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Professor Krzysztof Krzemieniecki Award for the best case report accepted for publication

Case Report Contest Policies

This policy defines the scope, requirements and regulations regarding **The Krzysztof Krzemieniecki Award** for the best case report published in "Oncology in Clinical Practice" (OCP) Fifth Edition.

1. The aim of the contest is to encourage submission of quality case reports related to oncological practice and to promote them in the scientific deliberations.
2. All respective manuscripts submitted to OCP between June 1st, 2020 and May 31st, 2021 and accepted for publication will qualify.
3. Manuscripts should be prepared in line with Authors' guidelines and should be submitted only through the manuscript system available at Journal's website: https://journals.viamedica.pl/oncology_in_clinical_practice
4. All submitted manuscripts will be evaluated during the peer review process and authors will be informed about their qualification for publication in OCP. Accepted papers will be evaluated by the Contest Committee based upon fulfillment of the Contest criteria as well as practical significance, originality, applicability and addressing of current/critical concerns.
5. The first author of the winning paper will be eligible for a prize of gross 1000,00 Euro gross (one thousand euro).
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7. Winner will be notified via email.
8. Contest Committee may exclude a paper from participation in case of potential conflict of interest or ask submitting author for adequate clarifications.
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10. The award amount shall be paid based on the copyright transfer agreement to the paper.
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Patronage NOVARTIS

Skin carcinomas

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Key words: skin, carcinoma, vismodegib, Merkel cell carcinoma, avelumab, cemiplimab

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. The quality of scientific evidence

I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials

II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-randomized cohort studies)

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III — Scientific evidence obtained from retrospective observational studies or case-control studies
IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
A — Indications confirmed unambiguously and absolutely useful in clinical practice
B — Indications probable and potentially useful indications in clinical practice
C — Indications determined individually

Introduction

Skin cancers, with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), responsible for about 98% of all skin cancers, are the malignancies with a marked preference for lighter-skinned people. Skin carcinomas, also defined as non-melanoma skins cancers (NMSC), are responsible for about 1/3 of all new cancer diagnoses in men.

Despite low metastatic potential and relatively low death risk associated with NMSC, they remain a significant clinical challenge. Skin carcinomas are characterised by local aggressiveness and a tendency to infiltrate surrounding structures, such as bones and cartilages. Aesthetic defects resulting from such damage significantly impair long-term quality of life and arise as an important social problem due to the high prevalence of NMSC. Among patients within the high-risk group (e.g. immunocompromised patients or those with a genetic predisposition to develop UV radiation-induced cancers), the course of the disease is different because skins carcinomas in these patients are more aggressive and often result in death. Additionally, patients with a history of skin cancer have elevated risk of developing other cancers, including melanoma, when compared to the general population.

Due to limited space, the presented manuscript does not cover the topic of premalignant skin lesions (such as actinic keratosis) or squamous and basal cell carcinomas originating from urogenital organs, nail bed, and oral cavity [1–13].

Epidemiology

Skin carcinomas are responsible for 30–50% of all newly diagnosed cancer cases. Absolute risk of a skin cancer diagnosis during a lifetime exceeds 20% in the Caucasian population. Morbidity rises with age, with the highest prevalence in the 8th decade of life. In 2017 in Poland 13,478 new cases (6543 in males and 7025 in females) of skin carcinomas were registered, which results in morbidity of, respectively, 7.9% and 8.5% [14]. Unfortunately, skin carcinomas might be significantly under-registered within the National Cancer Registry (Krajowy Rejestr Nowotworów), and estimated morbidity might be underrated.

The most common type of skin carcinoma is basal cell carcinoma (BCC), which represents about 80% of cases. The second most common type is squamous cell carcinoma (SCC), responsible for the next 15–20% of cases [10, 13]. Other forms of skin carcinoma are less common [1–13].

Basal cell and squamous cell skin carcinomas

Risk factors

The rising prevalence of both BCC and SCC is mostly caused by excessive ultraviolet (UV) radiation exposure.

Risk factors responsible for the rising BCC and SCC morbidity include: lifestyle changes in modern society; popularity of tanning; migration of people with skin phenotypes I, II, and III to regions with high sun exposure; living at high altitudes and nearer the equator; and usage of tanning lamps emitting UV radiation ("solariums"). Significant risk might be attributed to occupational exposure to UV radiation in people working outside and not utilising any form of photoprotection [1–11]. Table 1 summarises risk factors associated with developing skin carcinomas.

Hedgehog (Hh) pathway activation is present in most BCC cases, usually through inactivation of PTCH1 (Patched 1) receptor or oncogenic activation of SMO (Smoothened) receptor. In Gorlin-Goltz syndrome (naevoid basal cell syndrome), an autosomal dominant disease characterised by a multifocal development of BCC, presence of facial and skeletal abnormalities, and an increased risk of medulloblastoma and rhabdomyosarcoma development, abnormalities in gene coding PTCH1 receptor are present.

Diagnosis

Initial diagnosis is based on physical examination and characteristic clinical appearance of BCC/SCC lesions. About 80% of skin carcinomas arise within the head and neck; the remaining 20% usually localise within torso and extremities.

Skin carcinomas often arise multifocally, especially in patients older than 70 years, with a high degree of skin injury based on UV radiation and a long-term history of growing lesions because most BCC enlarge slowly. In some cases, the presence of multiple BCC

Table 1. Skin carcinoma risk factors [1, 2]

Risk factor		SCC	BCC
Environmental factors	Cumulative UV dose		×
	Intensive intermittent sunbathing	×	
	Ionising radiation	×	×
	Exposure to chemical substances*	×	(×)
	HPV infection	×	
	Nicotinism	×	
Genetic factors	Skin phenotype I	×	×
	Xeroderma pigmentosum	×	×
	Oculocutaneous albinism	×	(×)
	Epidermodysplasia verruciformis	×	
	Epidermolysis bullosa	×	
	Ferguson-Smith syndrome	×	
	Muira-Torre syndrome	×	(×)
	Bazex syndrome		×
	Rombo syndrome		×
	Gorlin-Goltz syndrome		×
Chronic skin diseases	Chronic ulcerations/wounds	×	
	Long-term active: — skin lupus erythematosus — lichen planus (erosive) — lichen sclerosus	×	
	Porokeratosis	×	
	Nevus sebaceous		×
Immunosuppression	Prior transplant recipient	×	(×)
	Other forms of immunosuppression, e.g. AIDS syndrome or HPV infection	×	

*Chemical substances: arsenic, mineral oil, coal tar, soot, nitric yperite, aromatic polycyclic compounds — biphenyl derivatives, 4,4'bipyridine, psoralen (including UVA) [1–11]. BCC — basal cell carcinoma; SCC — squamous cell carcinoma; HPV — human papilloma virus

lesions, along with numerous areas of actinic keratosis and Bowen disease, or even melanomas, might be coincident. Due to this, patients with NMSC should undergo a full and precise physical examination, including evaluation of the whole skin area. Because dermoscopy has proven its value in several publications dedicated to the early diagnosis of cancer, this fast and affordable diagnostic modality should be considered as a standard part of clinical examination skin carcinoma is suspected. Dermatoscopy can provide essential value in untypical cases requiring differential diagnosis, in evaluation of smaller lesions or in differentiating between actinic keratosis and early SCC (*in situ*). Evaluation of cancer expansion before treatment initiation, assessment of treatment radicality, and monitoring after the treatment might also benefit from routine incorporation of dermatoscopy (Tables 2, 3). Detailed recommendations on dermoscopic examination of basal cell carcinoma and squamous cell carcinoma have been presented in a separate study [15, 16].

The most important part of diagnosis is the pathological examination of specimens obtained by an excision or a biopsy. A pathology report should include not only the histological type of carcinoma but should also define the specific subtype (especially in cases of high-risk subtype). The maximal size of the lesion and the depth of invasion should be evaluated in invasive carcinomas. Assessment of surgical margins is necessary. Presence of vascular and/or perineural invasion provides additional data regarding diagnosis and prognosis. Usually, a microscopic image known to any pathologist is sufficient to determine the type of cancer. The presence of intercellular bridges and keratosis indicates a squamous cell carcinoma, while atypical, mitotically active basaloid cells arranged in the form of peripheral palisade are typical for basal cell carcinoma. In case of doubts regarding the histological type (BCC *vs.* SCC), the pathological examination should be supplemented with the basic differentiating immunohistochemical panel — BerEP4(+), EMA(–), CK5/6(–) in basal cell carcinoma, CK5/6(+), EMA(+) and BerEP4(–) in squamous cell carcinoma.

Histopathological type of carcinoma, stage of disease, and patient's performance status are essential when deciding on further care. In cases strongly suspicious from a clinical perspective, radical resection should be preferred. Clinically indeterminate cases require biopsy, with a further treatment according to the results of pathological examination (biopsy of a part of lesion or a full excisional biopsy — the latter can be additionally considered as therapeutic in some cases).

Suspicion of the local invasion (deep infiltration of surrounding tissues and structures, e.g. muscles, bones, nerves, lymph nodes or eye bulb) require further evaluation with radiological imaging (computed tomography or magnetic resonance imaging). Presence of clinically or radiologically detected enlarged lymph nodes should be verified with fine-needle biopsy or an excision of a whole lymph node [1–6, 9–11].

Evaluation of prognostic factors and staging

The next step includes evaluation of prognostic factors in a malignant lesion, which correspond with low or high relapse risk (Tables 4, 5) and a proper staging according to American Joint Committee on Cancer guidelines (revision from 2009 and 2017) (Table 6) [1–6, 9–11].

Table 2. Dermatoscopic signs of BCC/SCC and their differentiation (based on [7])

	Dermatoscopic signs of non-melanocytic BCC	Dermatoscopic signs of melanocytic BCC	Dermatoscopic signs of non-melanocytic SCC	Dermatoscopic signs of melanocytic SCC
Early stage	— Light rose/rose unstructured area — Irregular, small vessels within lesion — Thin, branching microvessels/ /telangiectasias/ /small, atypical, irregular vessels within white areas of lesion — Corkscrew vessels — Small ulcerations — Small eschars — White shining dots and streaks (visible in polarised light)	— Grey-blue dots, spots, and balls — Brown or rose balls — "Wheel with spokes" structures — Brown or grey-blue "maple leaf" structures — + Non-melanocytic early BCC signs	**Non-melanocytic actinic keratosis** **On face**: — "strawberry pattern" = white dots on rose background = rose/red pseudo-network — white or yellow scale on surface of lesion — thin, corrugated, twisted vessels surrounding follicular openings — white annuluses surrounding yellowish plugs located in a follicular opening — white rosette in follicular opening (visible in polarised light) **Outside of face:** — white/yellow scale on surface — thin, irregular telangiectasias **Bowenoid actinic keratosis:** Glomerular vessels covering surface of lesion **Bowen's disease (SCC *in situ*):** — white/yellow scale of surface — glomerular vessels in clusters; those vessels can be visible as red dots or balls — small ulcerations/eschars	**Melanocytic actinic keratosis:** **On face**: — asymmetric colouring of follicular openings — annular-granular — rhomboidal structures — pseudo-network consisting of yellowish corneal plugs in follicular openings surrounded by grey halo **Melanocytic form of Bowen disease (SCC *in situ*):** — brown or grey dots forming radiant lines in perimeter — rose or colourless, structureless, pigmentations situated peripherally — glomerular vessels/red dots situated randomly or in clusters in perimeter — desquamation of lesion surface
Advanced stage	— Thick, sharply branching vessels visible in perimeters, directed towards centre of lesion (only nodular type) — Ulceration — Eschar — White, shining dots and streaks, "rainbow" sign (visible in polarised light)	— Huge, grey-blue nests of oval/oviform structures — + Non-melanocytic advanced BCC signs	— Centrally located yellow plug/keratin mass/ /ulceration surrounded concentrically by "hairpin" vessels/irregular linear vessels — White annulus on white/rose background — Vessels (polymorphic) surrounded by white halo — Eschars — red/orange/brown/even black/ /ulcerations — In central part of lesion structure typical for early lesions might be found	— Extensive bluish colouring — Irregularly distributed blue and grey granular structures — If ulceration present: formation of black or dark brown eschar — Poorly visible vessels
Differentiation	— Melanoma/other cancer metastases — Spitz nevus — Dermal rose/skin colour nevus	— Nevus — Melanoma — Melanoma metastases — Seborrheic keratosis	— Spitz nevus — Non-melanocytic BCC — Melanoma — Keratoacanthoma	— Melanoma/LMM (on face) — Melanocytic BCC — Lichen keratosis

BCC — basal cell carcinoma; SCC — squamous cell carcinoma; LMM — lentigo maligna melanoma

Table 3. Classification of actinic keratosis currently considered as IEN or SCC *in situ* (based on [17–19])

Broadness and number of actinic keratosis (AK) lesions	Histopathologic appearance	Clinical appearance
Single AK lesions ≥ 1 and ≤ 5 palpable or visible lesions on a certain body part/ /skin area	**I type AK = early SCC *in situ*** Presence of atypical keratinocytes in basal layer and lower 1/3 of epidermis	**Stage I — mild** Lesions more palpable than visible with bare eye
Multiple AK lesion ≥ 6 palpable or visible lesions on a certain body part/skin area	**II type AK = early SCC *in situ*** Presence of atypical keratinocytes in lower 2/3 of epidermis	**Stage II — moderate** Lesions are both visible and palpable
Cancerisation fields ≥ 6 AK palpable or visible lesions on a certain body part/skin area and vast areas of chronically sun-damaged skin with hyperkeratotic changes	**III type AK — Bowenoid AK/SCC *in situ*** Presence of atypical keratinocytes in lower 2/3 of epidermis up to whole epidermis thickness	**Stage III — severe** Lesions are covered with hyperkeratotic scale and they are evident
Immunosuppressed patients with signs of AK Any number and size of AK lesion with a concomitant immunosuppression	**Invasive SCC** Nests of keratinocytes infiltrates dermis Cancer cells are large, with an abundant eosinophilic cytoplasm and evident enlargement of nucleus Different stages of keratosis present, keratin pearls might be visible Depending on SCC differentiation cells might exhibit different pleomorphism, mitotic activity and squamous epithelium characteristics Depending on pathological subtype different levels of inflammation and stromal reaction might be visible	**Suspicion of invasive SCC** When signs are present: — major criteria: ulceration, infiltration, bleeding, size > 1 cm, rapid growth, erythema — minor criteria: pain, pruritus, colouring, hyperkeratosis, palpable

AK — actinic keratosis; BCC — basal cell carcinoma; SCC — squamous cell carcinoma

Treatment

The primary objective in the treatment of skin carcinomas is a complete and radical removal of all cancer tissues. Therefore, modalities with the highest probability of obtaining full radicality and the least risk of local failure should be preferred.

Factors influencing treatment choice include:
— clinical evaluation, including number and size of lesion;
— histological type and subtype;
— stage and grade of the tumour, as well as the risk of local and distant failure;
— possible organ/part of the body function preservation and expected aesthetic effect;
— treatment efficacy evaluated as relapse rate within both 4–6 months and 3–5 years (verified by a physical examination, dermatoscopy, and histopathological evaluation);
— treatment tolerance (pain, length of the treatment, adverse events risk);
— availability of specific treatment modality;
— the efficiency of the immune system;
— patient preferences.

Figure 1 shows the recommended diagnostic and treatment algorithm in case of skin carcinoma suspicion.

Surgical treatment is often the quickest and most efficient curative modality. However, adequate treatment strategy demand consideration of patient's age, comorbidities, psychological aspects of treatment, and expected aesthetical outcomes. Therefore, some cases require modalities other than surgery (especially in cases with low relapse risk). Possible methods include:
— superficial treatment: 5-fluorouracil, imiquimod (modulator of immunological response used topically for 6–8 weeks), diclofenac, chemical peeling, or photodynamic therapy;
— local treatment:
  • without margin assessment: laser therapy, cryotherapy, electrocoagulation, radiotherapy;
  • with margin assessment possible: radical surgical excision (alternatively Mohs micrographic surgery).

Table 4. Relapse risk factors for squamous cell carcinoma (SCC) [1–6, 9–11]

Risk factors for SCC local and distant relapse		
	Low-risk lesion	**High-risk lesion**
Localisation and size	Area L < 20 mm	Area L ≥ 20 mm
	Area M < 10 mm	Area M ≥ 10 mm
		Area H
Margins of the lesion	Well-defined margins	Indefinite margins
Primary or relapsed lesion	Primary	Relapsed
Immunosuppression	No	Yes
Prior radiotherapy or chronic inflammatory process within the lesion	No	Yes
Rapid growth of the lesion	No	Yes
Neurological symptoms	No	Yes
Histopathological grading	Low or intermediate grade G1, G2	High grade G3
Thickness of the lesion	< 2 mm I–III Clark's level	≥ 2 mm IV–V Clark's level
Vascular or perineural invasion	No	Yes
Histopathological subtype	Metatypicus Verrucosus Fusiformis Mixtus	Acantholiticus Desmoplasticus Adenoidalis, adenoidosquamousus Mucosoadenoidalis Fusiformis (after radiotherapy)

Area L — torso and extremities with the exception of anterior surface of crus, hands, feet, ankles, and nails; area M — cheeks, forehead, hairy parts of head skin, neck, anterior surface of crus; area H — head and neck with an exception of M area, genital area, hands, and feet

Table 5. Relapse risk factors for basal cell carcinoma (BCC) [1, 20]

Relapse risk factors for BCC		
	Low-risk lesion	**High-risk lesion**
Localisation and size	Area L < 20 mm	Area L ≥ 20 mm
	Area M < 10 mm	Area M ≥ 10 mm
		Area H
Margins of the lesion	Well-defined margins	Indefinite margins
Primary or relapsed lesion	Primary	Relapsed
Immunosuppression	No	Yes
Prior radiotherapy	No	Yes
Histopathological subtype	Superficial Nodular Fibroepithelioma Keratotic Folliculocystic	Cicatricial Sclerodermal Metatypical Infiltrating Micronodular changes in any part of the lesion
Perineural invasion	No	Yes

Area L — torso and extremities with the exception of anterior surface of crus, hands, feet, ankles, and nails; area M — cheeks, forehead, hairy parts of head skin, neck, and anterior surface of crus; area H — head and neck with an exception of M area, genital area, hands, and feet

It should be emphasised that we currently lack good quality data regarding comparison of different methods used in skin carcinoma treatment. Most of the available publications apply only to cancers in locations associated with a low risk of relapse or low invasiveness. Surgery remains a "golden standard" of skin cancer treatment, with the exception of inoperable cases [1–13, 21].

