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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) Third 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, 2018 and May 31st, 2019 and accepted for publication will qualify.
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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.
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Cutaneous melanomas

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Key words: melanoma, diagnosis, therapy

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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

Skin melanomas are malignant neoplasms deriving from neuroendocrine melanocytic cells. Melanoma are relatively rare in Poland — the standardised incidence rate reaches about 5/100,000, which represents 3600 new melanoma cases per year during the last few years (about 1800 men and about 1800 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 2.4/100,000 men and 1.5/100,000 women, which represents, during the last years, respectively, about 760 and 680 melanoma-related deaths [1, 2].

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

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 [3, 4].

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.

Diagnostics

Medical history should include questions concerning skin condition (information concerning changes

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)

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) [5, 6]. 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 x magnification [6]. 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 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. However, in higher stages (pT1b–pT3a), a scan should be performed by ultrasound examination of regional lymph nodes, and a suspected biopsy should be performed with

Table 2. Clinical differential diagnostics ofcutaneous melanoma

Early skin melanoma	— Pigmented naevus, including junction nevus (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

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 or PET may be considered in patients with diagnosed skin melanoma in clinical stage IIC and III (especially if the clinical metastases to the lymph nodes are present) or with isolated metastases to the distant organs. In the case of the clinical metastases to the inguinal lymph nodes it is recommended that CT or magnetic resonance imaging (MRI) of the pelvis and abdomen 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).

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, 3, 4, 7]. There are no indications for prophylactic excision of skin moles that are not suspected of being skin melanoma.

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

1. Macroscopic assessment
   a. Size of the excised skin section with the lesion (three dimensions);
   b. Size of the lesion (two dimensions);
   c. Pigmentation (homogenous, heterogeneous);
   d. Border of the lesion (regular, irregular);
   e. Nodule (present, not present);
   f. Margins (lateral and deep margin).
2. Microscopic assessment
   Microscopic features/characteristics that are required:
   a. Breslow thickness of infiltration (in millimetres) is measured from the top of the granular layer of the epidermis, or if the surface is ulcerated — from the base of the ulcer, to the deepest invasive cell across the broad base of the tumour;
   b. Presence or absence of ulceration including the whole thickness of the epidermis covering the tumour as well as information about the extent

of ulceration, measured either as the diameter or percentage of tumour width;

c. 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);
d. Growth phases (horizontal [radial] — intraepidermal, in situ with microinvasion and sagittal [vertical], always skin invasion);
e. Presence or absence of microscopic satellite sites (sites composed of melanocytes with diameter > 0.05 mm remoted > 0.3 mm and < 2 cm from the invasive component of the primary melanoma tumour — parameter N).
f. Peripheral margin (measured from the in situ to the invasive component) and in depth;
g. Clinical stage pT;

Recommended elements:

h. Presence and extend of tumour regression;
i. Clark level of invasion (level I, II, III, IV, V);
j. Histopathological subtype (superficial spreading melanoma [SSM], lentigo maligna melanoma [LMM]; arising from a lentigo or in a Hutchinson age spot, nodular melanoma [NM], acral lentiginous melanoma [ALM] — subungual, other types — e.g. desmoplastic);
k. Cell type (epithelioid, fusiform, small, pleomorphic, other);
l. Presence and grading of the lymphocytic infiltration (tumour infiltrating lymphocytes [TILs]; evaluated only in a vertical component; absent, moderate — TILs non-brisk, abundant — TILS brisk);
m. Presence or absence of lymph and blood vessel infiltration;
n. Presence or absence of nerve trunk infiltration;
o. Presence of a mole.

WHO classification of skin tumours 4th Edition 2018 distinguishes the following types of melanoma [8]:

- 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;

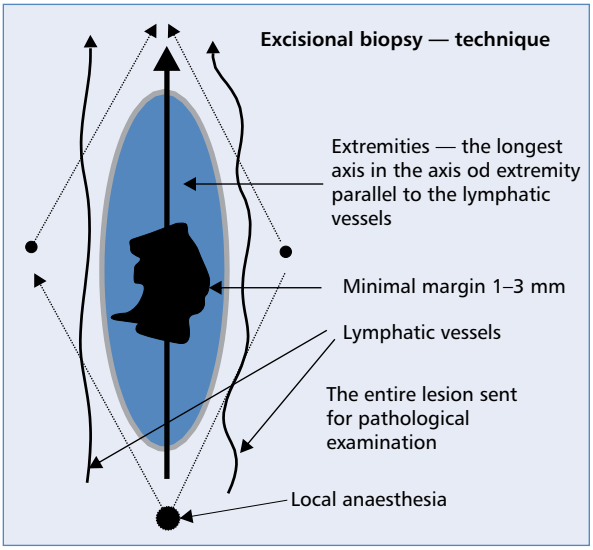

Figure 1. (According to W. Ruka) Recommended direction of the cut during the excisional biopsy. Spindle-shaped excision of the suspected pigmentary lesion should be made collaterally to the regional lymph vessel (toward the nearest draining lymph node/lymph vessel confluence), in the majority of cases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

- nodular melanoma, naevoid melanoma, and metastatic melanoma.

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 1–2 mm of healthy skin. The surgical specimen should include not only the whole thickness of the skin but also a superficial layer of the adipose tissue. The fascia should not be excised, and the wound should be closed by a primary suture. The skin should be cut as an ellipse specimen following the lines of relaxed skin tension (Fig. 1). Only the cut of the face lesion should follow the aesthetic lines. Transversal cuts should never be done (on the limb area) because in the case of repeated surgery they give a poor cosmetic effect and are inconsistent with oncological recommendations.

Results of 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 mucosa melanomas). In patients with disseminated (primary or secondary) melanoma, testing for *BRAF* gene mutation in the FFPE is obligatory in the case of high risk of relapse of melanoma (clinical stage IIIA > 1 mm, IIIB, IIIC and IIID) and for *KIT* and *NRAS* mutation is optional (V, A). There is no need for repeated sampling of the metastases to detect the presence of molecular disorders. Genetic tests should be performed in referral centres that undergo quality audits. It is not recommended that mutations are tested for inpatients with skin melanoma and no metastatic sites [4].

Sentinel node biopsy (microstaging II)

A sentinel node biopsy should be done in patients (II, A) [1, 3, 4, 9, 10]:

- 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 UICC/AJCC 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 [11]. 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 vascular invasion. Immunohistochemical exam with use of specific markers (e.g. HMB45, Melan-A) may visualise tiny conglomerates of the neoplastic cells.

The results of the prospective study Multicentre Selective Lymphadenectomy Trial 1 (MSLT-1) suggest that a sentinel node biopsy melanoma helps to identify patients with high risk of metastases, helps to assess the clinical stage of the disease, ensures excellent local disease control, and enables qualification of patients to clinical trials with the use of homogenous criteria [9]. 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) [9].

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 [12] (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 randomised studies [13, 14] did not prove any survival benefit in patients who had CLND due to a positive sentinel node biopsy. However, an improvement in regional lymphatic basin control was achieved. Crucial prognostic value of the sentinel node biopsy was also confirmed in these studies.

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 [15].

Staging and risk 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) [4, 7, 11, 16].

