PD-L1 (nivolumab or pembrolizumab) in monotherapy [I, A]. The issue of combined therapy with anti-CTLA-4 antibodies requires further investigation.

Molecularly targeted therapy

The presence of mutation of the RAS/RAF/MEK/ERK MAP kinase pathway is detected in 75% of skin cancers. The major mechanism leading to hyperactivity of RAS/RAF/MAPK pathway I skin melanoma is a mutation of a kinase BRAF encoding gene mutation. Somatic mutations in *BRAF* gene are observed in 50–70% of skin cancers occurring on the skin areas not exposed to long-term solar radiation. Published in year 2011, the results of the registration phase III study of vemurafenib use in first-line therapy in patients with present *BRAF* V600 mutation showed 48% overall response to therapy rate in patients receiving BRAF inhibitor (BRAFi) compared to 5% in patients on dacarbazine, as well as significant improvement of disease progression time (five months difference) and of overall survival (three months difference) [35]. Vemurafenib has been registered to treat patients with advanced melanoma with presence of *BRAF* mutation (testing for this mutation is possible in Polish centres with use of a validated test) [I, A]. Even though in the majority of patients resistance to therapy will develop (median disease progression-free survival totals 6–7 months), the results of phase II–III revealed a 13–16-month long median overall survival time, in patients with metastatic melanoma, which is significantly better than any other reported survival benefit in this subset of patients. Vemurafenib is characterised by significant skin toxicity (hypersensitivity to UV radiation), hepatotoxicity typical for kinase inhibitors, and by formation of secondary neoplasms (cancer or keratoacanthoma of the skin in about 20% of treated patients). The secondary skin neoplasms may develop within a few weeks after the onset of the therapy with vemurafenib. Diagnosis of secondary skin cancers requires local therapy but not interrupting the drug. The adverse events quite often require reduction of vemurafenib dose. In the year 2012 a therapeutic efficacy of another BRAF inhibitor, dabrafenib, was proven (characterised by efficacy similar to vemurafenib but by a different toxicity profile, e.g. lower skin toxicity). The median disease progression-free time reached 6.7 months for dabrafenib vs. 2.9 months for dacar-

bazine, whereas the median overall survival time on dabrafenib therapy reported in the year 2013 reached 18.2 months [36] [I, A]. In a phase III trial, the efficacy of MEK inhibitor (MEKi) has also been confirmed trametinib — in patients with metastatic melanomas with present *BRAF* gene mutations [37] [I, B]. The efficacy of MEK inhibitors has also been observed in patients with *NRAS* gene mutations [38]. The results of recent studies (COMBI-d, COMBI-v, and coBRIM) showed that in patients with metastatic melanomas with present *BRAF* gene mutation the use of combination of BRAF and MEK inhibitors (dabrafenib and trametinib or vemurafenib with cobimetinib) yields better results than monotherapy and no increase of toxicity [39–43] [I, A]. The median overall survival time on the combination of both drugs was improved to about 23–25 months and median disease progression time of 12 months. The best overall survival is achieved in patients with normal LDH activity and serum concentration and less than three organs involved with metastases. Both drug combinations are currently accessible in Poland in the Drug Program in the first- or second-line therapy in patients with advanced melanoma with confirmed presence of *BRAF V600* mutation.

The above-mentioned drugs have a beneficial influence also in patients with stable and/or asymptomatic metastases to the brain, and until now this localisation was inaccessible for the systemic therapy of melanoma patients with melanoma and *BRAF* gene mutation, in whom asymptomatic brain metastases have been detected may receive a first-line therapy with BRAF inhibitor (in combination with MEK inhibitor).

A new option of the molecularly targeted therapy is to restart the combined therapy with BRAF and MEK inhibitors after this therapy has been stopped due to a disease progression. A phase II study revealed that restarting a therapy with dabrafenib and trametinib resulted in partial remission in 8 of 25 patients (32%) and in stabilisation of the disease in another 40% of patients. The median disease progression-free time to so-called 'rechallenge' reached 4.9 months [44]. The analysis of data of 116 patients with advanced melanoma, who had received therapy with BRAF inhibitor, progressed and received another therapeutic modality, and then were restarted on combined therapy with BRAF ± MEK inhibitor was presented at the ASCO meeting in 2017. The median time of treatment duration was 9.4 and 7.7 months for the primary and reused molecularly targeted therapy, respectively. After restarting the use of BRAF ± MEK inhibitors the response rate was 43%: complete responses rate 3%, partial responses rate 39%, stabilisation of the disease 24%, and progression of the disease 30% (no data 4%). The median overall survival time from the restart of the therapy reached 9.8 months [II, B] [45].