Table 6. Staging of skin cancer (according to AJCC 2009)

T stage (primary tumour)*

Tx	The primary tumour cannot be evaluated
T0	No evidence of primary tumour
Tis	Cancer *in situ*
T1	The tumour is 2 centimetres at its largest dimension with less than two high-risk factors#
T2	The tumour is more than 2 centimetres in its largest dimension OR Any size tumour with 2 or more high-risk factors#
T3	The tumour invades maxilla, mandibular, orbit, or temporal bone
T4	The tumour invades spine or perineurally infiltrates skull base

*Does not apply to squamous cell carcinoma of an eyelid; #high-risk factors of the primary lesion (T stage)

High-risk factors

Deepness of the primary tumour infiltration	> 2 mm Clark's stage ≥ IV Perineural invasion
Lesion location	Auricle Vermillion Vermillion border
Differentiation	Poorly differentiated or undifferentiated

N stage (regional lymph nodes)

Nx		Regional lymph nodes cannot be evaluated
N0		No evidence or lymph node involvement
N1		Single, ipsilateral lymph node involvement, with greatest dimension of lymph node ≤ 3 cm
N2		Single, ipsilateral lymph node involvement, with greatest dimension of lymph node > 3 cm but < 6 cm; OR Multiple ipsilateral lymph nodes involved, without any lymph node longer than 6 cm in greatest dimension; OR Bilateral or contralateral lymph node involvement, without any lymph node longer than 6 cm in greatest dimension
	N2a	Single, ipsilateral lymph node involvement, with longest dimension of lymph node > 3 cm but < 6 cm
	N2b	Multiple ipsilateral lymph nodes involved, without any lymph node longer than 6 cm in longest dimension;
	N2c	Bilateral or contralateral lymph node involvement, without any lymph node longer than 6 cm in longest dimension
N3		Any lymph node involvement with more than 6 cm in greatest dimension

M stage (distant metastases)

M0	No evidence of distant metastases
M1	Distant metastases present

→

Table 6 cont. Staging of skin cancer (according to AJCC 2009)

TNM staging

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

Histopathological grading (G)

Gx	Not evaluable
G1	Well differentiated
G2	Intermediately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Additional classification of head and neck skin cancers (version from 2020)

T stage (main tumour mass)

Tx	The primary tumour cannot be evaluated
T0	No evidence of primary tumour
Tis	Cancer *in situ*
T1	The tumour is less than 2 cm in greatest dimension
T2	The tumour is between 2 and 4 cm in greatest dimension
T3	The tumour is more than 4 cm in greatest dimension with a minor bone invasion OR perineural invasion OR deep infiltration (no more than 6 mm of subcutaneous tissue invasion)
T4	Major infiltration of bones, the base of skull and/or skull foramens by the tumour
T4a	The tumour deeply infiltrates bones
T4b	The tumour infiltrates the base of skull and/or skull foramens

N stage (regional lymph nodes)

Nx	Regional lymph nodes cannot be evaluated
N0	No evidence or lymph node involvement
N1	Single, ipsilateral lymph node involvement, with greatest dimension of lymph node ≤ 3 cm and without extranodal extension
N2	Single, ipsilateral lymph node involvement, with greatest dimension of lymph node > 3 cm, but ≤ 6 cm; OR Multiple ipsilateral lymph nodes involved, without any lymph node longer than 6 cm in greatest dimension; OR Bilateral or contralateral lymph node involvement, without any lymph node longer than 6 cm in greatest dimension All above without extranodal extension present
N2a	Single, ipsilateral lymph node involvement, with greatest dimension of lymph node > 3 cm, but ≤ 6 cm without extranodal extension
N2b	Multiple ipsilateral lymph nodes involved, without any lymph node longer than 6 cm in greatest dimension without extranodal extension
N2c	Bilateral or contralateral lymph node involvement, without any lymph node longer than 6 cm in greatest dimension without extranodal extension
N3	Any lymph node involvement with more than 6 cm in greatest dimension and without extranodal extension OR any lymph node involvement with extranodal extension
N3a	Any lymph node involvement with more than 6 cm in greatest dimension and without extranodal extension
N3b	Any lymph node involvement with extranodal extension

Additionally, U or L mark might be use for, respectively, metastases above or below the lower margin of cricoid cartilage →

Table 6 cont. Staging of skin cancer (according to AJCC 2009)

M stage (distant metastases)

M0	No evidence of distant metastases
M1	Presence of distant metastases

TNM staging

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

Histopathological grading (G)

Gx	Not evaluable
G1	Well differentiated
G2	Intermediately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Skin cancer treatment — basic methods

Resection with histological evaluation of surgical margins

This is the most commonly used procedure in skin cancer treatment (in cases associated with both high- and low-risk of relapse).

Surgical margin of at least 4 mm in cases of BCC and 6 mm in cases of SCC is highly recommended (II, A). High-risk skin cancer requires additional intraoperative radicality evaluation (Mohs micrographic surgery). If such a procedure cannot be undertaken, wider excision with at least 10 mm of surgical margin is advised. When margins require resection of normal skin that would lead to unacceptable aesthetic effects, radical resection within narrower margins (R0 margin) might be considered. Such a margin might be achievable with a utilisation of Mohs micrographic surgery. In Mohs micrographic surgery the tumour is removed layer by layer, and each layer undergoes intraoperative histopathological evaluation as a frozen specimen. Every excised layer is labelled in a fashion that allows further resection of those margins in which cancer cells are present. This procedure allows for a radical resection of the tumour with a maximal sparing of surrounding normal tissue [1–6, 9, 11, 13, 22, 23].

Radiotherapy

In case of non-melanocytic skin cancer (BCC and SCC), radiotherapy might be an alternative curative approach when surgical procedure is not feasible or not accepted by a patient (III, A). Additionally, it is the treatment of choice in inoperable cases, when specific aesthetic effect must be obtained, or when function preservation is priority (mainly in patients older than 60). Radiation should be considered in tumours more than 5 mm in diameter located proximally to mouth, tip and flaps of nose, and more than 2 cm in proximity to ears, forehead, and scalp [24], especially when surgery would result in a major cosmetic defect. Effectiveness of radiotherapy is high, with five-year control rates of 94.4% for BCC and 92.7% for SCC and 15-year control rates of, respectively, 84.8% and 78.6%, in retrospective data [25]. Available meta-analyses estimate the local relapse rate to be around 10% for both SCC and BCC [26–28]. However, trials comparing surgical treatment with radiotherapy in BCC suggest superiority of a surgical approach, with a four-year local relapse rate of 0.7% after surgery and 7.5% after radiotherapy [29]. In radical radiotherapy of skin cancers both conventional fractioning (60–70 Gy in 6–7 weeks or 45–55 Gy in 3–4 weeks) and hypofractioning (40–44 Gy in 2 weeks or 30 Gy in 5 fractions for 2–3 weeks) might be used [30]. Adjuvant radiotherapy is used in locoregionally advanced skin cancer (especially if perineural invasion is present), after lymphadenectomy for locoregional lymph node involvement in SCC, and after non-radical surgical procedure when radicalisation with subsequent surgery is not feasible. Radiotherapy should be also considered after non-radical treatment with Mohs micrographic surgery. Additional risk factors for local recurrence include: head and neck localisation; lesion more than 2 cm in size; poor differentiation; previous recurrence; and immunosuppression [31]. Usually, 50–66 Gy in a period of 5–7 weeks is used in an adjuvant setting, with a higher dose delivered when surgical margins are positive or when unresected metastatic lymph nodes are present [30]. Radiotherapy is also a valuable option in the palliative treatment. In selected cases of superficial tumours (up to 2 cm depth) and after non-radical surgical procedures, brachytherapy might be an option.

The major disadvantage of radiotherapy includes the risk of adverse effects, which tend to exacerbate with time. Acute forms of radiation-induced skin reactions include erythema, dry or wet desquamation, or even skin necrosis, and chronic reactions usually take the form of telangiectasias, pigmentosus changes

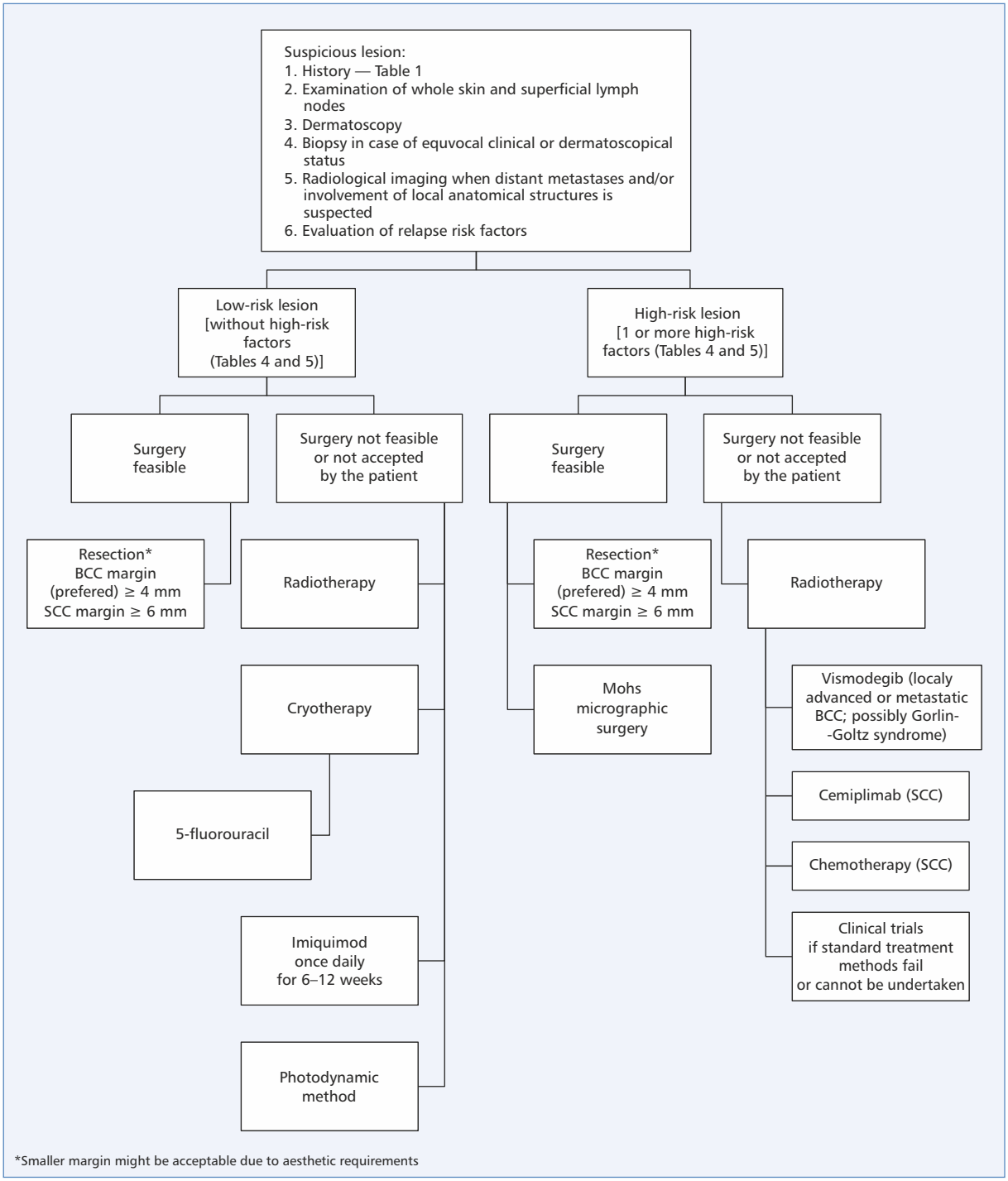

Figure 1. Recommended diagnostic and treatment algorithm in case of skin carcinoma suspicion

(including persistent skin discolouration), and fibrosis. Due to this fact, aesthetic effects of radiotherapy might worsen with years. Additional adverse effects of radiotherapy include increased risk of radiation--induced secondary malignancies, mostly non-melanocytic skin cancers, especially after irradiation at early age [32–34].

Contraindications for radiotherapy include:

— age below 60 years (relative contraindication);
— connective tissue disease (e.g. systemic lupus erythematosus; scleroderma) (relative contraindication);
— genetic syndromes associated with a high-risk of skin cancer [e.g. Gorlin-Goltz syndrome (naevoid basal cell carcinoma syndrome); xeroderma pigmentosum];

— cicatricial basal cell carcinoma;
— tumours localised within hands (especially on dorsal surface), sole of foot, extremities (principally below knees and elbows);
— recurrence after radiotherapy.

Chemotherapy

No data confirm the benefit of cisplatin, either as monotherapy or combination with 5-fluorouracil, interferon, or cis-retinoic acid, in patients with metastatic SCC. Limited evidences suggest potential activity of EGFR inhibitors (such as cetuximab or gefitinib), but clinical application of those drugs requires further evaluation in clinical trials [1–5].

Hedgehog pathway inhibitors

In patients with a genetic predisposition to develop multifocal BCC (Gorlin-Goltz syndrome), metastatic BCC, or locally advanced BCC refractory/unsuitable for surgical and radiotherapeutic approach, treatment with vismodegib (small molecule Hedgehog signalling pathway inhibitors) should be considered (II, A). Vismodegib, used at a daily dose of 150 mg, prolongs progression-free survival and achieves a response rate between 30 and 60%. Phase I–II trials confirmed vismodegib activity in advanced BCC and confirmed the response rates as mentioned. The ERIVANCE BCC clinical trial evaluated vismodegib (150 mg daily) in patients with metastatic BCC (mBCC) or locally advanced BCC (laBCC; unresectable and/or unqualified for radiotherapy) [35]. The primary endpoint was overall response rate (ORR). An independent radiological assessment showed 33.3% ORR in the mBCC group and 47.6% ORR in the laBCC group (including 22.2% of complete responses). Median duration of response was 14.8 months in the mBCC group and 26.2 months in the laBCC group, and median progression-free survival was 9.3 months and 12.9 months, respectively. Most of the patients in both groups experienced a reduction of tumour size [36]. The long-term results of this study confirmed the durability and efficacy of vismodegib in both groups of patients with ORR 48.5% in the mBCC cohort and 60.3% in the laBCC cohort. The median overall survival (OS) was 33.4 months in the mBCC cohort and was not achieved in the laBCC cohort. Efficacy of vismodegib in this setting was confirmed in a large (> 500 patients) STEVIE trial, which showed similar results [37]. Similar results were also obtained in the Polish analysis of patients treated under the appropriate NHF drug program [38].

In a multicentre, randomised, placebo-controlled phase II trial (n = 41) activity of vismodegib in patients with Gorlin-Goltz syndrome was evaluated [34]. Development of new BCC lesions was significantly lower in patients receiving vismodegib compared to placebo (respectively 2 *vs.* 29 new cases within a year). Additionally, reduction of already existing BCC lesions was seen in patients receiving vismodegib, without any case of BCC progression during vismodegib treatment.

Vismodegib is used orally at a 150 mg dose once daily until disease progression or unacceptable toxicity (in Poland as part of a drug access programme). The most common adverse events (> 30% of patients) include muscle cramps, taste alterations, decrease of body weight, fatigue, and nausea [1–4, 35, 40–43]. During and within the consequent 24 months after therapy cessation, usage of contraception is advised. Based on the results of the phase II BOLT trial, a novel Hedgehog pathway inhibitor, sonidegib, is already registered within the USA [44].

Immunotherapy in the treatment of advanced SCC

A phase 1/2 study confirmed the activity of anti-PD-1 immunotherapy with cemiplimab in the treatment of patients with advanced (unresectable or metastatic) SCC. Response rate was 50% in a group of 26 patients in the phase I study and 47% in a group of 59 patients in the phase II study. The responses were long-lasting and exceeded 6 months in 57% of responding patients. Adverse events occurred in 15% of patients and in only 7% they were the reason for treatment discontinuation [45, 46]. Cemiplimab was registered in 2019 for the use in the treatment of adult patients with metastatic or locally advanced squamous cell carcinoma of the skin not eligible for radical surgery or radical radiation therapy (II, A). The safety of cemiplimab therapy was assessed in 591 patients with advanced solid-organ cancers, including 219 patients with advanced squamous cell carcinoma of the skin who received cemiplimab monotherapy in 2 clinical trials (R2810-ONC-1423 and R2810-ONC-1540) [45, 46].

Clinical trials

Patients with an advanced BCC or SCC, either local or systemic, who exhausted possible therapeutic options, should be offered inclusion in a clinical trial, if possible [1–5]. Currently recruiting trials evaluate PD-1 inhibitors ("checkpoint inhibitors") in patients who progressed on Hedgehog pathway inhibitors. For several years there have been publications suggesting effectiveness of immunotherapy with PD-1 inhibitors in patients with advanced BCC or SCC [47–53].

In a case described by Hauschild et al., a patient with type E xeroderma pigmentosum, four de novo melanomas, multiple invasive and non-invasive SCC, and with extended areas of cancerisation, received pembrolizumab due to metastatic melanoma. The authors observed not only the response of melanoma metastases, but also a rapid decline of actinic keratosis areas and regression of invasive SCC [54].

Generally, treatment of advanced skin cancers with radiotherapy, chemotherapy, or targeted therapy should be performed at highly specialised and experienced cancer centres.

External treatment of skin cancer

Cases of BCC and SCC associated with low-risk of recurrence might by treated with superficial methods. Due to the clear inferiority of such an approach, it should be limited only to patients with contraindications to standard modalities (especially surgery). Superficial treatment might be also considered in patients with a shallow, low-risk BCC, when a significant benefit in aesthetic outcomes might be expected.

5-fluorouracil (0.5%)

The drug is used in the treatment of actinic keratosis, superficial BCC and AK/SCC *in situ.* 5-fluorouracil is applied twice daily for a period of 4, 6, or 11 weeks in cases of superficial forms of BCC, with a complete response obtained in about 90% of patients.

Imiquimod (5%)

The drug is used in the treatment of actinic keratosis, SCC *in situ*/Bowen's disease and non-invasive forms of the superficial BCC. The cream is currently used for longer periods (12 weeks instead of 6) and applied more often (two times daily) because those prolonged treatment results in lower rates of failure (III, A). Application as an occlusion in superficial and nodal forms of BCC up to 2 cm in size offers similar efficacy. About 84% of patients with a superficial form of BCC had no signs of disease after five years of follow-up. In immunocompetent patients the cream might be used as a sole modality, but in immunocompromised patients imiquimod should be combined with cryotherapy, Mohs microsurgery, or photodynamic method [1–6, 11–13, 22, 23, 55].

Photodynamic method

The use of the PDT method in the treatment of NMSC is associated with restrictions related to registration of both photosensitizing substances (which may differ in the USA and Europe) and light sources (specific light length/specific device), which constitute a therapeutic protocol [56]. It should be emphasized that PDT is a second-line treatment for BCC with a low risk of recurrence and is reserved for superficial forms of BCC (I, A) and Bowen's disease (I, A), therefore an adequate histological examination should be available when abandoning surgical treatment.

The effectiveness of the photodynamic method in the treatment of basal cell carcinoma (superficial and/ /or below 2 cm) has been evaluated in numerous studies that have shown higher efficacy and a lower recurrence rate (14% *vs.* 30.7%) using MAL/PDT [56, 57]. A study by Christiansen with the longest published follow-up period (10 years after treatment) showed: 75% overall complete response rate for selected BCC subtypes treated with ALA/PDT; 60% of complete responses after a single exposure and 87% after a double exposure [58]. Zou et al. presented a meta-analysis comparing PDT with surgical resection, confirming its similar effectiveness, better cosmetic effect but higher recurrence rate — 14% *vs.* 4% during a 5-year follow-up in one study [59]. Vinciullo et al. evaluated the effectiveness of MAL/PDT in "difficult-to-treat" BCC defined as: large in size or located in the H zone characterized by the highest relapse rate or in patients with a high risk of postoperative complications [60]. The study showed a therapeutic failure rate of 18% after 12 months and 24% after 24 months. In 2013, a consensus of photodynamic treatment of BCC in patients with Gorlin-Goltz syndrome has been published [61]. Based on the analysis of 9 review papers summarizing the results obtained in 83 patients, the usefulness of the photodynamic method was recognized as safe and effective in the treatment of superficial forms of BCC and nodular BCC with infiltration depth less than 2 mm. The authors of consensus recommended that the frequency of follow-up visits depends on the number and location of BCC lesions as well as the frequency of relapses. The possibility of simultaneous treatment of many lesions was emphasized as an important advantage of photodynamic therapy.

MAL/PDT can also be used to treat Bowen's disease while it has a different therapeutic protocol [56]. It should be emphasized that we currently do not have studies on a large number of patients which results could be directly compared head-to-head. We can assume response rates approx. 80% after about one year of observation and reccurence rate even 50% after about 40 months of observation [62]. However, the results of treatment of SCC *in situ* with PDT is characterized by higher response rates after one year of observation than cryotherapy and fluorouracil — 85–72% *vs.* 48–69% [63, 64]. Oncological "purity" index of 68–89% after 17–50 months can be achieved after an average 3 irradiations of a given lesion [65–67]. Considering the SCC metastatic potential as higher than BCC and the aforementioned data, qualification for PDT treatment should be reasonable and the patient should be closely monitored using a dermoscope.

Cryosurgery

Cryotherapy leads to tumour necrosis via decrease of tissue temperature to between –50 and –60°C. Its applications include the treatment of superficial skin cancer with low-risk of recurrence and size under 2 cm or lesions of actinic keratosis. Cryotherapy is not recommended in the treatment of nodular changes. As multiple different cryotherapy techniques are commonly used, head-to-head comparison of outcomes from different studies is vastly limited (IV, B) [1–6].

Commentary

Due to the lack of reliable scientific data based on randomised controlled trials, usage of curettage and electrodessication in the treatment of skin cancers is not recommended.