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*)		
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	No
N0	0	No
N1	One lymph node with metastatic transformation or presence of in-transit metastases satellite and/or microsatellite foci without involvement of the lymph nodes	
N1a	Metastasis to one lymph node detected by sentinel biopsy (micrometastasis*)	No
N1b	Metastasis to one lymph node assessed by clinical exam (macrometastasis**)	No
N1c	No metastases to regional lymph nodes	Yes
N2		
N2a	Micrometastases to 2 or 3 lymph nodes	No
N2b	Metastases to 2 or 3 lymph nodes, at least one clinically involved	No
N2c	Metastasis to 1 lymph node (assessed by sentinel lymph node biopsy or clinically)	Yes
N3	≥ 4 lymph nodes or a conglomerate of lymph nodes or in-transit/satellite changes with coexisting metastases to at least lymph nodes	
N3a	Micrometastases to at least 4 lymph nodes	No
N3b	Metastases to at least 4 lymph nodes and at least one as clinically overt or conglomerate of lymph nodes	No
N3c	Metastases to 2 or more lymph nodes and/or conglomerate of lymph nodes	Yes
Parameter M	**Localisation of the metastases**	**Serum LDH activity**
M0	Without distant metastases	
M1a	Skin, subcutaneous tissue, or non-regional lymph nodes	
M1a(0)		Normal
M1a(1)		Increased

→

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

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

*Micrometastasis to the lymph node — detected by the microscopic exam of the clinically asymptomatic (not enlarged) lymph node, after performing the sentinel node biopsy; **macrometastasis to the lymph node — confirmed by the microscopic exam of the clinically palpable lymph node (enlarged) after a therapeutic lymphadenectomy; ***micro-/satellitosis — neoplastic infiltration or nodules (macro or microscopic) 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 assessment of presence of metastases. Consequently, clinical staging may be applied only after complete excision of the primary site of the skin melanoma (excisional biopsy) and evaluation of the regional lymph nodes and distant organs for the presence of metastases; **pathologic grading/staging includes micrograding of the primary site and a pathological assessment of the regional lymph nodes: after a sentinel lymph node biopsy or after a radical lymphadenectomy (except from stage 0 and IA in which no procedure is applied to the regional lymph nodes); ***clinical staging does not include any subgroups of stage III

Metastases to the regional lymph nodes (clinical stage III)

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

Metastases to the distant organs (clinical stage IV)

Localisation of metastases and LDH activity are the major prognostic factors in patients with extranodal metastases. The worst prognosis in this group of patients is with metastases to the central nervous system

Clinical staging — classification

The actual clinical and pathological stage classification system of skin melanoma according to TNM was revised in 2010 and 2017, and formulated based on the multifactor analysis of the data of 38,000 patients (Table 3) (II, A) [16].

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 used only in special situations, and in patients with metastatic disease it should be tailored to the clinical situation. The essential and obligatory recommendation is to refer patients to a multidisciplinary team of specialists experienced in diagnostics and treating melanomas.

Surgical treatment

Primary site

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

Based on the results of six multicentre, randomised trials it was decided to derogate from extended excisions of the primary melanoma site (with margin ≥ 3 cm) in favour of narrower margins of healthy tissues. 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 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, 3, 9, 17].

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);

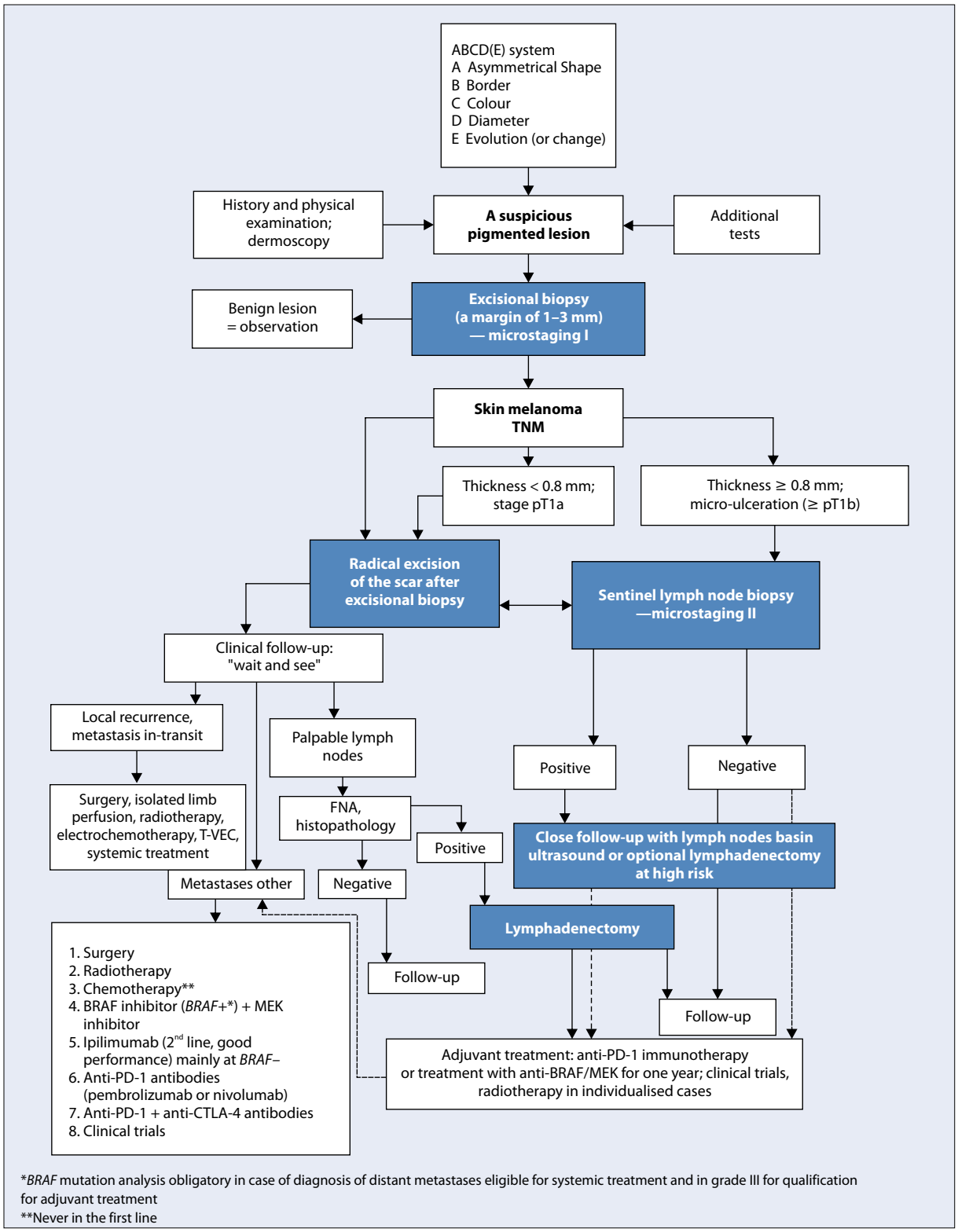

Figure 2. A schedule of diagnostic and therapeutic recommendations in patients with skin melanoma. FNA — fine-needle aspiration biopsy; TNM (tumour–node–metastasis) — classification of tumour/node/metastasis stage

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

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

— 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-2) 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. If HILP is contraindicated, systemic therapy should be administered [1, 4, 7, 17–19].

Adjuvant therapy

Currently, dabrafenib with trametinib, pembrolizumab and nivolumab (the latter also after grade IV metastasectomy) are registered for systemic adjuvant treatment in clinical practice in patients after radical primary surgery and lymphadenectomy, and complementary radiotherapy may only be considered in very specific situations. 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 (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 [20, 21]. 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) [22, 23].