BRAF inhibitors (+ MEK inhibitors) induce a prompt response and neoplasm control in the majority of patients with advanced melanomas with present *BRAF* gene mutation. However, the response duration is limited due to activation of mechanisms of resistance to therapy. Due to these characteristics this therapy should be considered as a treatment of choice in patients with symptomatic disease and/or big tumour mass. There are no final data concerning the optimal sequence of immunotherapy and molecularly targeted therapy in patients with melanomas with presence of *BRAF* gene mutation. However, the activity of BRAF inhibitor is maintained after immunotherapy and of immunotherapy (anti-PD-L1) after treatment with inhibitors. In rare cases of patients with melanomas carrying some *KIT* gene mutations, the activity of KIT kinase inhibitors has been observed [40] [II, B].

Follow-up after therapy completion

The frequency and type of control examinations as well as duration of the observation should be established based on the individual disease relapse risk (which depends on the initial clinical stage of the disease). However, we should bear in mind that the relapse may occur even 10 years after the primary treatment [46, 47] (Table 5). The relapse risk is the highest in the first three years post therapy. That is why it is recommended to apply in this period a more intense schedule of control exams in order to detect a loco-regional relapse, which may be cured by surgery. Assessment of scars post primary site excision and post lymphadenectomy constitutes the most important part of the observation. The evaluation of the regional lymph confluence should be done carefully (a possible in-transit dissemination). To evaluate the local lymph nodes we may use palpation and ultrasonography. A patient may detect a majority of loco-regional relapses and that is why he/she should be trained to make a self-control of the area of the melanoma excision and of the regional lymph nodes. There are some premises that a less intensive control schedule has no negative impact on the survival in patients with early melanomas.

Imaging exams are not recommended in asymptomatic patients with clinical stage IA–IIA. Imaging exams (e.g. CT exam) may be considered in asymptomatic patients with clinical stage IIB–IIIC during the first 2–3 years of follow-up (taking into consideration the availability of some new, effective drugs in the therapy of disseminated melanomas. The earlier data evaluating the intensive schedule of the control imaging exams demonstrated only a minimal benefit — maximally two months prolongation of the overall survival time). Then, in patients with clinical symptoms suggesting the pres-

Table 5. Exams recommended in monitoring melanoma patients

Clinical stage of melanoma	Type of exam	Frequency of control exams
Early melanomas after the excision of the primary site without any metastases to the lymph nodes (clinical stages IA–IB)	Physical examination and anamnesis, especially a careful examination of the whole skin surface and of the regional lymph nodes as well as of the area of the scar post excision of melanoma Radiologic image (RT) of the chest — optionally Other exams (e.g. US, CT) in the case of presence of suspected symptoms Ultrasound of regional nodes when no sentinel node biopsy has been performed, in skin melanomas \geq pT1b There are no indications for any additional test except form physical exam in patients post excision of melanoma pT1a Patients should be trained to perform a self-control examination	Every 6–12 months during the first 5 years, then once a year (follow-up may be done outside the specialist centre)
Locally advanced melanomas post excision of the primary site without metastases to regional lymph nodes (clinical stages IIA–IIC)	Physical examination and anamnesis, especially a careful examination of a whole skin surface and of the regional lymph nodes as well as of the area of the scar post excision of melanoma Radiologic image (RT) of the chest, ultrasound of the abdomen Blood morphology and biochemistry (liver tests and activity of lactate dehydrogenase) — optionally Other tests (e.g. CT) in the case of presence of suspected symptoms Ultrasound of regional nodes when no sentinel node biopsy has been performed, in skin melanomas \geq pT1b In patients with clinical stage IIB–IIC a CT exam may be done every 6–12 months and optionally MRI of CNS once a year (during the first 2–3 years) Patients should be trained to perform a self-control examination. In clinical stage IIC more intensive monitoring schedules may be used as in clinical stage III	Every 3–6 months during first 2–3 years, then every 6–12 month during next 5 years and then once a year
Post excision of the metastases to the regional lymph nodes or of a local relapse/satellite or in-transit lesion (clinical stages IIIA–IIIC)	Physical examination and anamnesis. Especially a careful examination of a whole skin surface and of the regional lymph nodes as well as of the area of the scar post excision of melanoma Radiologic image (RT) of the chest Blood morphology and biochemistry (liver tests and activity of lactate dehydrogenase) — optionally Ultrasound of abdomen and eventually of the regions of the removed lymph nodes CT exam of the chest, abdomen and pelvis every 6–12 months and optionally in clinical stage IIIC, once a year a MRI of the brain (during the first 3 years) Patients should be trained to perform a self-control examination	Every 3–4 months during the first 2 years, every 3–6 month during the next 3 years and then once a year
After therapy of distant metastases (clinical stage IV)	Evaluation of the imaging exams depending on the localisation of the measurable metastatic sites Serum activity of LDH	An individual monitoring schedule for each patient