For the same reasons, the Oncology Section of the Polish Society of Dermatology (Polskie Towarzystwo Dermatologiczne; PTD) and the Melanoma Academy Section of the Polish Society of Surgical Oncology (Polskie Towarzystwo Chirurgii Onkologicznej; PTChO) do not recommend other tissue destructive methods (laser therapy, dermabrasion, chemical peeling with trichloroacetic acid) because they indispose proper evaluation of radicality [15, 16].

A few randomised trials evaluating the effectiveness of intratumourally administered interferon in BCC showed modest efficacy in the treatment of superficial and small nodal BCC, with a high rate of early failures (around 30%) and high rates of adverse events [1–6]. Vismodegib is currently the therapeutic standard for use in adult patients with symptomatic metastatic or locally advanced basal cell carcinoma not eligible for radical surgery or radiotherapy (II, A).

Observation after oncological treatment

The necessity for close follow-up after treatment for skin cancer arises from multiple conditions, including:
— in about 30–50% of patients who develop skin cancer, a subsequent skin cancer will develop within next five years;
— 70–80% of SCC recurrences will occur within the first two years of follow-up;
— patients who developed skin cancer have a 10-fold increase of developing subsequent skin cancer compared to the general population;
— patients who developed skin cancer have a higher risk of developing melanoma;
— immunocompromised/immunosuppressed patients have a higher risk of developing invasive forms of SCC.

Every suspicion of skin cancer recurrence should be verified by a histopathological examination. Dermatoscopy often enables diagnosis of early-stage recurrence and precisely identifies the best site for biopsy.

The presence of enlarged regional lymph nodes justifies at least fine-needle biopsy (less commonly excision of a whole lymph node for a histopathological examination) and proper radiological imaging (CT, MRI) as a method of staging.

Follow-up principles:
— **BCC or SCC**
  • whole-year photoprotection SPF 30–50+,
  • patient's self-control monthly,
  • dermatological and dermatoscopic examination of whole skin surface every 4–6 months for five years and every 6–12 months thereafter;
— **locally advance or metastatic BCC/SCC**
  • whole-year photoprotection SPF 30–50+,
  • patient's self-control monthly,
  • dermatological and dermatoscopic examination of whole skin surface: every 1–3 months in e year, every 2–4 months in the second year, every 4–6 months in the third year, and every 6–12 months thereafter for life,
  • multidisciplinary care (e.g.: dermatological, oncological, radiotherapeutic, neurological, ophthalmological).

Surveillance of patients after organ transplantation during chronic immunosuppressive treatment:
— whole-year photoprotection SPF 30–50+;
— patient's self-control monthly;
— dermatological and dermatoscopic examination of whole skin surface: every 6–12 months for life;
— after skin cancer occurrence a control visit should be performer every 3–6 months for life.

Surveillance over patients with genetic predisposition for skin cancer development:
— whole-year photoprotection SPF 30–50+;
— patient's self-control monthly;
— dermatological and dermatoscopic examination of whole skin surface: every 3–6 months for life;
— in patients with xeroderma pigmentosum reversal of circadian rhythm might be deliberated and strict occupational avoidance of UV, IR, and X-ray radiation should be recommended.

Skin cancer prevention

Primary prevention:
— strict surveillance over patients with genetic predisposition for skin cancers induced by UV radiation;
— population-based education regarding proper skin photoprotection and skin cancer awareness.

Secondary prevention:
— patient-aimed education regarding proper skin photoprotection;
— patient-aimed education about signs and symptoms of skin cancer and the importance of systemic self-control;
— regular dermatological control (including dermatoscopy) according to a prearranged schedule;
— in patients receiving immunosuppressants, who develop actinic keratosis and/or NMSC, consider reduction of calcineurin inhibitor/antimetabolite doses in favour of mTOR inhibitors.

Merkel-cell carcinoma (primary neuroendocrine carcinoma of skin)

Merkel-cell carcinoma (MCC) is a rare, but highly aggressive skin cancer that arises from neuroendocrine cells (Merkel cells) [68, 69].

The incidence rate of MCC is low and estimated at 0.25–0.32 per 100,000 persons annually, with a higher prevalence in men than in women (ratio of 1.5:1). MCC occurs more often in Caucasians than in other races. The incidence rate rises with age, as MCC rarely develops in people younger than 50 years old, with a clear rise of incidence in people between 50 and 65 years old. The mean age at MCC diagnosis in men is five years lower than in women. The most common site of occurrence is the skin of the head and neck (44–48% of cases), then the skin of the upper (around 19% of cases) and lower extremities (between 16 and 20% of cases) [70, 71].

Most of the MCC cases arise from skin. Other sites of primary lesions (such as mucous membranes or metastatic MCC with unknown primary site) are extremely rare [72].

Aetiology

The aetiology of MCC remains unknown, but several factors predisposing to MCC development have been well described. The most important of them include:

— exposition to UV radiation [natural or artificial, such as phototherapy using psoralens (PUVA, psoralen ultraviolet A) for psoriasis] [73, 74];
— diseases associated with immunosuppression, e.g.:
  • HIV infection or AIDS (11-fold increase in risk of MCC) [75],
  • immunosuppression after organ transplant (five-fold increase in risk of MCC) [76, 77],
  • chronic lymphatic leukaemia;
— specific viral infections, with polyomavirus infection recognised most often (variant characteristic for MCC: Merkel cell polyomavirus, MCPyV) [78, 79].

Diagnosis

MCC usually forms as a rapidly growing tumour or solid skin infiltration, often red to violet in colour. Ulcerations occur rarely. Sometimes, due to a rapid spread through lymphatic vessels, satellite lesions develop. The tumour is often asymptomatic and, in most cases, not painful [80]. Because of this uncharacteristic clinical symptomatology, MCC is rarely suspected before obtaining histopathological results from biopsy or excised specimens.

Anglo-Saxon literature suggests a mnemotechnic acronym as an aid in MCC diagnostics — AEIOU (A — asymptomatic; E — expanding rapidly; I — immune suppressed; O — older than 50 years; U — UV-exposed skin). Only about 7% of MCC patients fulfil all criteria, but nearly 90% fulfil at least three of them [80].

Signs, symptoms, and brisk onset of lesion may suggest malignant nature and should legitimise excisional biopsy, performed according to standard oncological procedures. Microscopic examination of the removed tumour allows a valid diagnosis. In pathological examination, Merkel cell carcinoma is made of small round cells with scanty cytoplasm, nuclear chromatin is granular (neuroendocrine type), and high mitotic activity is observed. Pathological examination might be enhanced by immunohistochemical staining that allows differentiation of MCC from other small round-cell cancers. A typical immunoprofile of Merkel cell carcinoma is CKAE1/AE3(+), CK20(+), CD56(+), synaptophysin(+/–), chromogranin(+/–), NSE(+), LCA(–), TTF1(–), CDX2(–), p40(–).

MCC diagnosis requires retaking of physical examination and obtaining additional radiological imaging to assess the stage of the disease. Depending on individual indications, radiological assessment [X-rays, computed tomography (CT), magnetic resonance imaging (MRI)] might be combined with a pathological or cytological (fine-needle biopsy) evaluation of suspicious lesions.

In some cases, when results from histopathological examination are dubious and when systemic spread of disease is suspected (skin metastases of other than MCC neuroendocrine neoplasms, e.g. small-cell lung cancer), positron emission tomography-computed tomography (PET-CT) might be indicated and provide valuable clinical data.

Staging and prognosis

Staging is assessed according to American Joint Committee on Cancer (AJCC) 8th edition from 2017, which is based on typical TNM (tumour-node-metastases) criteria (Tables 7, 8) [72, 81–84]. The most important prognostic factors include size of primary lesion, range of lymphatic node involvement, and the presence of distant metastases.

Currently, 10-year survival rates for MCC are estimated to be around 65% in women and 50.5% in men (with a mean of about 57% for both sexes). Depending on the size of primary lesion 10-year survival rates are: for cancers less than and equal to 2 cm in diameter — 61%; for cancer greater than 2 cm in diameter — only 39% [72].

Treatment

The standard treatment for locoregionally limited MCC is surgery. Treatment of MCC should be limited to highly specialised cancer centres [13, 82, 85, 86].

Table 7. MCC staging (AJCC 8th edition; 2017)

Primary tumour (T)	
TX	The primary tumour cannot be assessed
T0	No evidence of primary tumour (e.g. nodal/metastatic presentation without associated primary tumour)
Tis	*In situ* primary tumour
T1	Maximal tumour diameter less than or equal to 2 cm
T2	Tumour diameter greater than 2 cm, but less than or equal to 5 cm
T3	Tumour diameter greater than 5 cm
T4	Primary tumour invades bone, muscle, fascia, or cartilage
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Metastatic involvement of regional lymph nodes
N1a (sn)	Micrometastasis (sentinel lymph node biopsy)
N1a	Clinical detection negative; presence of lymph node metastasis in pathologic examination
N1b	Clinical detection positive (physical examination or radiological evaluation), confirmed in pathologic examination
N2	In transit metastases without lymph node involvement
N3	In transit metastases with lymph node involvement
Distant metastases (M)	
M0	No distant metastasis
M1	Distant metastases present (beyond regional lymph node)
M1a	Metastases to skin, subcutaneous tissues, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral organs

Table 8. Staging/prognostic groups

Staging			
	T	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2–T3	N0	M0
IIB	T4	N0	M0
IIIA	T0	N1b	M0
IIIA	Any T	N1a(sn)/N1a	M0
IIIB	Any T	N1b–N3	M0
IV	Any T	Any N	M1

Stage I and II

In case of no signs of regional lymph node involvement, sentinel lymph node biopsy and a wide excision (with at least 1–2 cm margin) of a scar should be considered, with a possible addition of adjuvant radiotherapy. Metastases in sentinel lymph nodes are present in around 25–35% of patients with negative clinical examination. The risk of micrometastases presence rises significantly with the diameter of the primary lesion greater than 1 cm [87, 88].

Stage III

In cases with regional lymph node involvement (both micro- and macrometastases; stage III), a regional lymphadenectomy is recommended.

Despite the lack of evidence from randomised, controlled trials, available retrospective data suggest that adjuvant radiotherapy (at a dose of 50–60 Gy) results in improved locoregional disease control and improved overall survival (III, B) [89, 90].

Some authors suggest that in patients with a bulky nodal metastases, chemotherapy might provide benefit. No standard systemic treatment schedule exists in this group because the treatment might be delivered in both neoadjuvant and adjuvant settings. In some cancer centres lymphadenectomy is performed between chemotherapy cycles. Nevertheless, available data is insufficient to define the magnitude of benefit derived from chemotherapy in a bulky stage III MCC [90–92]. There are encouraging initial results of the use of immune checkpoint inhibitors in preoperative treatment of MCC. In 2018 the results of the phase I/II study using nivolumab in neoadjuvant treatment of patients with stage IIa–IV MCC (CheckMate 358) have been published. In pathological assessment, a complete pathological response was obtained in 47% of patients, and a greater pathological response (≤ 10% viable tumor cells) in 18% of patients. In some patients, the achieved response allowed for a surgery of smaller extent. The median progression-free survival (PFS) and median OS were not achieved. None of the patients who achieved a complete or greater pathological response experienced the recurrence of the disease [93].

Stage IV

Treatment of advanced, metastatic MCC has palliative character. Patients with sufficient performance status might receive palliative chemotherapy, despite the lack of data regarding efficacy and survival benefit from this kind of treatment (not including immunotherapy) [82, 94]. Several observations indicate a degree of chemosensitivity of MCC, although duration of responses does not exceed 8–10 months and with low rates of long-term survival (0–18%). Chemotherapy regimens commonly used include polychemotherapy

with cisplatin, doxorubicin, and vincristine or etoposide, as well as 5-fluorouracil or cyclophosphamide. Palliative surgical or radiotherapeutic procedures can be used if indicated. Due to the high efficacy of immune check-point inhibitors (mostly antibodies aimed at PD-1 and PD-L1 receptors), verified in phase II clinical trials, current guidelines recommend them as a treatment of choice in metastatic MCC (II, A).

Avelumab is the only registered drug in the European Union for the treatment of adult patients with metastatic MCC (II, A).

In case of generalized disease, the possibility of including the patient in a clinical trial should be considered.

The single-arm, phase II trial Javelin Merkel 200 showed an impressive efficacy of avelumab in metastatic MCC after chemotherapy failure, which allowed prompt registration of avelumab in this indication (at a dose of 10 mg/kg of body weight, administered intravenously every two weeks until progression or unacceptable toxicity). Objective response rate reached 31.8% [95% confidence interval (CI) 21.9–43.1; 28 patients], including eight complete responses (9%) and 20 partial responses (23%). An additional nine patients (10%) achieved stable disease [95]. Responses were durable and were ongoing in 23 (82%) patients at the time of analysis. In 92% of patients the duration of response was longer than six months. Median progression-free survival (PFS) was 2.7 months (95% CI 1.4–6.9) and the rate of progression-free survival at six months reached 40%. The PFS curve reached a plateau. The rate of six-month overall survival was 69% (95% CI 58–78), and the median OS was 11.3 months (95% CI 7.5–14.0). Objective response was noted in 20 out of 58 patients (34.5%) with positive PD-L1 expression, in three out of 16 (18.8%) PD-L1-negative patients, in 12 out of 46 (26.1%) MCPyV(+) patients, and in 11 out of 31 (35.5%) MCPyV(–) patients. More responses were seen in patients who received only one prior line of systemic therapy. Treatment with avelumab was generally well tolerated. Treatment-related adverse events occurred in 62 (70%) out of 88 patients. Treatment-related grade 3 adverse events developed as five events in four patients (5%): lymphopaenia in two patients, increase in creatine phosphokinase in one patient, increase in aminotransferases in one patient, and increase in cholesterol in one patient. No grade 4 toxicities or treatment-related deaths were observed. Serious treatment-related adverse events were noted in five patients (6%): colitis, drug infusion reaction, increase in aminotransferases, synovitis, and interstitial nephritis (each in one case). Potentially immunological-mediated adverse events included hypothyroidism (3%), hyperthyroidism (2%), pneumonitis (1%), and type 1 diabetes (1%). Two patients stopped the treatment due to adverse events (2%). Updated results with a median follow-up of 18 and 24 months published in 2018 confirm the effectiveness of avelumab in this indication. Based on the analysis of data obtained from 88 patients followed up with a median of 29.2 months (24.8–38.1), it was found that the median OS was 12.6 months (95% CI 7.5–17.1) and the 2-year survival rate was 36% (50% survival after 1 year and 39% after 1.5 years). Median duration of response was not reached (2.8–31.8 months; 95% CI 18.0–not reached). Long-term responses to avelumab determine stable PFS values after 1 year (29%), 1.5 years (29%) and 2 years (26%) [96, 97]. The phase 2 JAVELIN Merkel 200 study also led to the registration of avelumab for the 1st line treatment of patients with advanced MCC. Published in 2018 estimated survival data for these patients indicate an average survival of 49.9 months (6.3; 179.4) and 1-year and 5-year survival rates of 66% and 23%, respectively [98]. In 2019, the results of more than 15 months of observation of patients participating in part B of this study (1st line treatment) were published. A total of 116 patients were treated with avelumab, the median duration of treatment was 5.5 months (0.5–35.4) with a median follow-up of 21.1 (14.9–36.6). The ORR was 39.7% (95% CI: 30.7–49.2%). The CR and PR were achieved by 19 (16.4%) and 27 (23.3%) patients, respectively. The median duration of response in the whole group of patients participating in the study was 18.2 months [99]. Another phase II trial, with results published in 2016, evaluated pembrolizumab, an anti-PD-1 antibody, in treatment naïve, stage IIIB–IVC patients with MCC [100]. The trial included 26 patients treated with pembrolizumab (at a dose of 2 mg/kg of weight every three weeks) in a first-line treatment of metastatic MCC. The objective response rate reached 56% (four complete responses and 10 partial responses), and progression developed only in two out of 14 responding patients after a medial follow-up of 33 weeks. As with avelumab, responses occurred irrespectively of MCPyV status. The rate of six-month PFS was 67%. Analysing those two trials, it seems that there is a tendency towards higher response rates with fewer prior lines of treatment. Therefore, immunotherapy should be considered the treatment of choice in first-line treatment of metastatic MCC, especially considering the results from the pembrolizumab trial [101]. Responses were achieved irrespective of MCPyV status, and immunotherapy proved to be effective even in older patients, which is common for MCC.

In accordance with Polish and international recommendations anti-PD-1/anti-PD-L1 immunotherapy is currently a standard systemic treatment of patients with unresectable/metastatic MCC. Avelumab is registered in this indication in the European Union and in Poland is available under Emergency Access to Drug Technology Program in connection to the positive opinion of the Agency for Health Technology Assessment and Tariff

System (Agencja Oceny Technologii Medycznych i Taryfikacji, AOTMiT).

Treatment of local and locoregional recurrence

Local and locoregional recurrence are the most common forms of relapse and occur in nearly 30% of surgically treated patients (adjuvant radiotherapy reduces this rate to about 11%) [102].

Local and locoregional recurrence might be treated as primary MCC with adequate stage (I–III). If possible, the tumours should be resected with an appropriate surgical margin, and adjuvant radiotherapy should be considered if not given previously. Because relapse is associated with an inferior prognosis, adjuvant systemic therapy might be considered, despite the lack of data confirming benefit from such a treatment.

Other rare forms of skin cancer

Sebaceous carcinoma

This type of cancer arises from sebaceous glands and develops most commonly in the 7th decade of life. It is usually localised in the periocular region, sometimes as part of Muir-Torre syndrome. In early form it mimic chalazion or blepharitis, a common reason for delay in diagnosis. The primary tumour is usually treated surgically. Due to a 40% rate of regional lymph node involvement, some centres perform sentinel lymph node biopsy with a subsequent lymphadenectomy if indicated [103, 104]. No efficient systemic treatment exists. Nearly 22% of patients dies due to the development of distant metastases [105, 109].

Primary cutaneous apocrine carcinoma (apocrine adenocarcinoma)

Primary cutaneous apocrine carcinoma develops in periorbital, axillar, genital, and perianal areas of skin. The primary lesion often develops proximally to Paget's disease foci located outside of the breast. The presence of regional lymphatic node metastases and a tendency towards local recurrences were described. Therefore, besides radical resection with a wide margin, a sentinel lymph node biopsy is recommended [107, 108].

Eccrine carcinoma (also syringoid carcinoma)

Eccrine carcinomas form nodular tumours, located mostly on the skin of the head and upper extremities, and characterised by various growth dynamics. It usually affects people over 50 years old. Several subtypes can be distinguished, with different occurrence rates and clinical aggressiveness (MAC, microcystic adnexal carcinoma; eccrine porocarcinoma; hidrade- nocarcinoma; spiradenocarcinoma; eccrine mucinous carcinoma; malignant eccrine spiradenoma; malignant mixed tumour; malignant cylindroma; syringoid carcinoma) [110]. The most common subtype, MAC, requires vast, radical excision of the primary lesion or MMS procedure, due to its aggressive growth and a high relapse rate [111]. Inoperable lesions might be treated with radiotherapy. In other subtypes of eccrine carcinoma locoregional and distant metastases were observed in up to 60% of cases. A few publications suggest limited benefit from systemic treatment with cytotoxic drugs [112].

Cancer originating from hair follicle: trichilemmal carcinoma, trichoblastic carcinoma, malignant proliferating trichilemmal cyst, pilomatrix carcinoma

Surgery is a fundamental treatment modality. Due to its rare occurrence, no significant data regarding systemic therapy exists.

Conflicts of interest

P.R. received fees for lectures and participation in the Advisory Board from Novartis, MSD, BMS, Roche, Pierre Fabre, Pfizer, Sanofi, Blueprint Medicines, and Amgen.

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Cutaneous melanoma

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Key words: melanoma, diagnosis, therapy, immunotherapy, anti-PD-1, anti-CTLA-4, BRAF, MEK, sentinel lymph node biopsy

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-randomized cohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

Epidemiology and aetiology

Cutaneous melanomas are malignant neoplasms deriving from neuroendocrine melanocytic cells. Melanoma are relatively rare in Poland — the standardised incidence rate reaches about 6/100,000, which represents 3800 new melanoma cases per year during the last few years (about 1800 men and about 2000 women). However, 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 2.1/100,000 men and 1.4/100,000 women, which represents, during the last years, respectively, about 700 and 710 melanoma-related deaths [1–3].