Ipilimumab is registered in the United Stated for adjuvant therapy of patients after lymphadenectomy of involved regional lymph nodes. Randomised clinical trials [24] showed a significant improvement of disease-free survival and overall survival but with high toxicity of ipilimumab therapy (II, B) [25].

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 [24]. Updated data from 2018 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) [26]. 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) [27, 28]. 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) [29]. This indicates the need for an absolute multidisciplinary evaluation of all patients with melanoma in stage II–IV.

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, or head and neck region localisation (solo RT may be used for extensive LMM lesions). 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 [30, 31]. 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) [32]. No adjuvant RT should be applied after CLND.

Therapy of patients with advanced disease

The results of treatment of skin melanomas in clinical stage IV are still unsatisfactory. The median overall survival time exceeds 12 months (and is significantly higher for new therapies), but about 20–30% of patient survive for five years.

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

In the case of secondary changes to the skin, soft tissues, and non-regional lymph nodes (M1a, better prognosis), it is always recommended to consider excision. A similar approach should be applied for isolated (not necessarily single) metastases to the visceral organs. In the case of unresectable lesions, the choice of therapeutic approach depends on the presence of metastases to the central nervous system (CNS). If the metastases to the CNS are present neurosurgical treatment and/or radiotherapy of the central nervous system (usually stereotactic or radiosurgery [33]) 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). RT is also used in palliative therapy in patients with metastases to soft tissues (ulceration, pain) and to bones (pain).

The advance in therapy of advanced melanoma, considering the low efficacy of cytotoxic agents, results from the use of nonspecific immunotherapy with use of monoclonal antibodies anti-CTLA4 or anti-PD1, which inhibit the systemic mechanisms of immunosuppression in order to induce an antineoplastic response (activation of lymphocytes T) as well as from the use of molecularly targeted therapies with use of serine-threonine kinases inhibitors (I, A). 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, 3]. 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 [34, 35]. 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 [34–36]. 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 [35] 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) (I, A) [37–39] or in combination with anti-CTLA-4 antibodies (I, B) [40]. 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 [37–39]. 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 efficacy (the median disease-free survival was 11.5 months). The combination therapy was the best option in the case of low PD-L1 expression in the neoplastic tissue (< 5%). In the case of high PD-L1 expression (> 5%) the results of nivolumab therapy in monotherapy or in combination with ipilimumab were comparable, as were the overall survival results [40]. The results of combined ipilimumab and nivolumab therapy were also better when a *BRAF* gene mutation was present; however, in the whole group of patients [41] the improvement in three-year survival rates in the combination therapy arm compared to monotherapy with nivolumab reached only 6%: 58% *vs*. 52%, respectively. The adverse events in Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4 were significantly more frequent in the combined therapy arm (56.5%) compared to 19% in the nivolumab and 27% in the ipilimumab arm.

In the clinical study a therapy with anti-PD-L1 antibody, pembrolizumab, was maximally continued for two years. In the group of 104 patients who accomplished the two-year therapy period, 102 persons (98%) are still alive while the nine-month disease progression-free survival rate reached 91% (which means that in the majority of patients disease control 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 two years of treatment (CR, PR) / clinical benefit (II, B) [42].

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) [43]. 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) [44]. 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) [45]. The efficacy of MEK inhibitors has also been observed in patients with *NRAS* gene mutation [46]. 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) [47–51]. 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 [52]. 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) [53].

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 maintained after immunotherapy and of immunotherapy (anti-PD-L1) after treatment with BRAF inhibitors (Fig. 3, 4). In rare cases of patients with melanomas carrying some *KIT* gene mutations, the activity of KIT kinase inhibitors has been observed (II, B) [54].

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 [55, 56] (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. 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.

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 and to senti-

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 Blood morphology and biochemistry (liver tests and activity of lactate dehydrogenase) — optionally Other tests (e.g. CT) in the case of presence of suspected symptoms Ultrasound of regional nodes when no sentinel node biopsy has been performed, in skin melanomas ≥ 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

nel node procedure. In the case of clinical metastases to the regional lymph nodes a radical lymphadenectomy is a method of choice. It is recommended that patients with high-risk melanoma be included in prospective clinical trials evaluating the adjuvant therapy. A schedule of diagnostic and therapeutic recommendations in patients with skin melanoma is shown in Figure 3–4.

The presence of distant metastases is still associated with poor prognosis. It is recommended that patients with generalised disease be treated in clinical trials. *BRAF* mutation should be tested in all patients with advanced disease or with high disease relapse risk (III). Long-term survival is seen mostly in patients in clinical stage IV, who have had resection of singular metastatic lesions. In patients with present *BRAF V600* gene mutation, mostly in first-line therapy, a BRAF inhibitor may be used (preferentially in combination with MEK inhibitor). Immunotherapy with anti PD-1 antibodies (nivolumab or pembrolizumab) or alternatively ipilimumab (anti-CTLA-4 antibody in monotherapy or in

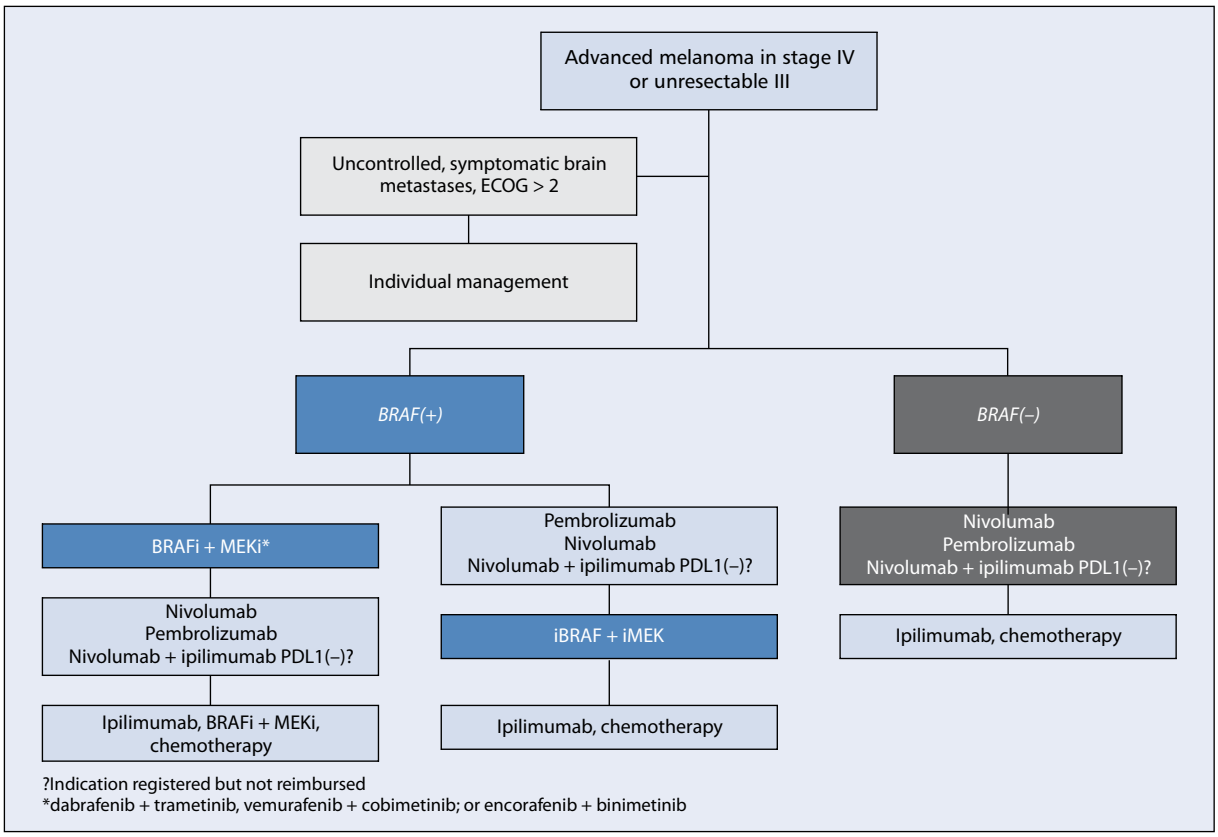

Figure 3. Recommended schedule of systemic therapy in patients with advanced melanoma in clinical stage IV or unresectable III. BRAFi — BRAF inhibitor; MEKi — MEK inhibitor