US — ultrasonography; RT — radiological exam; CT — computed tomography; MR — magnetic resonance; LDH — lactate dehydrogenase

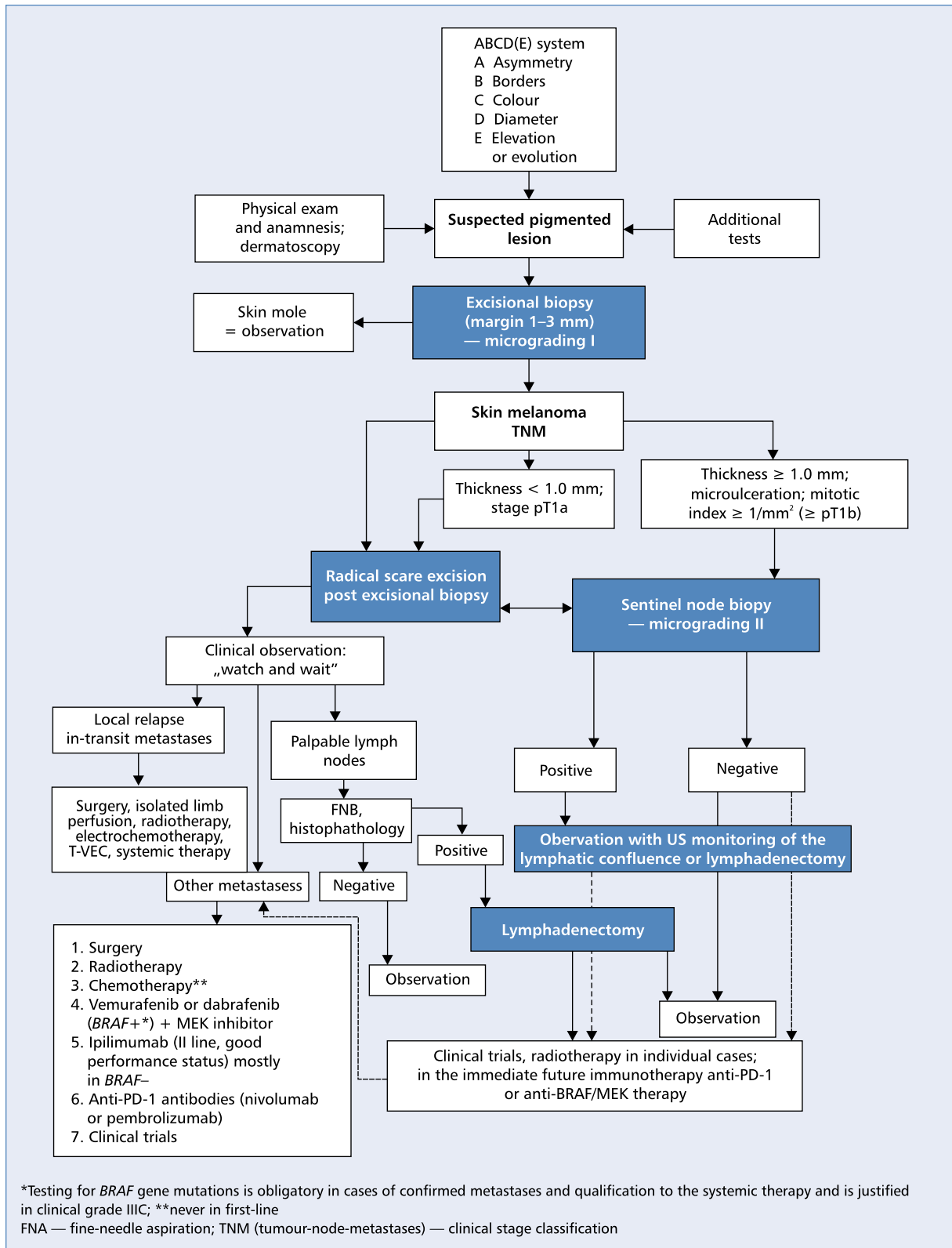


Figure 2. A schedule of diagnostic and therapeutic recommendation in patients with skin melanoma

ence of distant metastases (liver enzymes elevation, bone pains, neurological symptoms, cough, and weakness)

detailed imaging diagnostics should be done, with CT, MRI, and scintigraphy included.