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 (III, B). Protection against excessive action of ultraviolet light is the most important element of primary melanoma prophylaxis (III, A).

Cutaneous melanoma has a 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, localised 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 20–30% in regionally advanced and metastatic disease respectively with the use of modern systemic therapy.

The crucial recommendation is to treat a melanoma patient with a multidisciplinary team formed by specialists experienced in diagnosing and treating melanoma — this in particular concerns patients with stage III and IV melanomas [4, 5].

Diagnostics

Clinical symptoms

Skin melanomas may be suspected in both de novo skin changes and in alterations of pre-existing moles. There have been some attempts to create diagnostic systems based on clinical symptoms (Table 1). The most popular of these is the American mnemonic clinical system called ABCD(E), used mostly with educational intent because it is useful only in identification of some melanomas, mostly of the superficial spreading melanomas and 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 the patient their relatives.

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 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)

Diagnostics

Medical history should include questions concerning skin condition (information concerning changes of the pre-existing skin moles, the appearance of new pigmentary lesions, and accompanying symptoms, e.g. pruritus) and risk factors of cutaneous melanoma (e.g. sunburn, use of tanning beds, melanomas in relatives, and previous immunosuppressive treatment or HIV infection). It is important to stress that in more than 60% of melanoma diagnosed after physical examination patients did not report any specific data in anamnesis, which can be helpful to establish this diagnosis.

We should stress that whole 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).

The recommended test, used in preliminary, quick, non-invasive diagnostics, is dermoscopy (dermatoscopy) (II, A) [6, 7]. The examination consists of assessment of all lesions on the patient's skin by means of a manual dermoscope with polarised or non-polarised light with 10 × magnification [7]. Thanks to dermoscopy it is possible to improve the diagnostic sensitivity by about 30%. The simplest technique of dermoscopic assessment (the so-called three-point dermoscopic scale according to Argenziano) is based on the clinical suspicion of melanoma when two of the following three criteria are met: 1) asymmetric distribution of the dermoscopic 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 by verified by use of the confocal reflection microscopy (in the scope of a specialist dermatological consultation). 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.

Histopathological examination of the whole excised mole is crucial for diagnosing a skin melanoma. Procedures other than excisional biopsy (microstaging 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. First of all, a thorough physical examination should be carried out, including the examination of the whole skin (presence of other suspicious pigmented lesions, satellite and/or in transit changes), assessment of lymph nodes, and examination for the presence of possible distant metastasis. In low-risk clinical melanomas (pT1a), other tests are not routinely required.

Table 2. Clinical differential diagnostics ofcutaneous melanoma

Early skin melanoma	— Pigmented naevus, including junction naevus (naevus melanocyticus junctionalis, marginalis) and compound nevus (naevus melanocyticus 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	— Seborrheic keratosis (verruca seborrhoica, keratosis seborrhoica) — Dermatofibroma — Keratoacanthoma — Pigmented basal cell carcinoma (carcinoma basocellulare pigmentosum) — Haemangioma — Venous extravasation — Pyogenic granuloma (granuloma pyogenicum) and telangiectatic granuloma (granuloma telangiectaticum) — Pigmented hidrocystoma — Kaposi's sarcoma — Angiomyoneuroma — Other adnexal tumours, especially pigmented — Onychomycosis — Subungual or under cutaneous corn haemangioma

However, in higher stages (pT1b–pT4b), a scan should be performed by ultrasound examination of regional lymph nodes, and a suspected biopsy should be performed with a histological evaluation before the scar is removed and the sentinel node biopsy is performed. In patients without symptoms, there is no need to perform other additional tests, which mainly concerns computed tomography of the brain, chest, abdominal cavity and pelvis with contrast (CT) and positron emission tomography (PET-CT) (IV, A). CT or PET-CT may be considered in patients with diagnosed skin melanoma in clinical stage IIC and III (PET-CT if the clinical metastases to the lymph nodes are present) or with isolated metastases to the distant organs (potentially resectable). 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 be 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), in such a clinical situation other imaging tests are recommended (CT or PET-CT of brain, neck, chest, abdominal cavity, pelvis) (IV, B).

Differentiation

The conditions that should be considered in the differential diagnostics of 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, 5, 8]. 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 which should contain a standardized histopathological report (http:/www.pol-pat.pl/pliki/files/standardy_pdf/1.2_czerniak.pdf):

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. Tumour stage pT;

c. 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;
d. Mitotic count per square millimetre of the invasive melanoma (only in a vertical component, in the mitotic high-power fields that equates to 1 mm^2, so-called hot spots);
e. Growth phases (horizontal [radial] — intraepidermal, *in situ* with microinvasion and sagittal [vertical], always skin invasion);
f. Presence or absence of microscopic satellite sites (sites composed of melanocytes with diameter > 0.05 mm remoted > 0.3 mm and < 2 cm from the invasive component of the primary melanoma tumour — parameter N).
g. Peripheral margin (measured from the *in situ* to the invasive component) and in depth;

Recommended elements:

h. Presence and extend of tumour regression;
i. Clark level of invasion (level I, II, III, IV, V);
j. Histopathological subtype (see below: WHO histopathological classification of skin tumors World Health Organization; [WHO]);
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.

WHO classification of skin tumours 4th Edition 2018 distinguishes the following types of melanoma [9]:

- melanocytic tumours in intermittently sun-exposed skin;
  - superficial spreading melanoma, low-SCD melanoma);
- melanocytic tumours in chronically sun-exposed skin;
  - lentigo maligna melanoma;
  - desmoplastic melanoma;
- Spitz melanoma;
- acral melanoma;
- mucosal melanoma;
  - mucosal lentiginous melanoma;
  - mucosal nodular melanoma;
- melanoma arising in blue naevus;
- melanoma arising in giant congenital naevus;
- ocular melanocytic tumours;
  - uveal melanoma (epithelioid cell melanoma, spindle cell melanoma type A, spindle cell melanoma type B);
  - conjunctival melanoma;
- nodular melanoma;
- naevoid melanoma;
- metastatic melanoma.

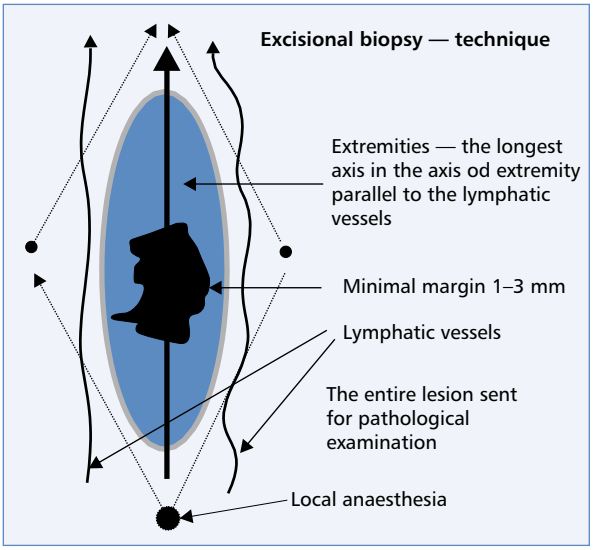

Figure 1. (According to W. Ruka) Recommended direction of the cut during the excisional biopsy. Spindle-shaped excision of the suspected pigmentary lesion should be made collaterally to the regional lymph vessel (toward the nearest draining lymph node/lymph vessel confluence), in the majority of cases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

An excisional biopsy is a simple surgical procedure that can usually be performed in an outpatient clinic. Excision of the suspected skin change is done in local infiltration anaesthesia. The lateral excision margin should include 1–3 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 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 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 mucosal melanomas, in the *GNAQ*, *GNA11* genes — melanomas derived from the blue naevus and the eye). In patients with disseminated (primary or secondary) melanoma, testing for *BRAF* gene mutation in the FFPE is obligatory as well as in the case of high risk of relapse of melanoma (clinical stage IIIA > 1 mm, IIIB, IIIC and IIID) qualified for systemic therapy 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 inpatients with skin melanoma and no metastatic sites [5].

Sentinel node biopsy (microstaging II)

A sentinel node biopsy should be done in patients (II, A) [1, 5, 10, 11]:

- 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 ≥ 0.8 mm or 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 AJCC/UICC 2017 classification); according to recommendations of the American Society of Surgical Oncology (SSO), the 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 0.8–1.0 mm and coexistence of additional risk factors, e.g. mitotic index ≥ 1/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 [12]. During the sentinel node biopsy, a preoperative lymphoscintigraphy and a intraoperative lymphoscintigraphy combined with staining should be done. A sentinel node biopsy should be performed after the excisional biopsy of melanoma, simultaneously with 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 the presence of embolisms of tumour cells in blood vessels. Immunohistochemical exam with use of specific markers (e.g. S100, SOX-10, 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 [10]. 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) [10].

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 [13] (especially when micrometastasis size exceeds 1 mm). An alternative option is an observation with use of ultrasonographic monitoring of the regional lymphatic basin every 4–6 months. The results of two published trials with random selection of patients [14, 15], one of which, however, had insufficient statistical power [15], did not show an improvement in melanoma-dependent overall survival in patients after CLND [14] nor of time to occurrence of distant metastases [15], but progression-free survival in persons after CLND was longer (fewer relapses in the nodal area). These trials also confirmed the basic prognostic role of a sentinel node biopsy (I, B). At present in clinical practice CLND is only performed in patients at high risk of metastases in nonsentinel lymph nodes (such as large size of metastasis to the sentinel node, metastases in > 2 sentinel nodes or extracapsular infiltration of the sentinel node).

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 < 0.4 mm) with no negative impact on the melanoma reoccurrence rate [16].

Evaluation of tumour stage and prognostic factors

Identification of the clinical and pathomorphological risk factors is aimed at understanding the biology of the neoplasm and planning 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 the 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) [5, 8, 12, 17].

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 clinically occult lymph node metastases 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 clinically apparent lymph node metastases (foci of neoplasm diagnosed during the microscopic exam of regional lymph nodes that are clinically enlarged and palpable, or visible on imaging studies). 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. The worst prognosis in this group of patients is with metastases to the central nervous system.

Clinical staging — classification

The current TNM classification system for the clinical and pathological staging of cutaneous melanoma comes from the 2017 revision (Table 3) (II, A) [17].

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 (Figure 2). In the case of detecting a metastasis in clinically palpable reginal 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. In fact, adjuvant therapy after surgery is a standard procedure, 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. The following are the current recommended margins of radical therapy of the primary melanoma lesion (excision of the scare after excisional biopsy of the primary site): melanoma *in situ* — margin 5 mm, melanoma with tumour depth ≤ 2 mm — margin 1 cm, and melanoma with tumour depth > 2 mm — margin 2 cm (Table 4) (II, A).

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 is 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 heterogenous 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 in patients with cutaneous melanomas is performed only in the case of metastases on

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
pTis (*in situ*)		
Tx the thickness of the infiltrate cannot be determined (e.g. diagnosis by curettage) T0 no primary tumor present (e.g. unknown primary site or complete regression of primary tumour)	Not applicable	Not applicable
T1	≤ 1.0	
T1a	< 0.8	Without ulceration
T1b	< 0.8	With ulceration
	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 (e.g. sentinel node biopsy was not performed or lymph nodes previously removed for other reasons). Exception: Pathological N category is not required for grade T1; cN should be used	No
N0	No metastasis to regional lymph nodes	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	Clinically occult metastasis to one lymph node (detected by sentinel node biopsy)	No
N1b	Metastasis to one lymph node assessed by clinical exam	No
N1c	No metastases to regional lymph nodes	Yes
N2	Metastases to 2 or 3 lymph nodes or presence of in-transit metastases, satellite and/or microsatellite lesions with simultaneous metastasis to one lymph node	
N2a	Clinically occult metastases to 2 or 3 lymph nodes (detected by sentinel node biopsy)	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	Metastases to 4 or more lymph nodes or presence of in-transit, satellite and/or microsatellite metastases with simultaneous metastasis to 2 or more lymph nodes or presence of matted nodes with or without in-transit, satellite and/or microsatellite metastases	
N3a	Clinically occult metastases to 4 or more lymph nodes (detected by sentinel node biopsy)	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

→

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

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
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

*Micro-/satellitosis — neoplastic infiltration or nodules (macro or microscopic) remoted 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	N0	M0
					T1b	N0	M0
IB	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
III***	Any T	N1	M0				
		N2					
		N3					
				IIIA	T1a/b–T2a	N1a	M0
						N2a	M0
				IIIB	T0	N1b/N1c	M0
						N1b/c or	
					T1a/b–T2a	N2b	M0
					T2b/T3a	N1a–N2b	M0
				IIIC	T0	N2b, N2c,	M0
						N3b or N3c	
						N2c or	M0
					T1a–T3a	N3a/b/c	M0
					T3b/T4a	Any N ≥ N1	
					T4b	N1a–N2c	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/histopathological 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-pTis/pT1 cN0 cM0 in which no procedure is applied to the regional lymph nodes); ***clinical staging does not include any subgroups of stage III

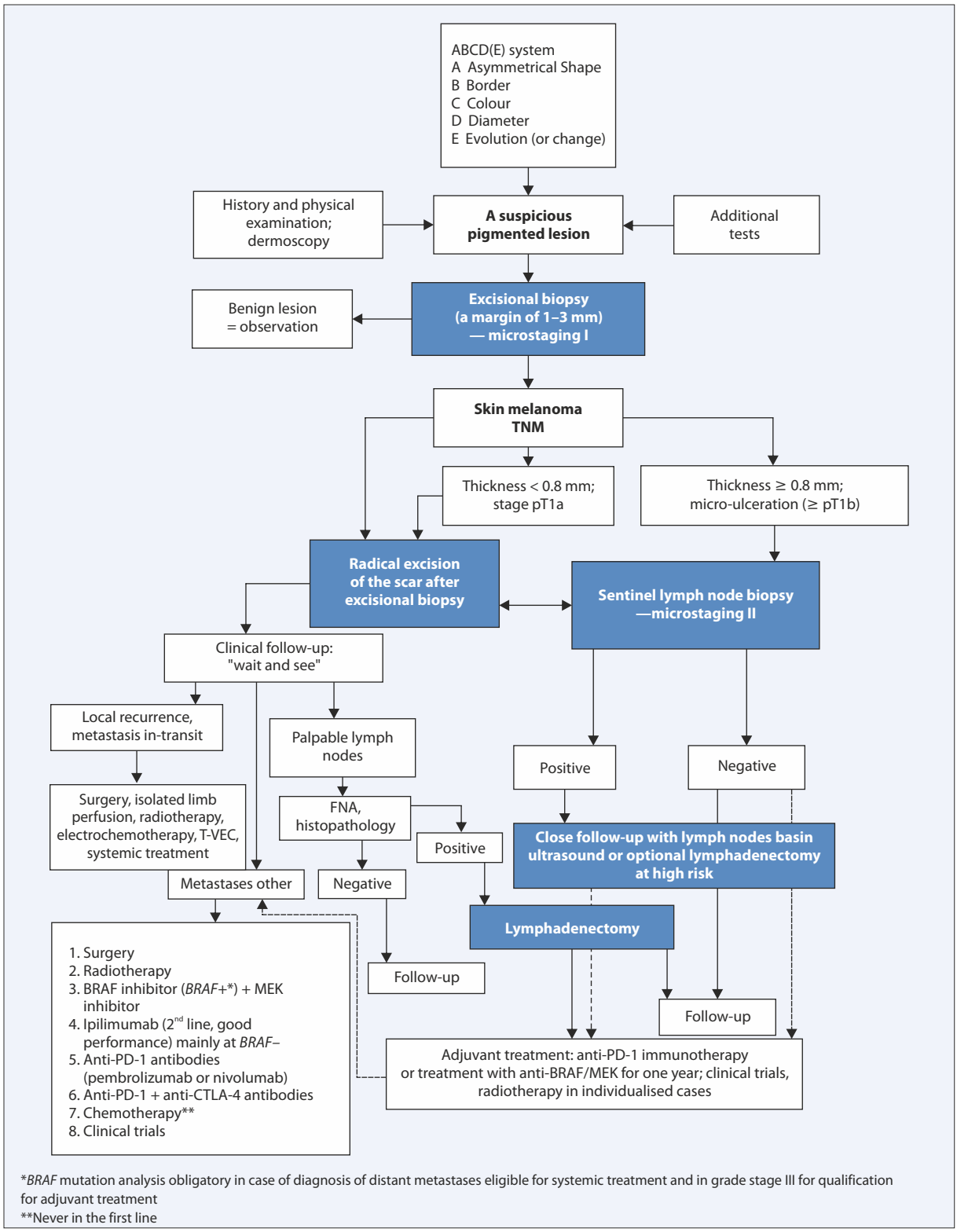

Figure 2. A schedule of diagnostic and therapeutic recommendations in patients with skin melanoma. FNA — fine-needle aspiration biopsy; TNM (tumour–node–metastasis) — classification of tumour/node/metastasis stage

the basis of examination of the material collected by fine-needle biopsy (in special cases — surgical biopsy) from enlarged and clinically suspected lymph nodes or in some cases in the confirmation of the presence of metastasis in sentinel nodes unsuspected clinically (microstaging II) [1, 10, 18].

Table 4. Summary of the recommendations of the National Comprehensive Cancer Network (NCCN) v. 1.2020, 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

Therapeutic lymphadenectomy

Qualification of patients for lymphadenectomy should be based on a clinical exam, laboratory test (including LDH serum level), and imaging techniques. 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 and in stage IIIC.

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 neck structures that contain superficial lymph nodes (anterior and posterior) and profound are dissected in one piece, limited posteriorly by profound jugular facia 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 may then transform into in-transit metastases. That is why in the majority of elaborates 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 metastases, their size, localisation, and clinical course (III, B). In the 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 the case of in-transit dissemination of melanoma limb amputation is not recommended. In the 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-22 — is not encompassed by the National Drug Reimbursement Program) or local immunotherapy (imiquimod is not registered for this indication) and electrochemotherapy (III, B) or systemic therapy. 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 melphalan. This method may be used only by experienced and trained centres (individual decisions on refunding). If HILP is contraindicated, systemic therapy should be administered [1, 5, 8, 18–20].

Adjuvant therapy

Currently, dabrafenib with trametinib (only patients with mutations in the *BRAF* gene), pembrolizumab and nivolumab (the latter also after grade IV metastasectomy) are registered for systemic (one year) adjuvant treatment in clinical practice in patients after radical primary surgery and lymphadenectomy, and complementary radiotherapy may only be considered in individual cases. The 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 (only patients with mutations in the *BRAF* gene) (I, B).

High doses of interferon α-2b (INF α-2b) have been registered based on the positive result of one of three clinical studies by the Easter 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 [21, 22]. The registration was based on the significant prolongation of the overall survival during a 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 results of meta-analyses show 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) [23, 24]. Interferon is not refunded in Poland in adjuvant treatment and is less effective than other drugs currently used in adjuvant treatment.

Ipilimumab is registered in the United Stated for adjuvant therapy of patients after lymphadenectomy of involved regional lymph nodes. Randomised clinical trials [25] showed a significant improvement of disease-free survival and overall survival but with high toxicity of ipilimumab therapy (II, B) [26]. Ipilimumab is not registered for adjuvant treatment in Poland.

Nivolumab in a randomised study in patients after stage IIIB, IIIC, and IV metastases showed a 10% improvement in recurrence-free survival compared to ipilimumab with lower toxicity (I, A), which is now a registered indication [25]. Updated data with a longer follow-up period confirm the beneficial effect of nivolumab in adjuvant treatment for a year regardless of the PD-L1 expression status and *BRAF* mutation with respect to RFS (HR 0.66) and DMFS (HR 0.76) [27], the percentage of 3-year progression free survivals was 58% and was over 10% better than for ipilimumab. Dabrafenib treatment with trametinib in patients with high-risk grade III *BRAF* (grade IIIA > 1 mm, IIIB/C) showed an improvement in recurrence-free survival and overall survival compared to placebo (I, A) [28, 29]. Actualized data from 4-year observations confirm the advantage of treatment with dabrafenib together with trametinib (RFS: 54%; HR: 0.49; DFS: 67%; HR: 0.53) [29]. Moreover, a model was presented evaluating the cure rate after using adjuvant therapy, which was in this case 17%. The results of the Keynote-054/EORTC 1325 study in 1019 patients also indicate a reduction in the risk of recurrence (HR for RFS 0.57) and DMFS using pembrolizumab adjuvant treatment for one year, compared to placebo, in patients with grade III resection risk (IIIA with micrometers > 1 mm, IIIB and IIIC) (I, B) [30]. This indicates the need for an absolute multidisciplinary evaluation of all patients with melanoma in stage II–IV. After a positive sentinel node biopsy, only adjuvant systemic treatment can be used without adjuvant lymphadenectomy. These drugs are available in Poland at present only in the scope of the Rescue Access to Drug Technology (RDTL) and have obtained a favorable opinion of AOTMiT for this indication.