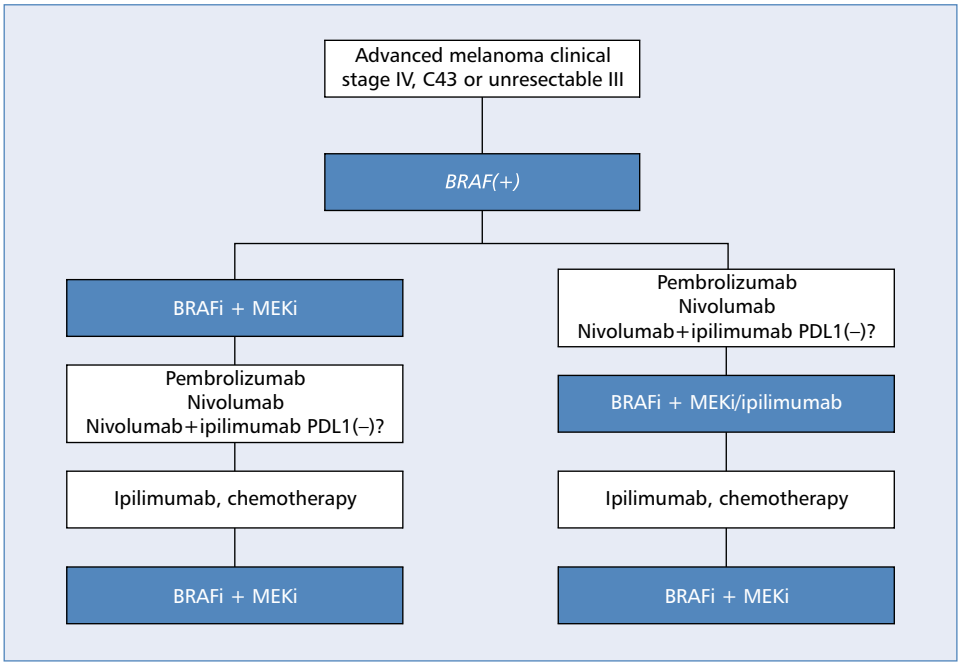

Figure 4. Recommended schedule of systemic therapy in patients with advanced melanoma in clinical stage IV or unresectable III with present *BRAF* gene mutation. BRAFi — BRAF inhibitor; MEKi — MEK inhibitor

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.

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Cancer of the lung, pleura and mediastinum

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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

Lung cancer

Epidemiology, aetiology, and prophylaxis

Lung cancer is the most frequent malignancy in Poland and the leading cause of cancer-related deaths [1]. It accounts for about 20% and 10% of all cancers in men and women, respectively (in recent years — about 15,000 and 7000 cases every year) and causes about 30% and 17% of all deaths caused by cancer (in recent years — annually around 16,000 and 7500 deaths, respectively). A higher number of deaths in relation to the number of cases indicates shortages in the registration of lung cancer cases. The incidence and mortality rate of lung cancer has been decreasing in recent years in men and at the same time increasing in women. Approximately 13.5% of patients with lung cancer in Poland survive for five or more years after diagnosis.

The risk of lung cancer morbidity depends primarily on exposure to the carcinogenic components of tobacco smoke (active and passive smoking) and, to a lesser extent, on certain physical and chemical environmental factors (e.g. radon, nickel, chromium, arsenic, asbestos, hydrocarbon compounds), as well as genetic factors (primarily polymorphisms of genes involved in the inactivation of harmful components of tobacco smoke and gene disorders responsible for the repair of DNA damage).

Previous attempts to pharmacologically prevent lung cancer and reduce mortality by using conventional X-ray screening (X-ray) and cytological sputum tests have been ineffective. Low-dose chest computed tomography (CT) is of higher value in the detection of neoplastic lesions in the lungs. National Lung Screening Trial (NLST) results showed a 20% reduction in lung cancer mortality among high-risk individuals (age 55–74 years and more than 30 pack-years smoking history) undergoing low-dose chest CT compared to the control group (X-ray examination) [2]. The results of the study became the basis for the development of early detection programs for lung cancer in the groups at highest risk in some countries. In 2017 and 2018, European [3, 4] and Polish [5] recommendations on screening were published, which have not been introduced in Europe so far (mainly due to difficulties in proving their effectiveness). Screening of people from the highest risk group has been financed since 2016 in the United States. Recently, the results of the NELSON study were presented — only in the form of a conference presentation — which after 10 years of observation showed a reduction in mortality from lung cancer (women — 39%, men — 26%) when low-dose

CT was performed in a risk group (eligibility criteria similar to NLST) [6].

Screening tests must be associated with — being of the highest importance — primary prevention (total elimination of exposure to tobacco smoke). They should also include the assessment of the occurrence of emphysema and cardiovascular risk by determining calcification in coronary vessels [3–5]. It is reasonable to carry out pilot early-detection programs to increase the possibility of radical treatment use (especially in regions with low detection of early-stage lung cancer). Early lung cancer detection programs should be carried out by highly specialised centres that have all the possibilities of recognising and treating patients with lung cancer and relevant experience.

Recommendations

— To reduce the lung cancer risk, exposure to tobacco smoke components should be eliminated (active and passive smoking) (I, A).
— In regions with low detectability of early lung cancer, it is reasonable to conduct early-detection programs using low-dose computed tomography to increase the possibility of radical treatment (III, B).

Pathomorphology and molecular biology

Primary lung cancer originates from epithelial cells. The most common are four histological types:
— adenocarcinoma (45% — increased frequency in the last period);
— squamous-cell carcinoma (30%);
— small-cell carcinoma (15%);
— large-cell carcinoma (10%).

Other histological types account for less than 1% of all primary lung tumours.

Lung cancer develops centrally — in the area of large bronchi (the so-called "perihilar" lesion) — or peripherally. Adenocarcinomas occur more frequently in the peripheral parts of the lungs. Metastases occur most frequently in regional lymph nodes (followed by liver, brain, second lung, bones, adrenal glands, subcutaneous tissue, and bone marrow). Metastases can also arise in distant organs without involvement of regional lymph nodes. Lung cancer can also spread locally by infiltrating the anatomic structures of the mediastinum and the diaphragm, pleura, and chest wall.