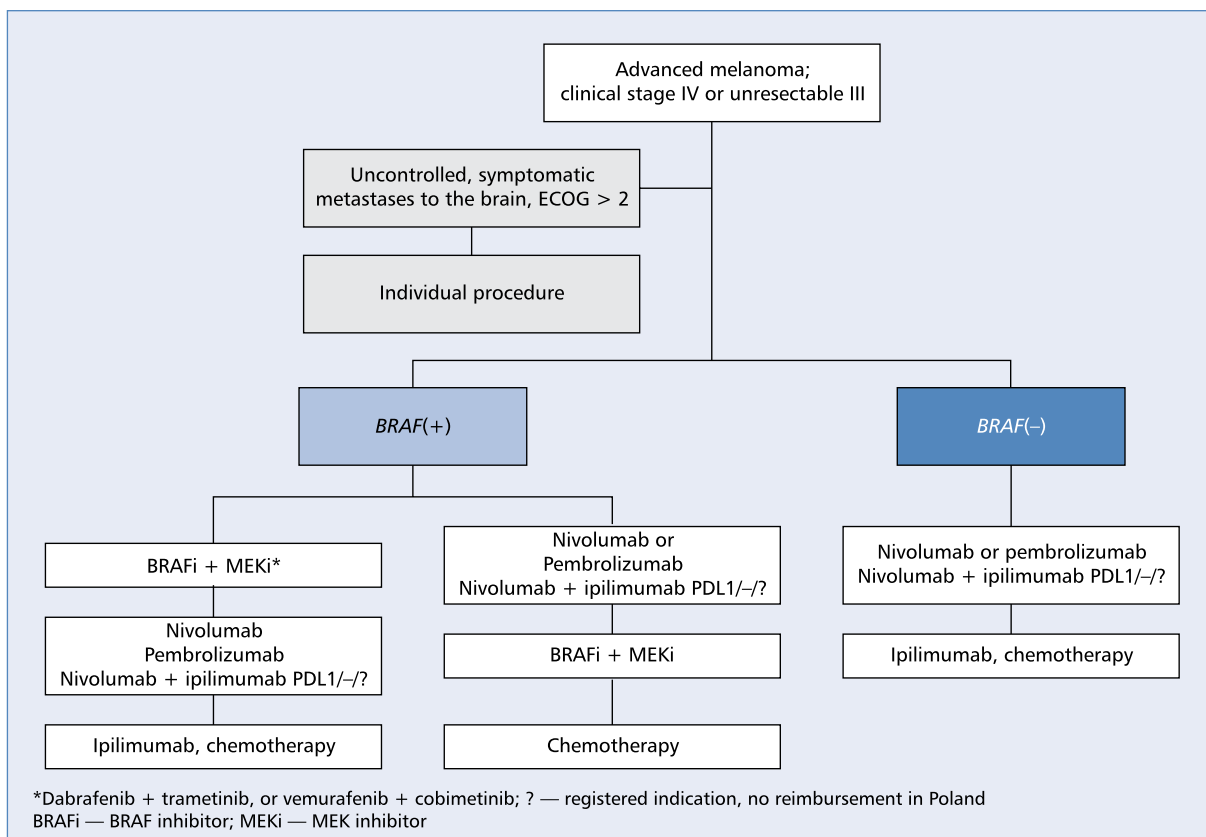


Figure 3. Recommended schedule of systemic therapy in patients with advanced melanoma in clinical stage IV or unresectable III

During the control exams we should carefully check not only the area of the primary melanoma lesion but also the whole skin surface. Melanoma patients have a statistically higher risk of developing a lesion of melanoma or of another skin cancer.