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 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 excited with narrow margins, presence of 'positive' surgical margins (especially after excision of the local reoccurrence), presence of satellite foci, significant neurotropism. In the case of excision of local reoccurrence 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 reoccurrence after prior resection [31, 32]. 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) [33]. No adjuvant RT should be applied after CLND.

Exclusively radiotherapy

Exclusively radiotherapy as a non-palliative treatment can be used only in the case of an extensive LMM tumour.

Palliative radiotherapy can be used for individual indications in the case of primary or metastatic tumours not responding to systemic treatment, non-resectable, painful or bleeding.

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 20–30% of patient survive for five years.

The significant prognostic factors in patients with melanoma in clinical stage IV are: performance status (according to the ECOG scale), 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 [34]) 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 (II, B). There are no indications for irradiation of the whole brain (WBRT) in the scope of adjuvant treatment after local treatment of melanoma metastases to the CNS, as this does not improve treatment ourcomes. Detailed indications on treating melanoma metastases to the brain have been published [35]. 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 (ipilimumab) or anti-PD1 (nivolumab, pembrolizumab), 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 (dabrafenib with trametinib, vemurafenib with cobimetinib or encorafenib with binimetinib, where the last drug combination is not refunded) (I, A). Systemic treatment should be provided in centers having a full range of therapeutic possibilities [36]. Patients with advanced melanoma should still be referred and screened for 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]. The only registered scheme of dacarbazine therapy is a five-consecutive-day schedule with a daily dose of 200 mg/m^2; an alternative schedule of administering a higher dose of a drug (850–1000 mg/m^2 every three weeks) has not formally 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 alkaloids (e.g. vinblastine) and nitrosamine derivates (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 significantly higher overall survival rates (a difference of about 3.5 months) compared to peptide vaccine gp100 in a second-line therapy, with no impact on the disease-free progression time [37, 38]. 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 (so-called pseudo 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 [37–39]. 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, colitis (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 (prednisolone [or equivalent] 1–2 mg/kg of body weight), and further therapy should be applied in collaboration with, or with assistance of, a referral centre. The appropriate algorithms of proceeding are accessible [38] 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 that this therapy be started in inexperienced centres with limited therapeutic options.

Currently, immunotherapy in skin melanomas is mostly related to the usage of immune control checkpoint PD-1 in monotherapy (nivolumab in fixed does 240 mg every two weeks or 480 mg every four weeks or pembrolizumab 200 mg every three weeks or 400 mg every six weeks) (I, A) [40–42] or in combination with anti-CTLA-4 antibodies (I, B) [43]. 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 [40–42]. In recently published results of a clinical trial that compared efficacy of nivolumab in monotherapy, ipilimumab in monotherapy, and a combination of both drugs, nivolumab was 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 (in comparison with ipilimumab) efficacy (the median disease-free survival was 11.5 months) [43]. The results of combined ipilimumab and nivolumab therapy were better when a *BRAF* gene mutation was present; however, in the whole group of patients [44] and after 5 year overall survivals in the combined branch were 52% (thus the median exceeded 60 months) in comparison with 44% for nivolumab monotherapy [45]. The adverse events in Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4 were significantly more frequent in the combined therapy arm (56.5%) compared to 19% in the nivolumab and 27% in the ipilimumab arm. Combined immunotherapy and not anti-PD1 monotherapy can be the preferred option in patients with a very good performance status with poorer prognostic factors (including the *BRAF* mutation, with high LDH levels and asymptomatic metastases to the brain) (II, B) [46, 47]. Nivolumab with ipilimumab at present is not refunded in Poland.

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 was maintained even when the active therapy had been stopped). Based on available literature data, it is now possible to consider discontinuing immunotherapy with anti-PD1 antibodies in patients who have an objective response after at most two years of treatment (CR, PR)/clinical benefit (II, B) [48].

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, the use of combination of anti-CTLA-4 with ant-PD-1 is specifically justified in patients with asymptomatic brain metastases to CNS (II, B).

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 skin areas not exposed to long-term solar radiation. Published in the 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 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) [49]. 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 dacarbazine, whereas the median overall survival time on dabrafenib therapy reported in the year 2013 reached 18.2 months (I, A) [50]. In a phase III trial, the efficacy of MEK inhibitor (MEKi) — trametinib has also been confirmed in patients with metastatic melanomas harbouring *BRAF* gene mutation (I, B) [51]. The efficacy of MEK inhibitors has also been observed in patients with *NRAS* gene mutation [52]. The results of recent studies (COMBI-d, COMBI-v, coBRIM and COLUMBUS) showed that in patients with metastatic melanomas with *BRAF* gene mutation the use of a combination of BRAF and MEK inhibitors (dabrafenib and trametinib or vemurafenib with cobimetinib or encorafenib with binimetinib) yields better results than monotherapy and no increase of toxicity (I, A) [53–59]. The median overall survival time on the combination of both drugs was improved to about 23–33 months and a median disease progression time of 12–14 months. The best overall survival is achieved in patients with normal LDH activity and serum concentration and less than three organs involved with metastases. The first two 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 disease progression. A phase II study revealed that restarting therapy with dabrafenib and trametinib resulted in partial remission in eight 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 [60]. 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 response rate 3%, partial response rate 39%, stabilisation of the disease 24%, and progression of the disease 30% (no data 4%). The median overall survival time form the restart of the therapy reached 9.8 months (II, B) [61, 62].

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 high 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

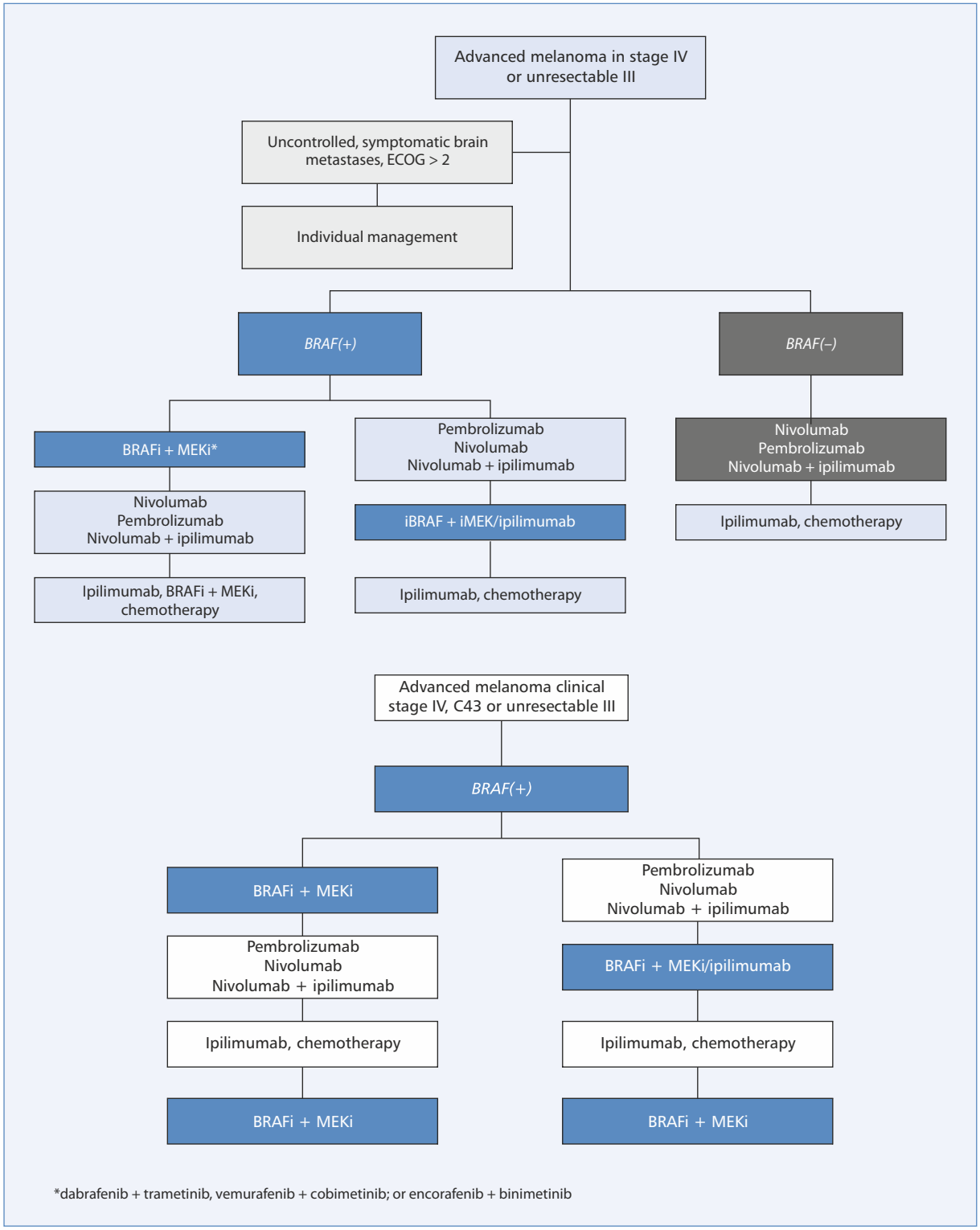

Figure 3. General approach to systemic treatment in patients with advanced stage IV or unresectable III melanomas and detailed plan of systemic treatment in patients with advanced stage IV or unresectable III melanomas with *BRAF* mutation, showing the possibility of restarting the treatment with BRAF + MEK inhibitors (rechallenge). BRAFi — BRAF inhibitor; MEKi — MEK inhibitor

maintained after immunotherapy and of immunotherapy (anti-PD-L1) after treatment with BRAF inhibitors (Fig. 3) [63]. In rare cases of patients with melanomas carrying some *KIT* gene mutations, the activity of KIT kinase inhibitors has been observed which are not refunded for this indication (II, B) [64].

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 scare 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 ≥ pT1b There are no indications for any additional test except for 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 scare post excision of melanoma Radiologic image (RT) of the chest, ultrasound of the abdomen 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 ≥ 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–IIID) or observation after detection of metastasis to the sentinel lymph node without complementary lymphadenectomy	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 scare post excision of melanoma Radiologic image (RT) of the chest Blood morphology and biochemistry (liver tests and activity of lactate dehydrogenase) — optionally Ultrasound examination of lymphatic drainage every 4–6 months in case of finding a positive sentinel node without performing lymphadenectomy 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/IIID, 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; CT — computed tomography; MR — magnetic resonance; LDH — lactate dehydrogenase

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 [65, 66] (Table 5). The relapse risk is the highest in the first three years post therapy. That is why it is recommended that a more intense schedule of control exams should be applied in this period 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 can 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 (IV, B). 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 presence of distant metastases (liver enzymes elevation, bone pains, neurological symptoms, cough, and weakness) detailed imaging diagnostics should be done, with CT, MRI, PET-CT, and bone scintigraphy included.

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.

Additional information for patients can be found on the web sites for example of scientific societies (e.g. www.akademiaczerniaka.pl). The scheme of control check-ups should be given to the patient in writing.

Summary

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 gives 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 0.5–2 cm depending on the thickness according to Breslow) and performing a sentinel node biopsy (stage ≥ pT1b). 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 qualification in systemic adjuvant treatment (nivolumab, pemrbolizumab, dabrafenib with trametinib). A schedule of diagnostic and therapeutic recommendations in patients with skin melanoma is shown in Figure 3.

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 (in combination with MEK inhibitor). Immunotherapy with anti PD-1 antibodies (nivolumab or pembrolizumab) or alternatively 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. Supplementary radiotherapy may be considered in cases at high recurrence risk after local surgery especially in the case of limited indications for systemic treatment.

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Clinical practice guidelines for diagnosis and treatment of colon (C18) and rectosigmoid junction (C19) cancer

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Key words: colon cancer, rectosigmoid junction cancer, guidelines, diagnostics, treatment

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1. Methodological notes

Guidelines developed on the basis of recommendations published between 2012 and 2019 by:
— French Research Group of Rectal Cancer Surgery (GRECCAR);
— French National Society of Coloproctology (SNFCP);
— European Society for Medical Oncology (ESMO);
— National Comprehensive Cancer Network (NCCN);
— European CanCer Organisation (ECCO);
— Association of Coloproctology of Great Britain and Ireland (ACPGBI).

The authors always tried to relate individual recommendations to the published recommendations, taking into account the source publication and (where possible) the grades of recommendations and the levels of evidence, according to the following criteria.

Levels of evidence

I *Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity.*

II *Small randomized trials or large randomized trials with suspicion of bias (lower methodological quality) or meta-analyses of such trials or trials with demonstrated heterogeneity.*

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III Prospective cohort studies.
IV Retrospective cohort studies or case-control studies.
V Studies without a control group, case reports, experts opinions.

Grades of recommendations

A Strong evidence for efficacy with a substantial clinical benefit — strongly recommended.
B Strong or moderate evidence for efficacy but with a limited clinical benefit — generally recommended.
C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs) — optional.
D Moderate evidence against efficacy or for adverse outcome — generally not recommended.
E Strong evidence against efficacy or for adverse outcome — never recommended.

2. Epidemiology

In recent years, malignant neoplasms of the colon and rectosigmoid junction are diagnosed in approximately 12,500 people per year, and the number of deaths is approximately 8,500. Whilst there is continuous increase in morbidity and mortality in the male population, in women the increase in mortality has been halted and has remained stable for over a decade despite the increasing morbidity [1].

3. Diagnostic tests required for diagnosis and staging

— Colonoscopy (up to and including the caecum) with the collection of tumor specimens and/or removal of the polyp/polyps; NCCN [2]; ECCO [3]; ESMO [4]; GRECCAR/SNFCP (III) [5].
— Computed tomography (CT) of the abdomen and pelvis; NCCN; ECCO; ESMO (III, A).
— Chest X-ray (CT of the chest in case of doubtful X-ray findings); NCCN; ECCO; ESMO (III, A).
— Determination of carcinoembryonic antigen (CEA) level; NCCN; ESMO (III, A).
— Basic laboratory panel (complete blood count [CBC], creatinine, bilirubin, protein concentrations, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP] levels) — to assess organ function (III, A).

In individual cases, an abdominal ultrasound (US) could be a valuable addition to the above-mentioned diagnostic workout. It is not recommended to routinely perform positron emission tomography (PET) within the initial diagnosis, as false-positive results may be caused by sigmoid diverticulosis or inflammatory bowel diseases (IBD). However, this examination may be helpful in the diagnosis of distant metastases, when the previously performed imaging tests (CT, magnetic resonance imaging [MRI], US) do not allow to establish the stage of disease. In addition, PET is performed in the diagnosis of cancer relapse in patients with increased CEA level without visible changes in other tests that may correspond to local and/or generalized recurrence.

4. Staging

Staging is based on the 8th edition of the TNM (tumor, node, metastasis) classification (2017). Details are presented in Tables 1 and 2.

5. Therapeutic management

The recommended therapeutic management in colon cancer patients is based on staging (Fig. 1).

5.1. Recommendations for surgical treatment

The surgical treatment guidelines are based on the recommendations of the National Consultant in the field of oncological surgery and the Polish Society of Surgical Oncology.

• **cT1–4 N0–2 M0** — a segmental bowel colon with the tumor and the regional lymphatic system of the relevant bowel segment should be performed.

ESMO; NCCN; ECCO

Recommendations:

— the extent of the colon cancer resection depends on the site of the primary tumor;
— the minimal number of regional lymph nodes that should be retrieved following colon resection is 12;
— minimal resection margins assessed on a fresh specimen before (proximal) and behind (distal) the tumor should be 5 cm;
— in the case of a tumor that infiltrates other organs through the continuity (cT4b), "en bloc" resection should be performed without dissection of the infiltrate;
— laparoscopic resections of colon cancer should now be considered as a standard surgical method, with

Table 1. TNM classification; colorectal cancer

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* — involving lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades visceral peritoneum, and in places without it — pericolorectal tissues
T4	Tumor invades through the visceral peritoneum and continues into adjacent anatomical structures and/or causes perforation of the visceral peritoneum
T4a	Tumor invades through the visceral peritoneum and causes perforation of the visceral peritoneum
T4b	Tumor invades through the visceral peritoneum and continues into adjacent anatomical structures
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s)
N2	Metastasis in 4 or more regional lymph node
N2a	Metastasis in 4–6 regional lymph node
N2b	Metastasis in 7 or more regional lymph node
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis is identified
M1a	Distant metastasis is identified, however, confined to 1 organ or site (e.g. extra-regional lymph node)
M1b	Distant metastasis to two or more sites or organs is identified
M1c	Distant metastasis to the peritoneal surface alone or with other site or organ metastases

Table 2. TNM stages; colorectal cancer

<table>
<tr><th colspan="2"></th><th>Tis</th><th>T1</th><th>T2</th><th>T3</th><th>T4a</th><th>T4b</th></tr>
<tr><td colspan="2">N0 M0</td><td>0</td><td colspan="2">I</td><td>IIA</td><td>IIB</td><td>IIC</td></tr>
<tr><td rowspan="3">N1 M0</td><td>N1a</td><td colspan="3" rowspan="3">IIIA</td><td colspan="2" rowspan="3">IIIB</td><td rowspan="3">IIIC</td></tr>
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<tr><td>M1b</td><td colspan="6">IVB</td></tr>
<tr><td>M1c</td><td colspan="6">IVC</td></tr>
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the oncological outcomes comparable to classic laparotomy. However, laparoscopic resection is allowed only in centers with sufficiently extensive experience.

• **cM1 (pTNM IV)** — surgical treatment of stage IV colon cancer should always be individualized.