The 2015 World Health Organisation (WHO) classification of epithelial pulmonary carcinomas [7] (Table 1) introduced some changes in comparison with the previous version from 2011, of which the most significant are:
— new division of adenocarcinomas and squamous-cell carcinomas;
— the need to use immunohistochemistry (IHC) and genetic tests in pathomorphological diagnostics in order to individualise treatment;
— the recommendation to recognise large-cell carcinoma only in the postoperative material only;
— combining in one group cancers with features of neuroendocrine activity.

IHC tests should be performed using a panel typical for the differentiation of adenocarcinoma (TTF1, thyroid transcription factor) and squamous-cell carcinoma (p40 or p63).

Small-cell lung cancer (SCLC) differs from other histological types in terms of many biological and clinical features (high proliferation rate, short doubling of tumour mass, outstanding predisposition to produce early metastases, chemosensitivity, and relative radiosensitivity) [8], which justifies in practice the division into SCLC and non-small cell lung cancer (NSCLC).

In the case of ambiguous histological picture and the impossibility to determine the NSCLC type based on tumour morphology, IHC, and neuroendocrine indices, it is possible to diagnose not otherwise specified (NOS) cancer, which, however, should not account for more than 10% of all NSCLC diagnoses. The percentage of NOS diagnoses can be reduced due to the greater availability of tissue material, whose examination allows the determination of the full histological diagnosis [7].

The ambiguous histological picture and the IHC examination of the expression of glandular differentiation markers justify the diagnosis of NSCLC corresponding to adenocarcinoma (NSCLC — favours adenocarcinoma), and in the case of squamous cell immunophenotype, the diagnosis of NSCLC corresponding to squamous-cell carcinoma is allowed (NSCLC — favours squamous-cell carcinoma) [7].

Histological classification of NSCLC is supplemented by division according to differentiation (histological malignancy), which distinguishes four degrees (G, grade): GX — no possibility to determine differentiation, G1 — high differentiation, G2 — moderate differentiation, G3 — low differentiation, G4 — undifferentiated cancer. However, the degree of histological malignancy is of limited importance in the choice of treatment method [7].

In patients with advanced NSCLC, it is necessary to evaluate *EGFR* and *ALK* and *ROS1* genes status to detect mutations in *EGFR* gene and translocations in *ALK* and *ROS1* genes [9–11]. The presence of these disorders is a predictor of targeted therapy with EGFR (in Poland, currently — afatinib, erlotinib, gefitinib, and osimertinib) and ALK or ROS1 (in Poland, currently, crizotinib is reimbursed in lung cancers with *ALK* translocation) tyrosine kinase inhibitors (TKIs). It should be remembered that *EGFR* and *KRAS* mutations as well as *ALK* and *ROS1* translocations almost always exclude each other [12].

Genes can be evaluated using tissue material or — in the case of a confirmed sufficient number of cells in the sample — cytological examination (preferred mate-

Table 1. 2015 World Health Organisation pathomorphological classification of lung cancer [7]

Type	Subtype
Adenocarcinoma	Lepidic adenocarcinoma
	Acinar adenocarcinoma
	Papillary adenocarcinoma
	Micropapillary adenocarcinoma
	Solid adenocarcinoma
	Invasive mucinous adenocarcinoma with variants in the form of mixed mucinous and non-mucinous
	Colloid adenocarcinoma
	Foetal adenocarcinoma
	Enteric adenocarcinoma
	Minimally invasive adenocarcinoma with variants in the form of mucinous or non-mucinous
	Preinvasive lesions
	— atypical adenomatous hyperplasia
	— adenocarcinoma *in situ* mucinous or non-mucinous
Squamous-cell carcinoma	Keratinizing squamous-cell carcinoma
	Non-keratinizing squamous-cell carcinoma
	Squamous-cell carcinoma *in situ*
Neuroendocrine tumours	Small-cell carcinoma with variants in the form of combined small-cell carcinoma
	Large-cell carcinoma with variants in the form of combined large-cell carcinoma
	Typical and atypical carcinoids
	Preinvasive lesion — diffuse idiopathic pulmonary neuroendocrine hyperplasia
Large-cell carcinoma	
Adenosquamous carcinoma	
Sarcomatoid carcinoma	Pleomorphic sarcomatoid carcinoma
	Spindle-cell sarcomatoid carcinoma
	Giant-cell sarcomatoid carcinoma
	Carcinosarcoma
	Pulmonary blastoma
Salivary gland-type tumours	Mucoepidermoid carcinoma
	Adenoid-cystic carcinoma
Unclassified carcinomas	

rial is paraffin-embedded). If inhibitors of the immune checkpoints are to be used, the PD-L1 (programmed death ligand 1) protein expression should be evaluated in the tissue material or, in its absence, in the cytological material [9].

Prognosis in lung cancer patients depends primarily on the primary stage, while the age and gender of patients are of lesser importance. The new pathomorphological classification indicates a different clinical course in individual histological subtypes of adenocarcinoma (e.g. better prognosis — lepidic and papillary subtypes, worse prognosis — micropapillary and solid subtypes), but the differences does not affect the choice of treatment method. In patients with advanced cancer stage, prognosis depends mainly on performance status (PS) and the degree of weight loss in the period preceding the diagnosis. The prognostic significance of activating *EGFR* and *ALK* gene mutations has not been definitively confirmed, but the presence of these disorders (10–15% and 3–5% of Caucasian patients, respectively) is strongly correlated with the activity of appropriate molecularly targeted drugs. The prognosis in SCLC is generally worse than in NSCLC. In SCLC, in addition to tumour stage, the high activity of lactate dehydrogenase (LDH), which is associated with tumour mass, has an unfavourable prognostic value.

Recommendations

— An absolute prerequisite for commencing treatment is to determine the pathomorphological diagnosis of lung cancer based on the examination of tissue or cellular material (IV, A).
— Pathomorphological diagnosis of lung cancer should take into account the principles and criteria of the current WHO classification (III, A).
— Pathomorphological diagnosis should be supplemented by immunohistochemistry and — according to indications — genetic tests (I, A).
— The genetic-molecular assessment can be performed based on tissue material examination or — in the case of a sufficient number of tumour cells in the specimen — cytological examination (II, B).