Summary

The excisional biopsy of the suspected pigmented moles, which may be early melanomas, is essential to diagnose and assess the main risk factors of melanoma (microstaging I). Early diagnosis and removal of melanoma not only improves the prognosis but also give a chance of cure in nearly 90% of patients. Usually the pigmented changes with transversal axis dimensions not exceeding 2 cm may be removed in an outpatient clinic during an excisional biopsy. The next stages of the proceedings include qualification of a patient to a radical, wide scar excision with appropriate surgical margins and to sentinel node procedure. In the case of clinical metastases to the regional lymph nodes a radical lymphadenectomy is a method of choice. It is recommended that patients with high-risk melanoma be included in prospective clinical trials evaluating the

adjuvant therapy. A schedule of diagnostic and therapeutic recommendations in patients with skin melanoma is shown in Figures 2–4.

The presence of distant metastases is still associated with poor prognosis. It is recommended that patients with generalised disease be treated in clinical trials. *BRAF* mutation should be tested in all patients with advanced disease or with high disease relapse risk [III]. Long-term survival is seen mostly in patients in clinical stage IV, who have had resection of singular metastatic lesions. In patients with present *BRAF V600* gene mutation, mostly in first-line therapy, a BRAF inhibitor may be used (preferentially in combination with MEK inhibitor). Immunotherapy with anti PD-1 antibodies (nivolumab or pembrolizumab) or eventually ipilimumab (anti-CTLA-4 antibody in monotherapy or in combination with anti-PD-1) may be used independently of the *BRAF* mutation presence. The optimal sequence of therapy (especially in the case of *BRAF* mutation) has not been assessed. The use of combined therapy with BRAF and MEK inhibitors involves a high response rate (about 70%) and rapid alleviation of symptoms of the disease. Therapy with anti-PD-1 antibodies results in lower response rates, but in the majority of patients the response is durable.

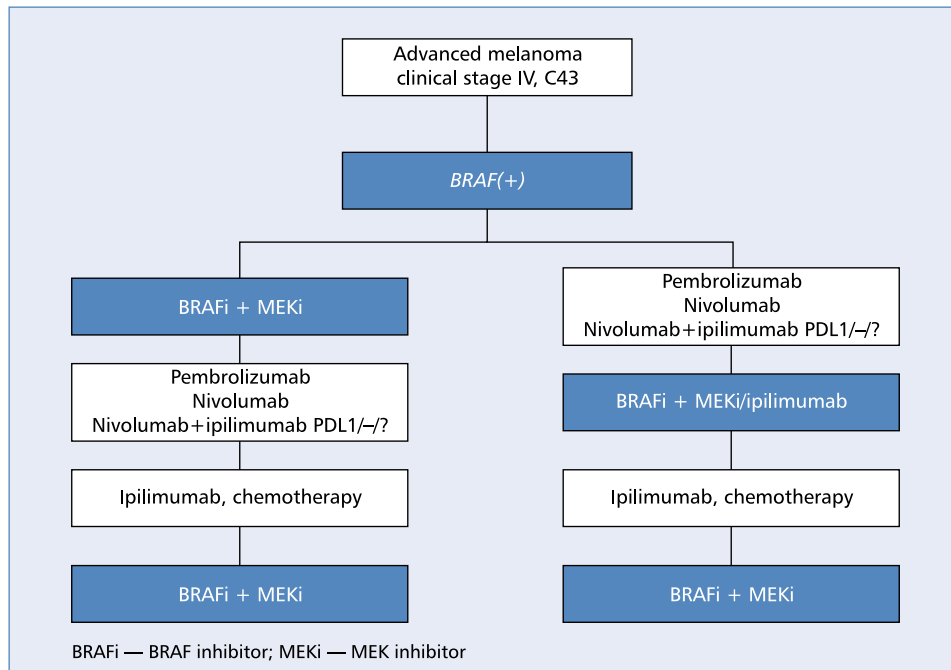


Figure 4. Recommended schedule of systemic therapy in patients with advanced melanoma in clinical stage IV or unresectable III with present *BRAF* gene mutation

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