Recommendations:

— in liver metastases, the possibility of radical excision (R0) should be considered, usually as sequential treatment with pre- or postoperative chemotherapy; ESMO (III, A); NCCN

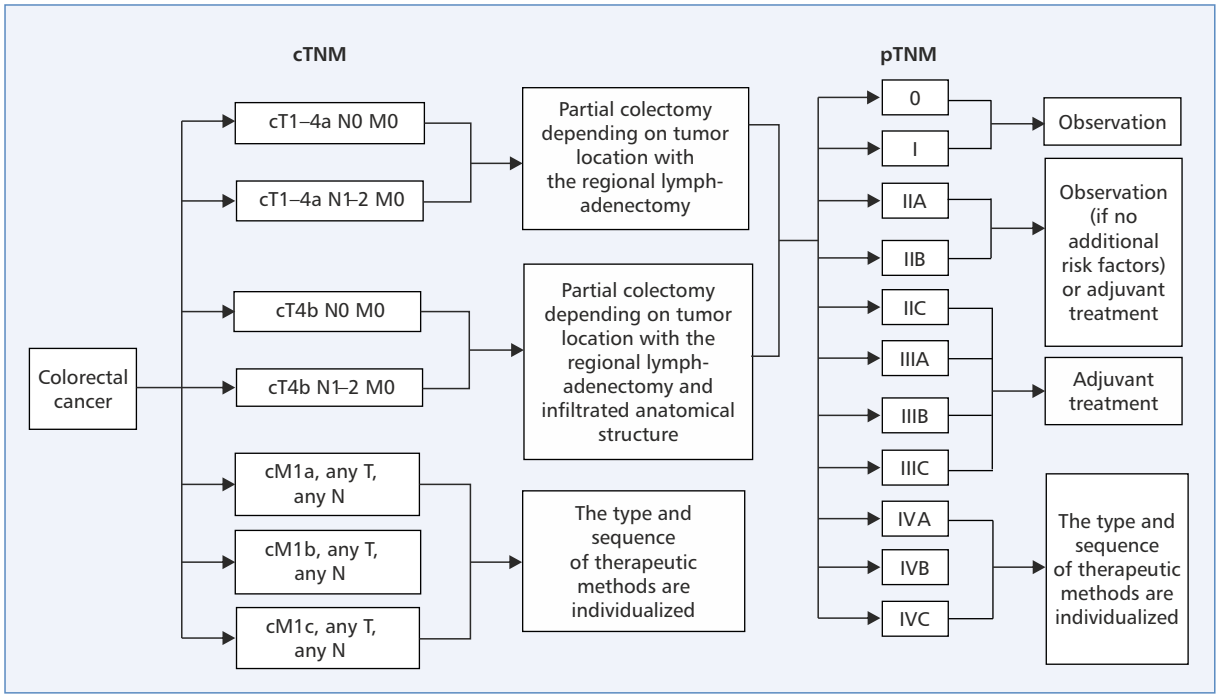

Figure 1. Therapeutic management depending on the clinical (cTNM) and pathomorphological stage (pTNM)

— ablation of liver metastases can be performed in patients ineligible for resection. Current ineligibility criteria for metastasectomy are defined on the basis of post-resection liver parenchyma volume (30% and less) and the number of lesions (5 and more) as well as the coexistence of metastases in other organs [6];
— complex treatment of liver metastases is possible, including anatomic and non-anatomic liver resections and ablative methods (e.g. segment II and III resection and ablation of segment VII lesions);
— resections or ablation of single metastatic lesions in other organs (e.g. in the lung) may be considered, provided that the primary colon tumor and any secondary lesions (e.g. in the liver) can be completely resected or successfully ablated;
— in patients with carcinomatosis peritonei, the so-called Peritoneal Cancer Index (PCI) is used to assess the advancement of changes (Table 3). Each region of the peritoneal cavity can be scored between 0 and 3 points. Total PCI score is obtained by adding up points from all regions (Table 3). If the PCI score is < 20 points, qualification for cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) may be considered — ESMO (IV, B); NCCN. However, a randomized clinical trial (RCT) showed that in systemically treated patients underwent effective cytoreduction HIPEC did not affect the prognosis compared to surgery alone (II, E) [7].

The 5-year survival rate in patients after radical resection of both the primary tumor and metastatic lesions in the liver ranges from 25–55%, while in patients in whom radical resection is not possible, it does not exceed 5%.The aim of surgical treatment of patients with disseminated colon cancer with the presence of unresectable distant metastases is to prolong the survival time. The management and its sequence (symptomatic treatment, chemotherapy-surgery, surgery-chemotherapy, chemotherapy alone) should be individualized depending on patient performance status (PS) and possible therapeutic benefits — ESMO; NCCN.

Final remarks

— In unresectable lesions, creating a stoma (ileostomy or colostomy) or bypass surgery should be considered.
— In case of an obstruction, resection (with anastomosis and/or stoma) or decompression-only surgery is possible. In the latter case, radical resection should always be considered after stabilization of the patient's general status.
— Radical tumor resection must include not only the cancerous colon segment with appropriate margins but also the entire area of regional lymphatic drainage. A detailed description of the topographic resection extent depending on tumor location is presented in oncological surgery textbooks („Chirurgia onkologiczna", Vol. 3: PZWL 2019).

Table 3. Peritoneal Cancer Index

Region of the peritoneal cavity	Lesion size score (LS)			
	LS = 0 (no tumor seen)	LS = 1 (tumor up to 0.5 cm)	LS = 2 (tumor up to 5 cm)	LS = 3 (tumor > 5 cm or confluence)
Central				
Right upper				
Epigastrium				
Left upper				
Left flank				
Left lower				
Pelvis				
Right lower				
Right flank				
Upper jejunum				
Lower jejunum				
Upper ileum				
Lower ileum				
PCI	**Total LS from all regions =**			

— In the case of colon tumor resection, the decision to perform a simultaneous anastomosis depends on many factors related to cancer stage and patient general condition, the intraoperative assessment of the conditions necessary for the healing of anastomosis and surgeon's experience. Tumor resection and stoma creation do not exclude the technical possibility of restoring the continuity of the gastrointestinal tract in the second stage of surgical treatment.
— The decision regarding appropriate management depends on patient's general condition and tumor stage.

5.2. Recommendations for radiation therapy

Both pre- and postoperative irradiation is not routinely used in colon cancer patients. A randomized study that compared postoperative irradiation combined with postoperative chemotherapy *versus* postoperative chemotherapy alone, showed no improvement in post-irradiation survival with greater toxicity. This is probably due to rare local recurrences as the only site of progressive disease; relapse is usually associated with distant metastases. In addition, a significant toxicity is caused by a large volume of small bowel to be irradiated.

Preoperative irradiation should be considered rarely, only in advanced cases. It could be justified by CT or MRI examination indicating extensive tumor infiltration, which limits the possibility of keeping surgical margins free or even makes complete resection impossible. An example is a sigmoid cancer, which extensively infiltrates the bladder or the sidewall of the pelvis near large vessels. Pre-operative irradiation results in tumor shrinkage, which in turn may enable R0 surgery. The irradiation area covers only visible neoplastic lesions with an appropriate margin but does not include the elective area of regional lymph nodes. Radio(chemo)therapy regimens are the same as in patients with rectal cancer. However, another possible option is the induction of chemotherapy (II, A) [8, 9].

There are rare indications for postoperative radio(chemo)therapy — only in the case of R2 resection with a small residual tumor or R1 surgery or a very close free surgical margin (less than 1 mm). In addition to classic irradiation regimens, stereotactic body radiotherapy (SBRT) is also used.

5.3. Recommendations for systemic therapy

Adjuvant chemotherapy

Stage I

Due to the very good prognosis, adjuvant therapy should not be used, and observation is the standard of care (IV, E).

Stage II

The RCTs did not show any unquestionable effect of adjuvant chemotherapy on the improvement of prognosis. They usually included patients with a higher risk of recurrence and only a slight increase in 5-year disease-free survival rate (< 5 percentage points) was observed. Except for the QUASAR trial, which also

enrolled patients with rectal cancer (increase in overall 5-year survival rate < 4 pp), there was no effect of adjuvant treatment on overall survival [10].

Therefore, adjuvant therapy should not be used in most patients, and observation remains the standard of care (II, D). Adjuvant chemotherapy using fluoropyrimidine for six months can be used in patients with high-risk factors for recurrence (presence of at least one of the following features: pT4 [pT4b category is generally considered sufficient to qualify for adjuvant treatment], the number of removed lymph nodes less than 12, high histological grade, perineural infiltration, intratumor vessels emboli, perforation or obstruction), however, factors related to the patient's contraindication (e.g. concomitant diseases or life expectancy) are equally important and should be also considered (II, B). The addition of oxaliplatin does not significantly increase the efficacy of adjuvant chemotherapy in stage II (II, D).

Stage III

Adjuvant treatment should be used in all patients without contraindications to chemotherapy because it prolongs disease-free survival and overall survival (I, A). Adjuvant treatment should be initiated as soon as possible after surgery, preferably within 4–6 weeks, because the greater the delay, the less the impact on prognosis improvement (IV, A). The only justification for delaying the initiation of adjuvant chemotherapy could be medical reasons (e.g. postoperative complications) (IV, B).

The 6-month chemotherapy with fluorouracil and calcium folinate or capecitabine significantly reduces the risk of relapse and increases overall survival rate (even by a dozen or so pp after 5 years) (I, A). Capecitabine was not shown to be more effective than fluorouracil and only a non-significant trend in favor of capecitabine was observed in phase III clinical trial [11].

The addition of oxaliplatin to a fluoropyrimidine (usually the FOLFOX or CAPOX regimen; the FLOX regimen is less frequently used due to toxicity) leads to significant (usually by a few pp) increase in long-term overall survival and such treatment should be the standard of care (I, A) [12, 13]. Another factor that may reduce the benefit of adding oxaliplatin is age over 65–70 years (II, C).

It has not been proven that a 3-month adjuvant therapy with oxaliplatin is non-inferior to standard 6-month therapy (I, D) [14]. The analysis of post hoc created subgroups of the IDEA study indicates that in patients with better prognosis (pT1–3, pN1) 3-month chemotherapy with the CAPOX regimen (instead of 6-month) can be used (II, B). In other patients, 6-month chemotherapy should be the standard treatment, and modifications of chemotherapy (including dose reduction or discontinuation of oxaliplatin) should be based on its toxicity (I, A).

Irinotecan regimens have no advantage over fluoropyrimidine monotherapy, and anti-EGFR drugs and bevacizumab added to chemotherapy are ineffective in adjuvant postoperative treatment (I, E).

In patients receiving fluorouracil in prolonged infusions, the use of portable infusers allows shortening hospital stay (IV, A). However, access to a large vessel (the so-called vascular port) should be ensured beforehand to avoid local complications (peripheral phlebitis) associated with high levels of cytotoxic drug.

Palliative treatment

General remarks

In patients with metastatic colon cancer, it is essential to determine whether radical local treatment is possible, both in the primary lesion and with regard to metastases. Therefore, in many patients for whom local treatment is possible, it is necessary to obtain the opinion of a surgeon experienced in liver surgery or a thoracic surgeon, depending on metastases location. In such situations, local treatment is usually combined with systemic treatment and in some patients, it is possible to achieve long-term survival (IV, A).

Before starting systemic treatment, in addition to information on organ capacity (e.g. CBC, biochemical tests to assess the liver and kidney function), in patients for whom at least doublet chemotherapy is planned, it is necessary to perform molecular diagnostics (exons 2–4 of *KRAS* and *NRAS* genes, *BRAF* V600 mutations), which is a prerequisite for the addition of a biological drug and also provides prognostic information (unfavorable prognosis in patients with the *BRAF* V600 mutation) (I, A).

In disseminated disease, when radical surgery (including metastasectomy) is not possible, systemic therapy prolongs overall survival (I, A).

The median survival time in patients enrolled in RCTs assessing first-line systemic treatment over the last few decades has gradually improved, accounting for about 12 months for fluoropyrimidine monotherapy, several months for multi-drug chemotherapy, and up to over 2 years (multi-drug chemotherapy with a biological drug). The improvement of prognosis is significantly influenced by the possibility of using several lines of treatment, not only the type of first-line therapy (I, A) [15].

First-line treatment

In addition to the availability of individual drugs, the choice of 1st line treatment depends primarily on:

— patients performance status, comorbidities, biological age (IV, A);
— cancer dynamics, cancer-related symptoms, laboratory abnormalities and the degree of critical organs involvement (IV, A);

— tumor molecular characteristics (I, A);
— prior adjuvant treatment (II, B);
— patient preferences regarding the expected toxicity (V, A).

In patients without contraindications to more intensive treatment, at least two-drug chemotherapy with the addition of a biological drug is used as a rule (I, A). The choice of the drug added to fluoropyrimidine in first-line palliative therapy must take into account the type of prior adjuvant treatment (the preferred use of irinotecan in patients receiving oxaliplatin in adjuvant treatment) (I, B).

For some combinations of anti-EGFR drugs with chemotherapy, e.g. cetuximab combined with FOLFIRI or FOLFOX chemotherapy and panitumumab combined with FOLFOX chemotherapy, improved overall survival (median difference usually several months) was directly proven in phase III clinical trials [16, 17]. The prerequisite for the successful anti-EGFR treatment is the normal state of exons 2–4 in *KRAS* and *NRAS* genes in tumor cells., i.e. wild-type *RAS* genes (I, A). It is also important to confirm the absence of the *BRAF* V600 mutation (II, B). Anti-EGFR drugs should not be combined with regimens containing capecitabine (II, E).

Data on the value of anti-angiogenic drugs are inconclusive, although bevacizumab combined with IFL has been shown to prolong survival. The practical value of this observation is small due to the fact that the IFL regimen is currently considered suboptimal and should not be used (I, C). A meta-analysis of 7 RCTs shows that adding bevacizumab to chemotherapy containing irinotecan or oxaliplatin and fluorouracil used in prolonged infusions significantly prolongs progression-free survival, but not overall survival (I, B) [18].

Direct comparisons of anti-EGFR drugs and bevacizumab combined with chemotherapy give conflicting results. In the FIRE-3 study, a significantly improved overall survival was observed (median difference of about 4 months) in patients receiving cetuximab instead of bevacizumab with FOLFIRI chemotherapy, but there were no differences in progression-free survival and objective response rate (II, B) [19, 20]. In the CALGB/SWOG 80405 study, in which the majority of patients received mFOLFOX6 regimen, the advantage of cetuximab was not shown and the survival time was similar regardless of the type of antibody used. Retrospective analyzes taking into account the primary tumor location (left or right) may indicate a greater benefit from the use of anti-EGFR drugs than bevacizumab in patients with left-sided tumors, but this observation alone should not determine the choice of management strategy, as well as suggestions about a possible predictive value of some molecular factors (e.g. microsatellite instability, tumor mutational burden [TMB], molecular subtype) (IV, C).

The intensification of chemotherapy involving the administration of three drugs, instead of two, with or without the addition of a biological drug, does not have a clear effect on prognosis improvement (II, C), and is associated with increased toxicity. However, in some patients in very good performance status, but at risk of developing an organ crisis or with unfavorable prognosis (e.g. *BRAF* V600 mutation), such management (e.g. FOLFOXIRI ± bevacizumab) may be the preferred option (II, B).

When used without a biological drug, irinotecan- or oxaliplatin-based regimens have similar efficacy (I, A) [21, 22], and the decision to select the type of chemotherapy should take into account the expected toxicity.

In patients preferring less intensive treatment, with poorer performance status, elderly, or with significant comorbidity a monotherapy with fluoropyrimidine (fluorouracil with folinic acid, capecitabine) (I, A). The addition of bevacizumab to fluoropyrimidine prolongs progression-free survival and overall survival (I, B) [18].

First-line treatment is continued until progression or unacceptable toxicity occurs (I, A). The value of de-escalation systemic treatment strategies has not been proven in well-designed RCTs (II, D). In particular, it has not been proven that pre-scheduled discontinuation of all oxaliplatin-based chemotherapy and its re-administration after progression is non-inferior to continuous treatment in terms of progression-free survival or disease control duration (II, D). However, the occurrence of oxaliplatin-specific toxicity (e.g. polyneuropathy) very often forces the discontinuation of this drug and the continuation of therapy with fluoropyrimidine alone (IV, A). However, it has been shown that treatment with the FOLFIRI regimen for 2 months, followed each time by 2-month interval is non-inferior to continuous treatment in terms of overall survival (an increase in the relative risk of death by 36% or more was excluded) (II, C) [23]. Data from studies with biological drugs also indicate that pre-planned discontinuation of chemotherapy and continuation of therapy with a biological agent alone may have an adverse effect on progression-free survival compared to continuous treatment or withdrawal of only one cytotoxic agent (II, D).

Second- and subsequent lines treatment

The decision to use the second-line treatment depends to the greatest extent on the patient's PS and the values of vital organs function indexes (IV, A).

The treatment regimen depends on what drugs were used in first-line therapy (I, A) [24]. The rule is to change the cytotoxic drug, i.e. oxaliplatin to irinotecan or vice versa, and administer it together with a fluoropyrimidine (if FOLFOX or XELOX was used in the first-line, then in the second-line FOLFIRI should be administered and vice versa).

For some combinations of anti-angiogenic drugs and chemotherapy (bevacizumab with FOLFOX, aflibercept with FOLFIRI and ramucirumab with FOLFIRI) a small effect on the increase in overall survival (median difference of approximately 1.5–2.0 months) was shown in phase III clinical trials (I, A) [25–27]. If bevacizumab was used in first-line treatment, continued administration of this drug along with switching of chemotherapy also slightly prolongs survival compared to switching chemotherapy alone (I, B).

In phase III clinical trials the addition of anti-EGFR drug to irinotecan-based second-line chemotherapy did not show an increase in survival time — only a slight increase in progression-free survival was observed (difference in medians of 2 months in the study evaluating panitumumab added to FOLFIRI and 1.4 months in the study evaluating cetuximab added to irinotecan) and an increase in objective response rates (25 and 12 percentage points, respectively) (I, C) [28].

In patients previously treated with fluoropyrimidine, irinotecan and oxaliplatin, the phase III EPIC study showed that cetuximab monotherapy prolonged overall survival compared to best supportive care (BSC) (difference in medians of 4.7 months) and improved quality of life (QoL) (I, A) [29]. The phase III ASPECCT study demonstrated that panitumumab was non-inferior to cetuximab and retained 82–130% of the overall survival benefit of cetuximab demonstrated in the EPIC study (I, A) [30].

In patients who previously received all available standard drugs, trifluridine/tipiracil and regorafenib slightly increase overall survival compared to placebo (difference in medians < 2 months) (I, A) [31, 32].

In uncontrolled phase II clinical trials in previously systemically treated patients with tumors showing the evidence of microsatellite instability or with impaired function of DNA repair genes, it was shown that immunotherapy with pembrolizumab or nivolumab, as well as nivolumab with ipilimumab, allows for 20–50% objective responses, the 1-year progression-free survival rate of approx. 70%, and overall survival rate of approx. 80% (III, A) [33].

In phase III study in systemically treated patients (approximately half of whom received irinotecan) with *BRAF* V600 mutation, the combination of encorafenib, binimetinib and cetuximab, as well as doublet therapy with encorafenib and cetuximab, prolonged overall survival (differences in medians 3.6 and 3.0 months respectively) compared to cetuximab in combination with irinotecan-containing chemotherapy (II, A) [34].

Induction therapy in patients with potentially resectable liver metastases

Good direct response to systemic treatment makes metastasectomy possible to perform. The optimal chemotherapy regimen has not been established, however, due to the desire to obtain a direct response, at least two-drug protocols are used. As phase III studies have shown that adding an anti-EGFR drug to chemotherapy increases the response rate, this treatment is also a good option in patients with liver-limited metastases (II, B) [35, 36].

Due to the possibility of harmful effect of long-term chemotherapy on healthy liver parenchyma, which may make it difficult to perform extensive resections, the operability assessment should be carried out quite early, after 2–3 months of treatment (IV, B).

Perioperative treatment of patients with resectable liver metastases

RCTs did not provide clear evidence that perioperative treatment improves the prognosis in patients with resectable liver metastases. Borderline effect of FOLFOX chemotherapy on PFS improvement was observed, but not on overall survival (II, C) [37]. The addition of an anti-EGFR drug to FOLFOX chemotherapy had an adverse effect on progression-free survival (II, E) [38].

However, the decision to use perioperative treatment may result from the need to postpone the second surgery (usually the primary tumor is removed first, followed by metastasectomy) (V, A).

After metastasectomy, adjuvant chemotherapy is usually used, as in stage III (preferably regimens with oxaliplatin) (II, B). The only exception are patients with metastases occurring relatively soon after post-operative adjuvant chemotherapy (V, D).

6. Post-treatment follow-up

The main goal of active observation of patients after completed oncological treatment is early detection of disease recurrence (local and/or generalized) and introduction of appropriate treatment. However, the current meta-analysis did not show that regular follow-up examinations prolong overall survival compared to less strict monitoring or no monitoring (II, C) [39].

There are numerous ongoing discussions regarding optimal patient monitoring regimen taking into account two basic requirements:

— the ability to detect an early and potentially curable relapse;
— the frequency of follow-ups according to the risk of recurrence.

The incidence of relapses in patients with stage I colon cancer and without other poor prognostic factors is so low that the dates and scope of follow-up examinations can be scheduled individually. On the other hand, in primary advanced cases, with no treatment options, or in patients whose clinical condition

Table 4. Long-term follow-up

Year	1							2				3			4		5
Time since treatment completion (months)	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CEA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Imaging of the abdominal cavity/pelvis[1]				X				X				X		X		X	
Imaging of the chest[2]				X				X				X		X		X	
Colonoscopy	X[3]			X										X[4]			

[1]CT preferred, US acceptable. In the case of CEA elevation, always CT with contrast *i.v.*

[2]CT preferred, X-ray acceptable. In the case of CEA elevation, always CT with contrast *i.v.*

[3]Only if a full colonoscopy before surgery not possible

[4]If the result is correct, the next examination in 5 years

is contraindication to any causal treatment (surgery, radiotherapy, chemotherapy), routine follow-ups to detect cancer recurrence are pointless. The general protocol of the proposed oncological surveillance is presented in Table 4 (V, B). It should be noted, however, that this is an intensive surveillance regimen which, if used, should also apply to patients at high recurrence risk (e.g. stage III).