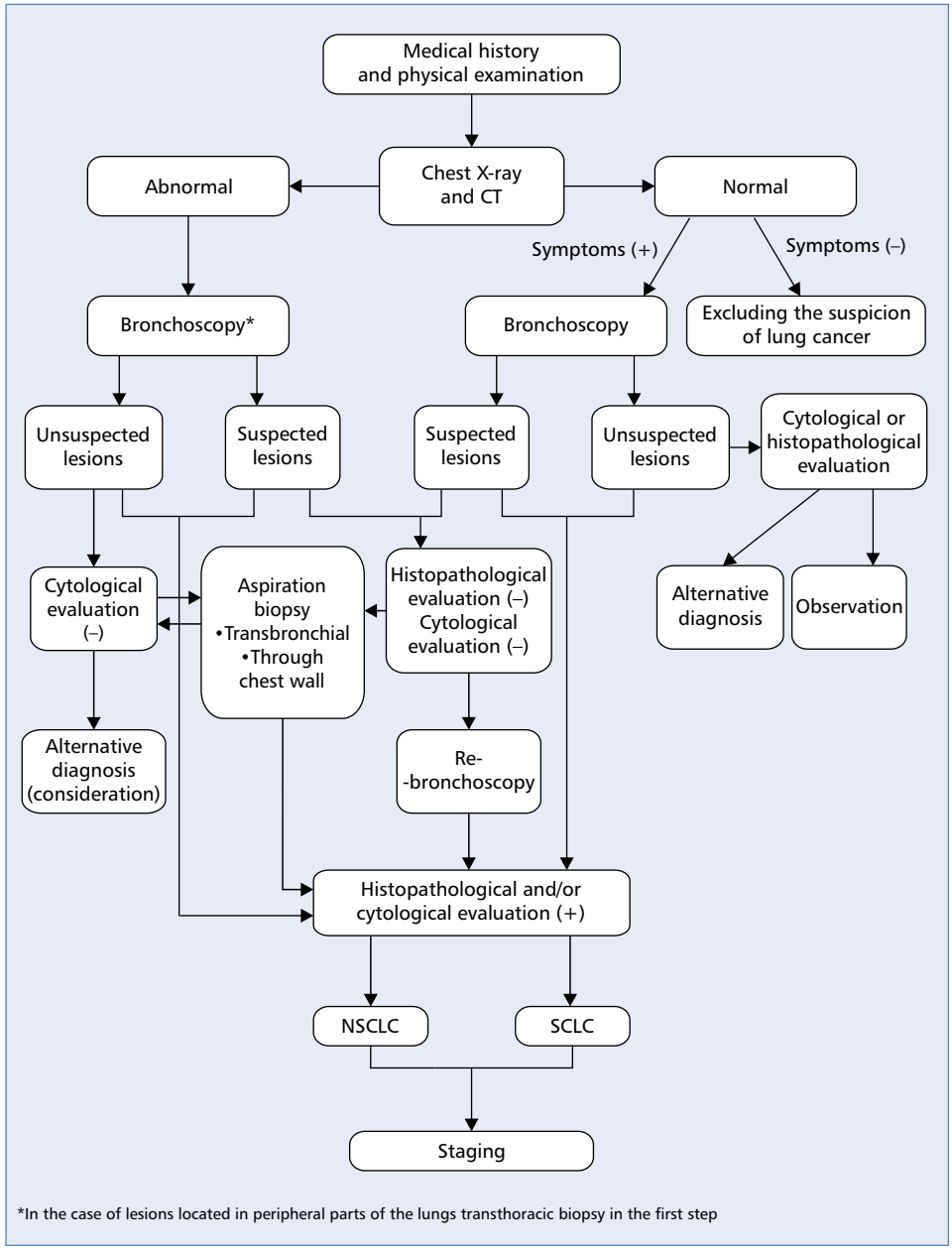

Figure 1. Principles of diagnostic procedures in lung cancer. CT — computed tomography; NSCLC — non-small cell lung cancer; SCLC — small cell lung cancer

— The diagnosis of NOS non-small cell lung cancer can only be made if it is not possible to obtain the appropriate material for the study (IV, A).
— The result of the pathomorphological postoperative examination should include the diagnosis of lung cancer (histological type and subtype and malignancy grade), the status of lymph nodes and blood and lymphatic vessels, and the assessment of surgical margins and tumour staging according to the current pathomorphological classification (IV, A).

Diagnostics

Diagnostic procedure includes determining the diagnosis and stage of lung cancer (Figure 1).

Medical history

Lung cancer is one of the malignancies in which the symptoms occur usually late. In the case of suspected lung cancer, medical history consists of an interview for symptoms (Table 2) and a careful assessment of active and passive exposure to tobacco smoke, familial

Table 2. Lung cancer symptoms

Symptoms associated with local tumour spread	General symptoms
Cough (especially a change in its character in smokers or non-smokers who are chronically coughing)	Arthralgia
Dyspnoea	General weakness
Haemoptysis	Weight loss
Pain in the chest	Increase in body temperature
Recurrent or prolonged pneumonia	Disorders of superficial sensation
Hoarseness	Thrombophlebitis
Swallowing disorders	Other symptoms of paraneoplastic syndromes
Pain in the shoulder	
Superior vena cava syndrome	
Horner's syndrome	

occurrence of tumours, and exposure to harmful environmental factors.

Physical examination

The occurrence of asymmetric symptoms in the physical examination of the respiratory system in a person burdened with an increased risk of lung cancer is an absolute indication for further diagnosis.

Physical examination of people with suspected lung cancer should particularly consider:

— symptoms associated with stricture or closure of bronchial lumen (asymmetry of thoracic tremor, percussion sound or alveolar murmur and weakening of alveolar murmur, suppression of percussion sound), localised (focal) wheezing over affected bronchi, bronchial murmur in the abnormal location;
— enlargement of peripheral lymph nodes (especially supraclavicular);
— symptoms of pleural effusion presence (suppression of percussion sound, weakening of alveolar murmur);
— symptoms of pericardial effusion presence and myocardial infiltration (enlargement of the heart silhouette, weakening of heart tones, jugular venous distension, liver enlargement, hepatojugular reflux, low blood pressure amplitude, arrhythmia);
— symptoms of superior vena cava *syndrome* (SVCS) (swelling of the face, increased dyspnoea, enlarged neck circumference, swelling of the upper limbs, widening of the jugular veins and on the chest wall, bruising of the face and mucous membranes);
— hepatomegaly;
— pain on pressure of the skeletal system and chest wall;
— paraneoplastic symptoms;
— symptoms from central and peripheral nervous system;
— body weight in relation to the expected value.

Performance status assessment

An essential element in lung cancer diagnosis is the assessment of performance status (PS), which should be carried out with use of WHO or Eastern Cooperative Oncology Group (ECOG) scale.

Imaging examinations

X-ray images of lung cancer can be very diverse. Suspicion of lung cancer should be made particularly by the finding in a conventional chest X-ray in posterior-anterior and lateral projections:

— well-rounded shadow (a completely solid or partially solid lesion or the image of so-called ground glass opacities);
— changes in hilar outline;
— air flow disturbances (asymmetry, atelectasis);
— infiltration change;
— pleural effusion.

Normal results of conventional X-ray does not exclude cancer located in areas with limited access (lung apex or mediastinum) or a small intrabronchial lesion. Therefore, all patients with suspected symptoms should have a chest CT scan with intravenously administered contrast agent (the test should additionally include the upper abdominal cavity with adrenal glands). In special situations, a magnetic resonance (MR) scan of the chest is performed, which can determine the state of the surrounding structures (e.g. lung apex, chest wall, diaphragm, or large vessels).

If a single nodule is present in lung parenchyma of undetermined character and up to 3 cm in diameter, the procedure proposed by the Fleischner Society [13] (Figure 2) is indicated, the main elements of which are determining the possibility of resection and the likelihood of malignant character of lesion (e.g. the character of ground glass opacities or microcalcifications with asymmetrical distribution, and especially marginal — the so-called *corona radiata*). Positron emission tomography (PET) in combination with CT (PET-CT) enables the differentiation of benign and malignant lesions and the determination of indications for other tests or follow-up.