Due to the possibility of synchronic diseases, a colonoscopy should be performed in every patient, regardless of stage, unless it was performed prior to surgery (IV, A).

7. Diagnostic and therapeutic management in special cases

7.1. Familial adenomatous polyposis (FAP)

This is a disease associated with germinal mutations in the *APC* gene, inherited in an autosomal, dominant manner. In about 25% of families, the disease appears without prior history of the genetic burden as "*de novo* mutation". Penetration of the *APC* gene is almost 100% in both genders.

- **Diagnostic panel necessary to diagnose and stage the disease**
  - as in point 3;
  - pedigree interview;
  - genetic testing for mutations in the APC gene.
- **Staging in case of cancer diagnosis**
  - as in point 4.
- **Therapeutic management**
  - surgery: diagnosis of FAP is an indication for elective proctocolectomy, regardless of the presence or absence of concomitantly diagnosed cancer.
- **Scheme of long-term observations**
  - in the case of confirmed colon cancer coexisting with FAP, the follow-up scheme is as in point 6 except performing a colonoscopy.

7.2. Hereditary non-polyposis colon cancer (HNPCC)

This is the most common hereditary form of colon cancer, characterized by mutations in the *MLH1*, *MSH2*, *MSH6*, *PMS1*, and *PMS2* genes. This form of hereditary colon cancer is clinically known as Lynch I or Lynch II syndrome. Lynch I syndrome is characterized by the presence of familial cancer located exclusively in the colon. In Lynch II syndrome, malignant tumors occur not only in colon but also in the uterus, stomach, kidneys, pancreas and ureters, bile ducts and small intestine.

- **Diagnostic panel necessary to diagnose and stage the disease**
  - as in point 3;
  - pedigree interview based on Amsterdam criteria and Bethesda guidelines;
  - immunohistochemical tests of postoperative material for microsatellite instability and defects in DNA mismatch repair proteins.
- **Staging in case of cancer diagnosis**
  - as in point 4.
- **Therapeutic management**
  - surgery: there is no scientific evidence for the advisability of removing the entire colon, neither in healthy mutation carriers nor in patients with HNPCC. The resection extent depends on tumor location and stage.
- **Scheme of long-term observations**
  - colonoscopy every 1–2 years;
  - gastroscopy every 1–2 years;
  - abdominal ultrasound every 1–2 years;
  - in women, gynecological examination with transvaginal ultrasound every 1–2 years and determination of CA-125 level every year;
  - others, as in point 6.

7.3. Cancer in a colon polyp

The margin of polypectomy resection is an important prognostic factor, although it can be difficult to assess

when the polyp has been fragmented. There is no uniform definition of a positive (infiltrated) polypectomy margin. The current European guidelines recommend that a margin of < 1 mm be considered infiltrated, as the presence of a tumor near the polyp resection margin is associated with a significant risk of residual tumor in the draining lymph nodes or the intestinal wall. If the resection margin is considered positive, surgical resection of the appropriate intestine segment is recommended, provided that the patient is fit enough to undergo such surgery — ACPGBI (B).

In the presence of cancer in the removed polyp, microinvasion of lymphatic vessels is associated with an increased risk of lymph node metastases. It most often occurs together with other unfavorable prognostic factors. If it occurs alone (without other poor prognostic factors), surgical treatment should be individually discussed with the patient — ACPGBI (C).

Low-grade cancer in a polyp is rare but is associated with a high risk of residual disease in the lymph nodes. It is usually associated with other risk factors for residual disease. If there is low-grade invasive cancer in a polyp, surgical resection of the appropriate intestine segment should be considered, provided that the patient is fit enough to undergo such surgery — ACPGBI (B).

- **Diagnostic panel necessary to diagnose and stage the disease**

— as in point 3.

- **Staging in case of cancer diagnosis**

— as in point 4.

- **Therapeutic management**

— surgery: before commencing surgical treatment, it is necessary to mark the site of a previously performed polypectomy by performing endoscopic tattooing. Moreover, the operation should be performed in a center capable of performing the intraoperative colonoscopy.

- **Scheme of long-term observations**

— in the case of confirmed colon cancer coexisting with FAP, the follow-up scheme is as in point 6.

7.4. Colon cancer and synchronous, unresectable distant metastases

- **Diagnostic panel necessary to diagnose and stage the disease**

— as in point 3.

- **Staging in case of cancer diagnosis**

— as in point 4.

- **Therapeutic management**

The optimal surgical management of primary colon tumor with coexisted persistently unresectable distant metastases raises a number of controversies, especially when the primary tumor does not show clinical symptoms. The most common complication in patients who did not undergo colon tumor resection before starting chemotherapy is gastrointestinal obstruction (8–29%). There are presumptions based on the results of numerous meta-analyzes and systematic literature reviews that resection of intestinal lesion in patients undergoing palliative systemic treatment improves the prognosis, but these analyzes are burdened with apparent selection bias (IV, B) [40]. Although surgery extends the time to start palliative chemotherapy, most patients can start systemic therapy, and primary tumor resection prevents some local complications (obstruction, bleeding). Therefore, the main challenge for the surgeon is to minimize the risk of severe postoperative complications, which could significantly extend the time to start palliative systemic treatment. Unfortunately, there are no reliable results of RTCs so far, which does not allow for a clear definition of the role of asymptomatic primary tumor resection in the treatment of patients with generalized colon cancer. The interim analysis of one study [41], including, however, twice as few patients as originally planned, presented at the beginning of 2020, indicates that resection of the primary tumor in the case of synchronous, unresectable metastatic lesions may not improve the prognosis (II, C).

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VIA MEDICA

ORIGINAL ARTICLE

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Immunotherapy or targeted therapy as first-line treatment of patients with advanced/metastatic melanoma with the *BRAF* mutation — a single-center analysis

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ABSTRACT

Introduction. One of the most important achievements of contemporary oncology is the discovery of new therapeutic possibilities: targeted therapy and immunotherapy associated with checkpoint inhibitors. It has not been unequivocally determined so far which therapy should be used as first-line treatment in patients with advanced/metastatic melanoma with the *BRAF* mutation.

Material and methods. 137 patients with advanced/metastatic melanoma with the *BRAF* mutation were analyzed. They received anti-PD1-1 therapy (IT) or molecularly targeted therapy iBRAF ± iMEK (TT) as first-line treatment in the scope of the national drug program. IT and TT therapies used as first-line treatment were compared.

Results. Median OS and PFS in the group were 14.0 and 7.3 months. Unfavorable prognostic factors for OS and PFS were metastases to the central nervous system, increased LDH levels and performance status > 1. Metastatic sites in > 2 locations were only unfavorable prognostic factors for OS. A statistically significant difference was found between TT and IT for OS ($p = 0.0011$; median for TT was 12.6 months and was not reached for IT). It should be noted that the group treated with TT was characterized by a worse prognostic factors. No differences in PFS were observed ($p = 0.292$, medians 7.2 and 9.0 months, respectively).

Conclusion. In patients with advanced/metastatic melanoma with a *BRAF* mutation without rapid progression, IT should be considered as first-line therapy.

Key words: melanoma, immunotherapy, targeted therapy, sequential therapy, *BRAF* mutation

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Introduction

In recent years treatment of patients with a melanoma diagnosis has changed greatly. The presence of specific mutations in melanoma cells, including the *BRAF* [1] mutation, was discovered. The *BRAF V600* mutation is present in approximately 50% of patients with metastatic melanoma and is a predictive factor for response to targeted therapies [2]. The use of targeted therapies with inhibitors of BRAF ± MEK (iBRAF ± iMEK) has contributed to a considerable improvement of the treatment results in respect to overall survival (OS) and progression-free survival (PFS) which has been confirmed in randomized trials [3–8]. Moreover, the development of immunotherapy associated with immune checkpoint inhibitors (ICIs) has improved the results of treatment of melanoma patients [9–18]. ICI action is independent of the presence of the *BRAF* mutation

[16–19]. Administration of ICIs may lead to long-term remission [8–16]. The dominant problem, however, is the low percentage of responses to immune checkpoint inhibitors as well as the length of time from the moment of initiating the therapy to the response to treatment [9–16]. The response to targeted therapies is different, as the percentage of responses to treatment is high and the time to response is very short [3–8].

Systemic treatment of patients with the *BRAF* mutation poses a significant therapeutic challenge. So far the therapy which should be applied as first-line treatment has not been determined unequivocally in patients with advanced/metastatic melanoma. There is little data on this subject and the results of randomized trials, which would directly compare the effectiveness of anti-PD-1 immunotherapy (IT) and targeted therapy iBRAF ± iMEK (TT) as first-line treatment in this group of patients are missing [20–26]. Currently, two clinical studies are ongoing DREMseg (NCT02224781) and SECOMBIT (NCT02631447) and EORTC EBIN which should answer to this question but the results are still awaited [27].

Therefore we decided to undertake a retrospective analysis comparing first-line TT or IT treatment in patients with advanced/metastatic melanoma with a *BRAF* mutation. The paper presents the analysis of 137 patients with advanced/metastatic melanoma with a *BRAF* mutation who received immunotherapy or targeted therapy as first-line treatment.

Material and methods

All patients with advanced/metastatic melanoma treated in the frame of national drug programs from January 2013 to June 2019 in the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Cracow branch were analyzed. 137 patients from the group with the *BRAF* mutation who had received IT or TT as first-line treatment were selected from this group. First-line IT treatment in patients with the *BRAF* mutation in the scope of national drug programs was initiated in 2017 as then new indications were included. In all analyzed patients data were collected concerning age, sex, location of the primary tumor, stage of the disease and type of therapy used as first, second and subsequent line. Information concerning the stage of the disease, metastasis location, lactate dehydrogenase (LDH) levels (LDH) and ECOG (Eastern Cooperative Oncology Group) performance status [17] were collected at the start of systemic first-line treatment.

Statistical analysis

To determine the p value of defined factors between the group treated with IT and the larger group treated with TT Fisher's exact test was used. The final points encompassed evaluation of progression-free survival (PFS), overall survival (OS) and evaluation of the overall response rate (ORR) and disease control rate (DCR) defined by the criteria of response evaluation RECIST 1.1. PFS or OS were calculated from the beginning of IT or TT to disease progression according to RECIST, death or the last documented contact. The Kaplan-Meier method was used to evaluate PFS and OS with a 95% confidence interval (CI) and survival curves were analyzed by log-rank analysis. The Cox proportional hazard model was used to evaluate, in a multidimensional model, the significance of the effect of prognostic variables on PFS and OS at the moment of initiation IT or TT therapy. Differences are considered significant if $p < 0.05$. All statistical analyses were performed using the STATISTICA 12 program.

Results

General characteristics of the analyzed group

In the group of 137 patients with advanced/metastatic melanoma with the *BRAF* mutation 110 (80%) patients received first-line TT therapy and 27 (20%) IT. TT in 45 (41%) patients was iBRAF (vemurafenib or dabrafenib) and in 65 (55%) iBRAF + iMEK (vemurafenib + cobimetinib or dabrafenib + trametinib). Before 2017, 64 patients received TT treatment. As IT anti-PD-1 (nivolumab or pembrolizumab) was used. 57 (42%) patients received second line treatment, among them 39 patients received the IT-TT sequence and 4 patients the TT-IT sequence. In the group receiving the TT-IT sequence, the second line treatment was nivolumab or pembrolizumab (19 patients) and ipilimumab (20 patients). In the IT-TT group, the second line treatment in all patients was iBRAF + iMEK. Third line and fourth line treatment were administered to 15 (11%) patients and 3 (2%) patients, respectively. In the group receiving TT, there were statistically significantly more patients with metastases to the CNS, elevated LDH levels and a higher grade of the tumor. Precise characteristics of the analyzed group are presented in Table 1.

Results of treatment in the whole *BRAF*+ group

Median overall survival (OS) and progression-free survival (PFS) in the whole analyzed group were 14.8 and 7.4 months, respectively. In monofactorial analysis unfavorable effects on OS and PFS were observed for metastases to the brain ($p < 0.0003$ and $p = 0.0071$, respectively), increased LDH levels ($p < 0.0001$ and $p = 0.0028$, respectively) and ECOG performance status > 1 ($p = 0.0002$ and $p = 0.0033$, respectively).

Table 1. Characteristics of patients in respect to first-line therapy used

Factors		IT n = 27 (20%)	TT n = 110 (80%)	p	Whole group n = 137
Age	Median (years)	59	58	0.5997	59
	≤ 65	20 (74%)	78 (71%)	0.9294	98 (72%)
	> 65	7 (26%)	32 (29%)		39 (28%)
Sex	Male	18 (67%)	60 (45%)	0.2497	78 (57%)
	Female	9 (33%)	50 (55%)		59 (43%)
Tumor stage	M1a	8 (26%)	15 (14%)	0.0096	23 (17%)
	M1b	7 (25%)	17 (15%)		24 (18%)
	M1c	10 (37%)	60 (55%)		70 (51%)
	M1d	2 (7%)	18 (16%)		20 (14%)
Presence of metastases to CNS	No	25 (96%)	92 (84%)	0.0071	127 (93%)
	Yes	2 (8%)	18 (16%)		20 (7%)
Number of metastatic sites	≤ 2	16 (59%)	50 (45%)	0.2840	66 (48%)
	> 2	11 (40%)	60 (55%)		71 (52%)
LDH	Normal	22(81%)	44 (40%)	0.0002	66 (48%)
	Above normal	5 (19%)	62 (56%)		67 (49%)
	No data	0 (0%)	4 (4%)		4 (3%)
LDH (×2)	≤ 2 × normal	26 (96%)	82 (78%)	0.0039	106 (81%)
	> 2 × normal	1 (4%)	24 (22%)		25 (19%)
ECOG/PS	0	4(15%)	11 (10%)	0,4326	15 (11%)
	1	22 (81%)	84 (76%)		106 (77%)
	2	1 (4%)	14 (13%)		15 (11%)
	3–4	0 (0%)	1 (1%)		1 (1%)
Localization of primary tumor	Skin	24 (89%)	91 (83%)	0,1337	115 (84%)
	Mucous membrane	1(4%)	0		1(1%)
	From unknown primary tumor location	2 (7%)	19 (17%)		21 (15%)

T — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors; LDH — lactate dehydrogenase; CNS — central nervous system; ECOG/PS — performance status

The presence of metastases in > 2 sites had a statistically significant unfavorable effect only on OS (p = 0.0113). Sex, age > 65 years, location of the primary site did not have a statistically significant effect on OS and PFS.

Treatment results depending on the type of first line therapy TT *vs*. IT in *BRAF*+ patients

Median overall survival (OS) in the group receiving TT was 13.3 months whereas median OS was not attained in the IT group (median observation in the TT and IT groups was TT and IT 22 and 18 months, respectively). A statistically significant difference in OS was observed between groups treated with TT and IT (p = 0.0011) (Figure 1A) as well as between groups treated with iBRAF + iMEK, only iBRAF and IT (p = 0.0084) and iBRAF + iMEK *vs.* IT (p = 0.0074) (Figure 1B and 1C). A statistically significant difference was also observed in OS between the group receiving TT before 2017 (p = 0.0071) and the group treated with IT (Figure 1 D). There was no difference in OS between groups receiving TT before 2017 and from the beginning of 2017 (p = 0.2634) (Figure 1E). Median progression-free survival (PFS) in the groups receiving TT and IT were 7.2 and 9.0 months, respectively, and no statistically significant difference between them was observed (p = 0.292). Similarly, there was no statistically significant difference in PFS between the group receiving IT and the group treated with TT iBRAF + iMEK (p = 0.1001), as well as between the group receiving IT and the group treated only with TT before 2017 (p = 0.3498). A precise analysis of the

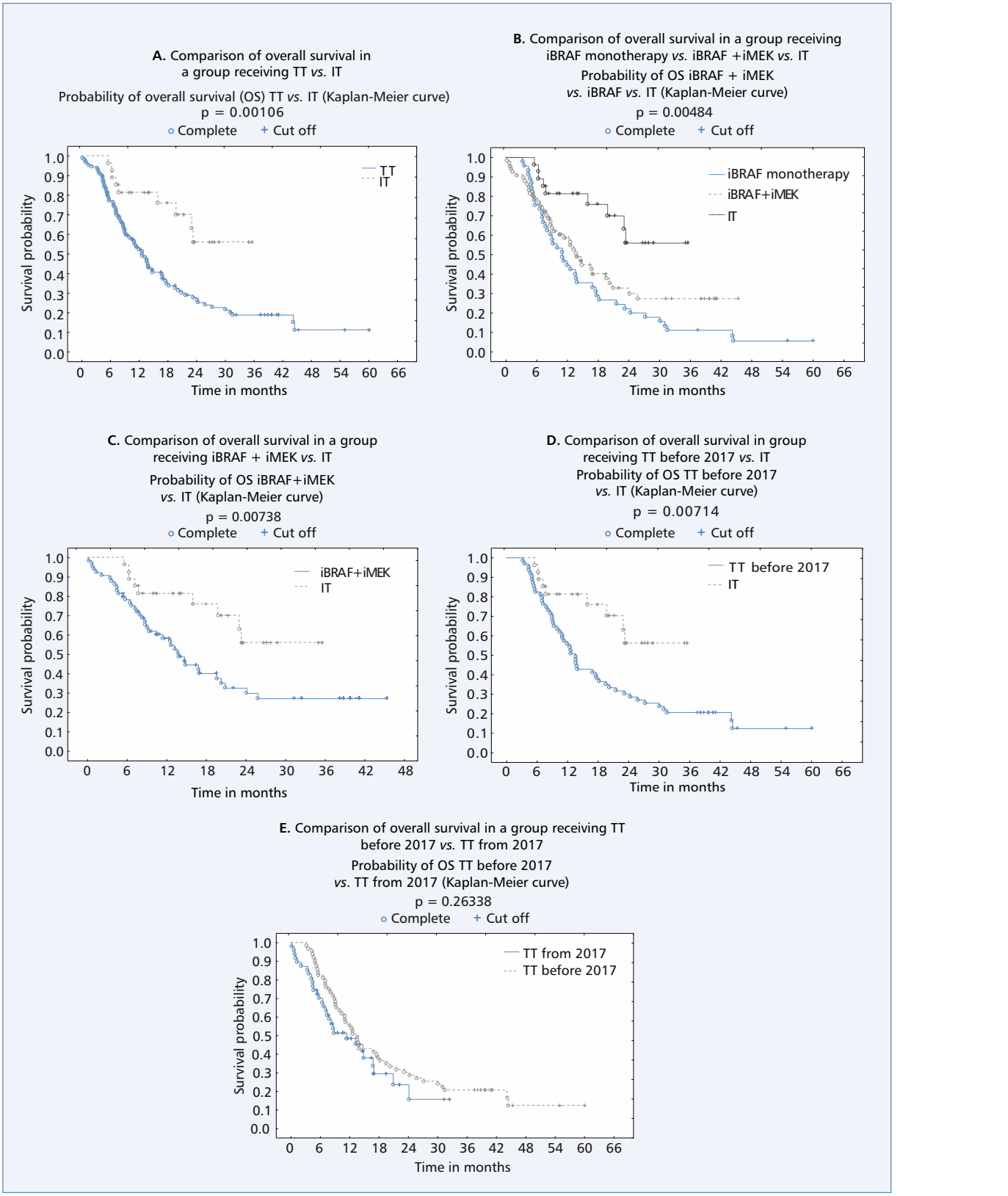

Figure 1. Kaplan-Meier survival curves. IT — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors (iBRAF ± iMEK)

Table 2. Results of treatment depending on the first-line therapy used

Type of therapy	IT n = 27 (20%)	TT n = 110 (80%)	Total n = 137 (100%)
OS (median in months) p = 0.0011	Not reached	12.6 (6.7–24.6)	14.0 (7.2–31.2)
6-month OS	94%	76%	80%
1-year OS	81%	52%	57%
2-year OS	56%	26%	29%
PFS (median in months) p = 0.292	9.0 (3.7–26.6)	7.2 (4.2–12.7)	7,3 (4.1–14.4)
Response to treatment			
CR	4%	5%	4%
PR	41%	58%	55%
ORR (CR + PR)	45%	63%	59%
SD	44%	24%	29%
DCR (CR + PR + SD)	89%	77%	88%
PD	11%	13%	12%

IT — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors; OS — overall; PFS — progression-free survival; CR — complete response; PR — partial response; SD — stable disease; PD — progression of disease; ORR — overall response rate; DCR — disease control rate

Table 3. Cox multifactorial analysis

Analyzed factors	PFS			OS		
	p	HR	CI	p	HR	CI
TT *vs.* IT	0.9768	1.0	0.6–1.7	0.0753	1.92	0.9–3.9
> 65 *vs.* ≤ 65	0.5618	0.88	0.6–1.4	0.5968	0.88	0.6–1.4
Female *vs.* male sex	0.7086	0.92	0.6–1.4	0.6881	0.91	0.6–1.4
Lack of metastases to CNS *vs.* metastases to CNS	0.0129	0.55	0.3–0.9	0.0021	0.46	0.3–0.8
Number of locations ≤ 2 *vs.* > 2	0.5334	1.15	0.7–1.8	0.7619	0.93	0.6–1.5
LDH normal *vs.* elevated	0.0150	0.58	0.4–0.9	0.0019	0.47	0.3–0.8
ECOG ≤ 1 *vs.* > 1	0.0013	0.38	0.2–0.7	< 0.001	0.28	0.2–0.5

T — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors; LDH — lactate dehydrogenase; CNS — central nervous system; ECOG/PS — performance status

treatment results for group TT and IT is presented in Table 2. In multifactorial analysis a statistically significant unfavorable effect on OS and PFS was found for increased LDH levels, the presence of metastases to the CNS and ECOG > 1. The other factors were not statistically significant (Table 3).