PET-CT is helpful in assessing the tumour burden before planned surgical treatment and radical irradia-

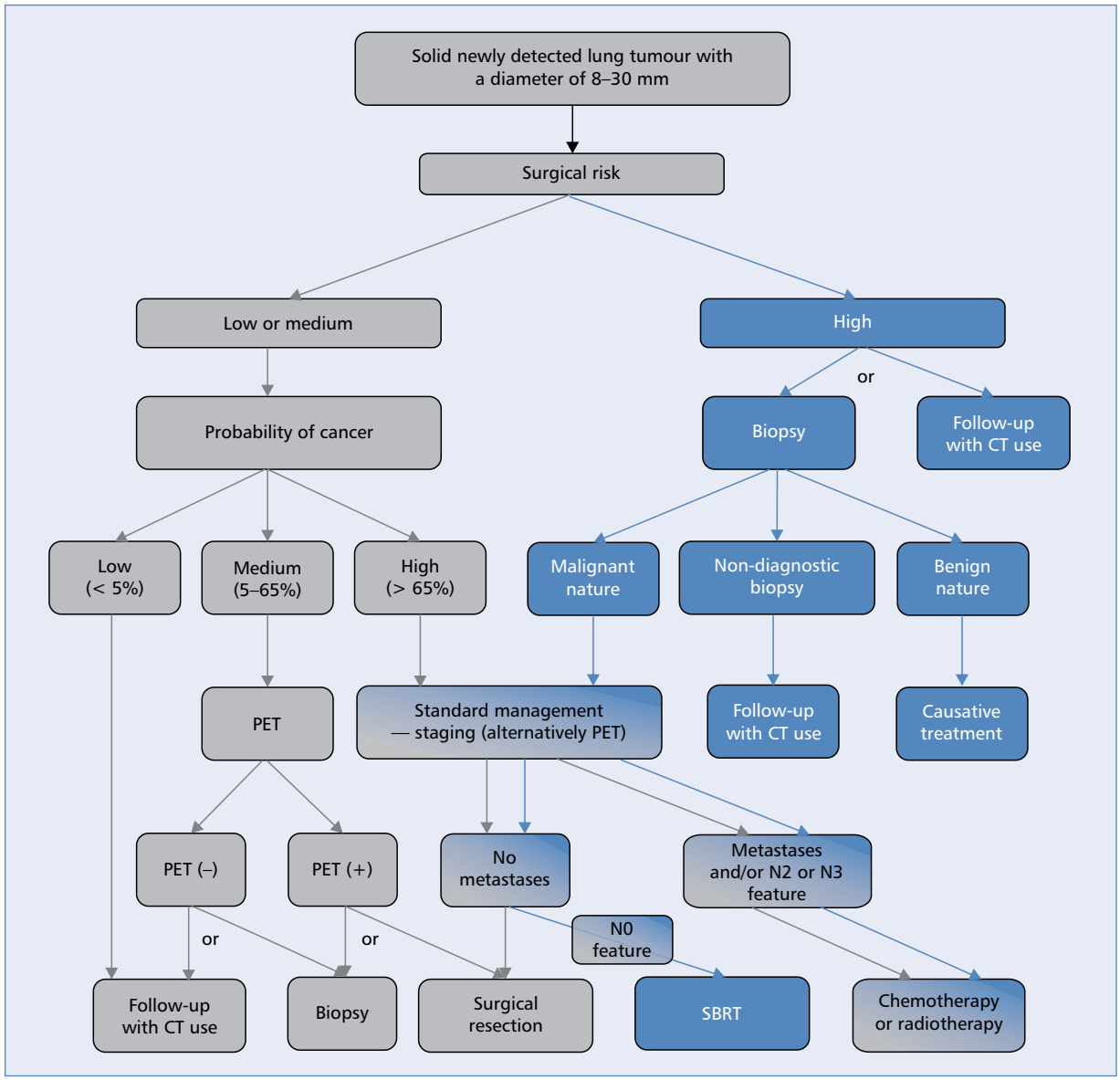

Figure 2. Guidelines for management in case of detection in chest CT scan a solid lung nodule with a diameter of 8–30 mm [13]. PET — positron emission tomography; CT — computed tomography; SBRT — stereotactic body radiation therapy

tion (the highest diagnostic accuracy in assessing the state of the mediastinal lymphatic system and detecting distant metastases) [14, 15] and should be performed in all patients qualified for surgical and radical radiotherapy (RT) or chemoradiotherapy (RCHT). The factor differentiating cancerous nature of lesions in PET-CT is the standardised uptake value (SUV), which depends on many variables (e.g. equipment parameters). For this reason, it is not always possible to draw final conclusions entirely on the basis of SUVs. It is advisable that each department performs analyses of the compliance of PET-CT results and pathomorphological post-operative reports regarding lymph nodes status. Due to the possibility of obtaining false positive or false negative results, PET-CT results should be treated with caution [15].

False positive results (especially in the lymph nodes) may occur in comorbidities with an inflammatory reaction (e.g. sarcoidosis, tuberculosis, or pneumoconiosis), while false negative results may in particular refer to adenocarcinomas. If PET-CT result is positive or borderline, a microscopic verification of possible neoplastic involvement of the lymph nodes using endobronchial ultrasonography (EBUS), oesophageal ultrasonography (EUS), or mediastinoscopy is necessary [15].

Brain imaging (preferably MR) is performed prior to planned radical treatment (patients in stages II and III before resection of pulmonary parenchyma and patients in grade III before combined radical RCHT; the remaining patients — only in the presence of suspicious symptoms). Evaluation of the bone system (scintigraphy

or X-ray) is indicated in patients with symptoms suggestive of metastases [15].

Endoscopic examinations

Bronchofiberoscopy is indicated in patients with suspected lung cancer because:
— is necessary when qualifying for surgical treatment (including radical);
— gives the possibility of obtaining cytological or histological sample;
— is helpful in cancer staging.

The diagnostic value of bronchofiberoscopy is significantly lower in peripheral changes. In the case of central lesions, at least five samples should be taken during endobronchial biopsy. It is recommended to perform a biopsy, a bronchial brushing, and a bronchoalveolar lavage (BAL) at the same time, since it may result in a sensitivity of cytological and histological evaluation of 80% [16].

Transbronchial needle biopsy — currently performed during EBUS or EUS procedures — is primarily used to determine the diagnosis and stage of lung cancer (sensitivity for NSCLC — 60–80%). It is performed using long (≥ 13 cm) cytological needles (usually 20–22 G) or histological needles (e.g. 19 G). It is recommended to take at least two samples from each location [17].

Laboratory tests

As part of the initial diagnosis it is necessary to perform a complete blood count (CBC) with a smear and clotting system parameters, biochemical tests (serum levels of glucose, creatinine, urea, sodium, potassium, calcium, bilirubin and transaminase, alkaline phosphatase, and LDH), and urinalysis. Other tests are carried out depending on individual indications. As part of the initial diagnosis and monitoring of the course of treatment, it is not recommended to assess serum markers, e.g. carcinoembryonic antigen (CEA) or fragments of cytokeratin 19 (CYFRA 21-1) [15].

Pathomorphological and molecular evaluation

The goals of pathomorphological evaluation in the diagnosis of lung cancer include determination of histological type and subtype as well as tumour range, differentiation of primary and secondary lesions, assessment of the so-called surgical margins, and detection of genetic disorders with significant importance for the choice of systemic treatment [7].

Primary tests in pathomorphological diagnostics of lung cancer include:
— histological evaluation tissue sample taken during bronchofiberoscopy;
— cytological evaluation of bronchial brushing or BAL;
— histological or cytological evaluation of the material obtained by means of a biopsy through the chest wall, bronchus, or oesophagus.

Pathomorphological evaluation should take into account the determination of neuroendocrine features on the basis of microscopic image, as well as IHC tests. The IHC test is necessary to determine the type and histological subtype of lung cancer and allows the differentiation of primary lung cancers and metastases of neoplasms with other sites, which in practice mainly concerns adenocarcinomas.