Discussion

In the presented analysis a comparison was made between first-line IT or TT treatments in patients with advanced/metastatic melanoma with the *BRAF* mutation. This is one of the very few analyses which encompass very homogeneous patient groups. All patients were treated in the frame of national drug programs and thus had to fulfil the same criteria for inclusion.

Among the first trials which determined the effectiveness of using immunotherapy before or after iBRAF were those performed by Ascierto et al. and Ackerman et al. [24, 25]. In these trials. ipilimumab was mainly used for immunotherapy and it was shown that immunotherapy administered before iBRAF does not decrease their effectiveness [24, 25]. Subsequent trials and (indirect) analyses confirmed that the use of immunotherapy in first-line treatment in patients with

a *BRAF* mutation could be a better option than targeted therapy [22, 23, 26].

Our analysis indicated higher effectiveness in first-line IT as compared to TT treatment in respect to OS ($p = 0.0011$) and lack of differences in respect to PFS ($p = 0.292$). This was, however, not confirmed in multifactorial analysis, which could be due to the small group receiving IT. Moser et al. and Schilling et al. who analyzed larger patient groups showed greater effectiveness in respect to OS for immunotherapy in first-line treatment in patients with advanced/metastatic melanoma with the *BRAF* mutation [20, 23]. In both these analyses, the OS for TT were similar (13.2 and 12.4 months) to our results (13.3 months) which indicates that the groups were similar and thus can confirm the similarity of the remaining results. It is worth mentioning that when immunotherapy was used in the BRAF+ group of the CheckMate067 trial, better results were obtained for combined anti-PD1 and anti-CTLA-4 immunotherapy than for anti-PD-1 monotherapy.

As recruitment of patients for IT treatment started in 2017, analysis of groups treated before 2017 and from 2017 was performed. The aim was to check if differences in OS between groups treated with TT and IT could be due to the fact that from 2017 patients with a worse prognosis qualified for TT treatment. No statistically significant difference was found for OS for patients receiving TT before and after 2017. A statistically significant difference was observed for patients treated with TT before 2017 and IT. The effectiveness of therapy with iBRAF, iBRAF + iMEK and IT was also compared. In all cases, IT was shown to prolong OS. It is worth noting that the results of treatment are worse in the analyzed group than in clinical trials, but better than in historical groups before new therapies were introduced.

Of course, our analysis has some limitations. First, it is retrospective, second, we compare small groups and moreover, they are unequal in size. Also, the fact that in the group receiving TT there were more patients with metastases to the CNS and elevated LDH levels (thus unfavorable prognostic factors) can affect the results of our analysis. Therefore, in order to unequivocally compare the effectiveness of TT and IT prospective, randomized trials should be conducted.

It can be stated with considerable certainty that in patients with advanced/metastatic melanoma with the *BRAF* mutation without rapid progression IT should be considered as first-line therapy.

Conflict of interest

Grants and consultancies:

Bożena Cybulska-Stopa — BMS, Novartis, Roche, Pierre Fabre, MSD; Karolina Piejko — MSD; Agata Sałek-Zań — BMS

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VIA MEDICA

REVIEW ARTICLE

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Neratinib in extended adjuvant therapy for HER2-positive early breast cancer

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ABSTRACT

HER2 overexpression is found in approximately 20% of patients with breast cancer and is associated with an unfavorable prognosis. The use of chemotherapy and targeted therapies blocking HER2 function in patients with early HER2 positive breast cancer has led to significant clinical benefits. Despite this, approximately 25% of patients initially treated with trastuzumab experience recurrence of invasive disease within 5 years of completion of adjuvant treatment. Neratinib is an oral, irreversible, small molecule tyrosine kinase inhibitor blocking the intracellular domain of the HER1, HER2 and HER4 receptor, whose activity in extended anti-HER2 adjuvant treatment in HER2-positive early breast cancer patients has been confirmed in ExteNET trial. It has been shown that the use of extended therapy with neratinib after adjuvant trastuzumab treatment in patients with early HER2-positive breast cancer led to a 33% reduction in the risk of invasive disease recurring, with a greater effect observed in ER/PgR positive patients and those with involvement 4 and more lymph nodes.

Key words: neratinib, extended adjuvant treatment, HER2-positive early breast cancer

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Introduction

Positive HER2 status (overexpression of HER2 receptor or *HER2* gene amplification) is found in approximately 20% of patients with breast cancer and is associated with an unfavorable prognosis [1]. The introduction of anti-HER2 therapy, which initially consisted solely in the use of trastuzumab and supplemented standard chemotherapy or hormone therapy, led to a significant improvement in clinical outcomes. During 12-years follow up of patients with HER2-positive early breast cancer, the use of standard adjuvant chemotherapy and anti-HER2 treatment for one year leads to absolute benefits in terms of disease-free survival (DFS) and overall survival (OS) of 12% and 9%, respectively [2].

Approximately 25% of patients initially treated with trastuzumab experience a recurrence of cancer within 5 years of completing adjuvant treatment, which justifies research on new therapeutic concepts to reduce the proportion of recurrent patients. One of them was based on the extended use of trastuzumab as adjuvant therapy. The results obtained during the 11-year follow-up in the HERA study indicate that the 12-month use of trastuzumab in patients with HER2-positive breast cancer leads to a significant reduction in the risk of disease recurrence or death compared to patients under exclusive observation (hazard ratio [HR] 0.76 and 0.74, respectively). Extending the adjuvant use of trastuzumab for up to 24 months did not lead to a significant improvement in progression-free survival (PFS) compared to that observed in the group of patients receiving 12-month treatment [3]. The estimated percentage of patients included in the study who survived 10 years without disease progression was 63% in the group undergoing follow-up after chemotherapy and 69% in patients receiving trastuzumab for 12 or 24 months. Lack of effect of extended treatment on disease-free survival was independent of estrogen receptors (ER) and progesterone receptors (PgR) state, although numerically it was slightly higher in the group of patients with ER/PgR expression. The was also no demonstrated impact of trastuzumab combined with lapatinib (ALTTO study) [4] or bevacizumab (BETH study) [5] on disease-free survival. Combination of trastuzumab and pertuzumab also did not signifi-

cantly improve the percentage of patients experiencing relapse after completion of adjuvant therapy — in the APHINITY study, combined use of pertuzumab and trastuzumab in adjuvant treatment led to a reduction in the risk of relapse by 19% (HR 0.81, P = 0.045], with 3-year relapse-free survival in 94.1% of patients receiving pertuzumab in combination with trastuzumab and 93.2% of patients receiving trastuzumab in combination with placebo. Subgroup analysis showed a slightly greater benefit of combination therapy in patients with axillary lymph nodes metastases (HR 0.77) [6].

The use of trastuzumab in combination with chemotherapy and hormone therapy remains a standard for the management of patients with HER2-positive early breast cancer.

The role of neratinib in extended adjuvant therapy of early HER2-positive breast cancer

Neratinib is an oral, irreversible, small molecule tyrosine kinase inhibitor blocking the intracellular domain of HER1, HER2 and HER4 receptor, with activity confirmed in patients with metastatic HER2-positive breast cancer and benefits similar regardless of prior treatment with trastuzumab [7, 8].

The mechanism of action of the drug is based on various phenomena listed below. Inhibition of autophosphorylation of the intracellular domain of the epidermal growth factor receptor (EGFR) leads to inhibition of stimulation of signalling pathways mediated by ERK family proteins or Akt protein [9]. Inhibition of pRb protein phosphorylation prevents the release of an E2F transcription factor from complexes containing pRb protein (E2F-pRb). Interactions of E2F protein with promoter regulatory sequences are crucial for the activation of transcription of genes encoding protein products determining the progression of the cell division cycle from the G1 to the S phase. The increase in p27 inhibitor protein expression leads to a decrease in cyclin D1 expression and formation of cyclin D1-cdk 4/6 complexes essential for phosphorylation of pRb protein, resulting in inhibition of cell proliferation at the G1–S interface [10]. As a result of neratinib action, the expression of HER2 receptor protein is also reduced by its ubiquitination and subsequent degradation in proteasomes in the cell cytoplasmic space [11].

Locating the drug binding site within the HER2 intracellular domain is particularly important in patients with trastuzumab resistance or primary absence of extracellular receptor domain.

The efficacy of neratinib in HER2-positive breast cancer has been well documented in patients with locally advanced or metastatic disease. As demonstrated in phase I and II studies, the use of neratinib in patients previously treated with anthracyclines, taxoids and trastuzumab resulted in objective responses rate of 32% and the clinical benefit of treatment in 44% of patients [8, 12]. For patients receiving adjuvant treatment, the data were obtained from a randomized, multicenter, phase III trial assessing the efficacy of extended adjuvant treatment with neratinib after discontinuation of anti-HER2 therapy in patients with HER2-positive breast cancer. The primary design of the ExteNET study was addressed to patients with stage II–III HER2-positive breast cancer after perioperative treatment completed within 2 years before randomization. The results of other analyzes published during recruitment [13–16] — indicating a high cancer recurrences rate observed at the end of adjuvant treatment with trastuzumab or shortly after its completion — formed the reason for limiting the ExteNET study to patients with primary involvement of regional lymph nodes and patients who discontinued adjuvant trastuzumab within 12 months before randomization. However, the above-cited papers containing also the results of analyzes carried out in patients without lymph nodes involvement showed a lower than initially assumed the risk of recurrence after the completion of adjuvant treatment.

As the inclusion and exclusion criteria changed, the definition of intended endpoints also evolved. Ultimately, the primary endpoint was invasive disease-free survival in the whole study population. Statistical analyzes to assess the significance of the effect of 12-months neratinib therapy on the primary endpoint were performed 2 years after stopping study medication instead of 5 years, as originally planned. The secondary endpoints of the ExteNET study included: recurrence of ductal carcinoma *in situ*-free survival, time to distant recurrence, distant metastases-free survival (including central nervous system metastases), overall survival (OS) and safety. The study included 2,840 HER2-positive breast cancer patients, with a comparable median time from discontinuation of trastuzumab to neratinib or placebo initiation of 4.4 months and 4.6 months, respectively. The percentage of pre- and postmenopausal patients was also comparable in both arms. Treatment with neratinib at a dose of 240 mg daily or placebo was continued for 12 months or until disease recurrence, unacceptable toxicity or consent withdrawal. Based on the analyzes a 33% reduction in the recurrence risk was demonstrated in the group of patients receiving extended treatment with neratinib compared to placebo (HR 0.67; P = 0091). The 2-year recurrence-free survival rate was 93.9% in the neratinib arm and 91.6% in the placebo group. There were no significant differences between the two groups in terms of dissemination-free survival and time from treatment cassation to distant metastases. The 2-year dissemination-free survival rate was 95.1% in the

patients receiving neratinib and was slightly higher than that observed in the group receiving placebo (93.7%). As demonstrated in the subgroup analysis, this effect was associated with hormone receptor expression (HR 0.51; P = 0.0013). Adjuvant treatment with neratinib was also relatively well tolerated. The most common toxicity was diarrhea, which in grade 2 or 3 was found in 33% and 40% of patients, respectively (the rates were significantly higher than observed in the placebo arm — 7% and 2%, respectively). The above data refer to patients with no antidiarrheal prophylaxis during treatment. The incidence of decreased left ventricular ejection fraction (LVEF), interstitial pneumonitis and pulmonary fibrosis was comparable in both groups. In patients receiving neratinib, hepatic dysfunction was observed twice as often (14% *vs*. 7%) and consisted of increased serum level of alanine aminotransferase (9% *vs*. 3%, respectively), asparagine aminotransferase (7% *vs.* 3%, respectively) and phosphatase alkaline (2% *vs*. 1% respectively) [17]. The analysis of the toxicity profile depending on the stratification factors was consistent with the general profile. In the group of patients with HER2-positive breast cancer with hormone receptors expression, the most common grade 3 or higher complication was diarrhea (39% *vs*. 1% in the placebo arm), nausea (1% *vs*. < 1%) and weakness (2% *vs*. < 1%). The occurrence of the above symptoms constituted the basis for the reduction of the dose of neratinib in 31% of patients, withholding treatment in 42% of patients or hospitalization in 6% of patients receiving neratinib) [18].

The results of preliminary analyzes presented above were supplemented with data from 5-year observations. As presented by Martin et al. [19], the use of extended adjuvant therapy with neratinib led to a 27% reduction in the risk of relapse in whole study population (P = 0.0083); 5-year invasive disease recurrence-free survival rate was 90.2% in the neratinib arm and 87.7% in the placebo group. Other benefits of neratinib were the reduction in the proportion of patients with distant relapses (6.4% *vs*. 7.8%, respectively) and local or loco-regional relapses (0.8% *vs*. 2.5%, respectively). However, there were no significant differences between the two groups of patients in terms of metastatic disease-free survival and time to disease generalization. Lesions in the central nervous system as the first relapse site were found in 1% of patients receiving neratinib and 2% of patients receiving placebo. The study also showed a beneficial effect of extended adjuvant therapy with neratinib in patients with hormone receptor expression compared to placebo. The absolute benefit in terms of invasive disease-free survival during 2-year and 5-year follow-up was 4.5% and 5.1%, respectively. A similar relationship was observed for distant metastases-free survival (the absolute benefit in the neratinib arm compared to patients receiving placebo was 3.2% and 4.7%, respectively) [18]. A similar effect, resulting from the use of neratinib, was not observed in patients without hormone receptor expression.

The aforementioned change in study inclusion/exclusion criteria allowed a comparison of treatment effects according to the time between discontinuation of maintenance treatment with trastuzumab and initiation of treatment with neratinib. Initiation of treatment with neratinib less than 1 year after stopping anti-HER2 therapy is associated with a significant impact on invasive disease-free survival compared to deferred treatment for more than 1 year (HR 0.70 *vs*. 1.0, respectively). Analysis of safety profile during 5-year follow-up did not show significant differences compared to already known from previous analyzes.

In summary, the results of 5-year observations in the ExteNET study allowed to formulate the following conclusions:

1. the use of extended therapy with neratinib after adjuvant trastuzumab in patients with early HER2-positive breast cancer leads to a 27% reduction in the risk of invasive disease recurrence (P = 0.0083);
2. the therapeutic benefit of neratinib results from a reduction in the frequency of local, loco-regional and distant relapses;
3. the effect on overall survival in patients receiving extended therapy with neratinib remains undetermined and final results are expected;
4. the effect of extended use of neratinib is mainly observed in patients with hormone receptor expression and metastases in 4 or more lymph nodes (in patients without receptor expression the effect of using neratinib is marginal);
5. the main symptom of treatment-related toxicity is diarrhea, which, when implementing appropriate preventive measures, does not force premature termination of extended adjuvant therapy.

The occurrence of the therapeutic effect of neratinib mainly in patients with hormone receptor expression results from the overlapping of ER-initiated and EGFR signalling pathways. It has been shown that inhibition of HER2 receptor function as a result of anti-HER2 treatment (trastuzumab, pertuzumab and others) leads to activation of ER-initiated signalling pathway, which results in the development of resistance to the drugs blocking HER2 function [17, 20]. The use of hormone therapy aimed at blocking ER and indirectly PgR function in cancer cells will also lead to an increase in HER2 receptor expression and activation of signalling pathways dependent on its stimulation [20].

The results of the ExteNET study were reflected in the recommendations of leading cancer societies. According to published in 2019 the European Society of Medical Oncology recommendations on the treatment

of patients with breast cancer, the extended use of neratinib can be considered in patients with HER2-positive early breast cancer at high risk of recurrence and with ER expression, in whom in adjuvant treatment HER2 double blockade was not used. The position results from not obtaining evidence in randomized clinical trials on the effectiveness of extended adjuvant therapy with neratinib in patients receiving in adjuvant treatment HER2 blockade other than trastuzumab. The authors of the recommendations also emphasize that the observed beneficial treatment effect on recurrence-free survival often occurs at the expense of severe diarrhea [21]. The British National Institute for Health and Care Excellence (NICE) recommendations are similar [22] and recommend considering the extended adjuvant treatment with neratinib in patients with HER2-positive breast cancer with hormone receptor expression who have completed adjuvant treatment with trastuzumab or in whom despite preoperative treatment invasive residual disease is still found in the primary location or regional lymph nodes. However, it is currently difficult to determine clearly the group of patients for whom extended adjuvant treatment with neratinib will be the best therapeutic option. This is due to several reasons. Firstly, a significant portion of HER2-positive breast cancer patients receives trastuzumab and pertuzumab in perioperative treatment. In the absence of results from randomized clinical trials, it is impossible to unequivocally determine the influence of HER2 double blockade on the effect of neratinib. Extended use of neratinib seems to be an option for patients without lymph nodes involvement, who are not the candidates for a combination of trastuzumab and pertuzumab. Further doubts about the extended use of neratinib concern patients with complete pathomorphological remission (pCR) after neoadjuvant treatment (absence of invasive cancer cells in the material from the primary tumor and axillary lymph nodes as well as signs of the infiltration of blood and lymphatic vessels by cancer cells). This definition allows for the presence of residual components of non-invasive cancer in post-operative tissue (based on the Union Internationale Contre le Cancer [UICC] and the American Joint Committee on Cancer [AJCC] recommendations). According to the inclusion criteria, the ExteNET study did not involve patients with pCR after preoperative treatment, hence the role of neratinib in this population is unknown. The efficacy of neratinib in the group of HER2-positive and hormone receptor-positive breast cancer patients who did not achieve pCR after preoperative treatment were presented only as a conference poster. The use of neratinib in this group of patients was associated with an increase in the disease-free survival rate of 5% and 7%, respectively during 2- and 5-year observations [18].

The National Comprehensive Cancer Network (NCCN) recommendations are less radical, allowing the use of extended adjuvant treatment with neratinib not only in patients with HER2-positive hormone receptor-positive breast cancer who have completed adjuvant trastuzumab treatment but also in patients in whom perioperative HER2 double blockade based on trastuzumab and pertuzumab was used. The authors of this recommendation emphasize, however, the lack of evidence for this approach from multicenter randomized clinical trials.

In summary, it is currently believed that the group of patients likely to benefit most from extended adjuvant treatment with neratinib are those with early HER2-positive breast cancer with hormone receptor expression whose adjuvant trastuzumab treatment has been discontinued no later than 12 months before neratinib. The value of the use of the presented therapeutic approach in patients receiving HER2 double blockade in perioperative treatment and achieving pCR as a result of preoperative treatment is still unknown.

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