Histological examination should be performed (e.g. in the case of biopsy through the chest wall — with use a core needle), because obtaining tissue material often allows more accurate determination of the type and subtype of cancer and facilitates the extension of molecular tests (particularly important in the case of choice of systemic therapy preceding local treatment and in patients who are not eligible for pulmonary parenchyma resection). Good quality and properly protected cytological material also allows reliable determination of tumour type and subtype as well as molecular tests [7, 9].

If material for pathomorphological evaluation cannot be obtained using the aforementioned basic procedures, other methods may be used, such as:
— biopsy of mediastinal lymph nodes during EBUS or EUS;
— cytological sputum examination (low-sensitivity test and used only when bronchoscopy or biopsy through the chest wall cannot be performed);
— cytological evaluation of pleural effusion and/or pleural biopsy;
— biopsy of peripheral lymph nodes;
— mediastinoscopy;
— mediastinotomy;
— fluorescence bronchofiberoscopy with biopsy;
— cryobiopsy;
— thoracoscopy;
— biopsy of metastatic lesion;
— thoracotomy (after all other possibilities have been exhausted) [7, 15].

Before the planned treatment it is necessary to establish a pathomorphological diagnosis. In cases of justified difficulties in obtaining the material for examination, with simultaneous clinical and radiological features indicating a very high probability of cancer, a multidisciplinary team may decide to start treatment without pathological diagnosis.

Current diagnostics of lung cancer also includes molecular tests. Evaluation of biomarkers can be performed in tissue and cytological material (e.g. in an aspirate obtained by means of a fine-needle biopsy through the chest wall or bronchi). It is necessary to confirm a sufficient number of cells in preparation, and in the case of cytological material it is advisable to use methods of "embedding" cytological material in a paraffin block [9, 10]. An alternative to molecular testing using tissue or cytological material is the use of plasma free DNA circulating in the blood (cfDNA), so-called liquid biopsy [9].

When qualifying for the treatment with EGFR tyrosine kinase inhibitors in patients with adenocarcinoma and NOS NSCLC, the presence of clinically relevant primary *EGFR* gene mutations (activating and responsible for resistance) should be evaluated, which *de novo* occur in 10–15% and 1% of patients, respectively. Evaluation of the *EGFR* gene within exons 18–21 should be carried out using a method with high sensitivity and specificity (preferably using a certified test for clinical diagnosis). In the case of treatment failure with EGFR inhibitors I or II generation, re-biopsy is recommended to evaluate the presence of a secondary T790M mutation in *EGFR* gene (mutation connected to resistance to EGFR TKIs). Evaluation of *KRAS* gene status is not necessary because it does not affect the choice of systemic treatment [10].

In patients diagnosed with adenocarcinoma or unspecified NSCLC without activating mutations in *EGFR* gene, *ALK* and *ROS1* genes should be evaluated in order to detect rearrangements that occur in 3–5% and 1% of patients, respectively. The presence of rearrangements in both genes should be confirmed by fluorescence *in situ* hybridisation (FISH). However, it is advisable to pre-select patients based on the evaluation of the expression of ALK and ROS1 fusion proteins by IHC. The presence of rearrangement of the *ALK* or *ROS1* gene is an indication for the use of crizotinib or other ALK tyrosine kinase inhibitors [11]. Currently, the new generation sequencing (NGS) method is being introduced to the practice, which enables simultaneous assessment of the condition of many genes and shortens the time of molecular research. Complexity and interpretation difficulties mean that the NGS test should be performed only in laboratories with proven experience in this area.

The simultaneous assessment of clinically significant biomarkers based on one medical referral is optimal and recommended [10].

In the case of development of other molecular-targeted drugs and their reimbursement, the scope of tests should be extended (e.g. mutations in *BRAF*, *ERBB2 — HER2*, and *MET* genes). High reliability of pathomorphological diagnostics with the use of IHC and diagnostics with molecular biology methods can be provided only by laboratories with properly documented experience, having for all tests a valid certificate of European quality control program, regularly subjected to periodic external quality control, and ensuring comprehensive and simultaneous execution of analytical procedures.

Recommendations

— In each patient with suspected lung cancer, a medical history and physical examination, chest imaging (conventional radiography and computed tomography, in justified situations — magnetic resonance imaging), and bronchofiberoscopy should be performed (IV, A).
— In each patient qualified for resection of pulmonary parenchyma or radio (chemo) therapy with radical intention, positron emission tomography should be performed (II, A).
— Brain imaging is performed in patients with stage II and III before planned resection of the pulmonary parenchyma and with stage III before radical radio (chemo)therapy (II, B).
— Performing other tests (including positron emission tomography) should depend on the clinical situation and the planned treatment (IV, A).
— It is not recommended to perform serum marker tests as part of the diagnosis of lung cancer (II, A).
— In the case of the presence of a single nodule in parenchyma of undefined nature and a diameter of up to 3 cm, the probability of its malignancy and the possibility of resection using positron emission tomography should be determined (IV, A).
— The basic tests performed to obtain the material to determine the pathomorphological diagnosis and molecular characteristics of the lung cancer are bronchoscopy and biopsy through the chest wall, bronchus, or oesophagus (IV, A).
— The results of pathomorphological evaluation in lung cancer should include determination of tumour histological type and subtype, and in case of postoperative examination should also include the diagnosis of lung cancer (histological type and subtype and grade), assessment of lymph node status, as well as blood vessels and lymphatic vessels, assessment of surgical margins, and tumour staging according to the current disease pathomorphological classification (IV, A).
— Pathomorphological diagnosis of lung cancer should be supplemented by immunohistochemistry and — in the case of patients with advanced lung cancer — genetic tests to detect disorders that are important when deciding on systemic treatment (currently — *EGFR* and *ALK* genes) (I, A).
— In the case of treatment failure with I- or II-generation EGFR inhibitors, re-biopsy is recommended to assess the presence of secondary T790M mutation in the *EGFR* gene (I, A).
— In patients with advanced lung cancer qualifying for immunotherapy with immune checkpoint inhibitors the expression of PD-L1 protein should be determined (II, B).
— Diagnosis of NOS non-small cell lung cancer can be made only if it is not possible to obtain the appropriate material for evaluation (IV, A).

Table 3. Examinations used for lung cancer staging

Primary tumour assessment	Lymph node assessment	Distant metastasis assessment
— X-ray	— CT (less frequently MR)	— US or CT of abdominal cavity
— CT (less frequently MR)	— Bronchofiberoscopy	— Biopsy of single lesion in adrenal gland with suspicion of metastasis
— Bronchofiberoscopy	— Mediastinoscopy	— CT or MR of the brain (SCLC — always; NSCLC — before planned radical treatment [details in the text] and in case of clinical suspicions)
— Transbronchial biopsy ("blind", "semi-blind" transbronchial biopsy with the use of radial ultrasound transducer, EBUS, EUS)	— Parasternal mediastinotomy	— Bone scintigraphy (SCLC — planned combination treatment, NSCLC — clinical suspicion)
— Biopsy through the chest wall (peripheral changes)	— PET-CT*	— PET-CT*
— Cryobiopsy of peripheral lesions	— Physical examination	— FNA or surgical biopsy of suspected lesions
— Cytological examination of pleural or pericardial effusion	— FNA or surgical biopsy of suspected supraclavicular lymph nodes	
— Thoracoscopy	— Thoracoscopy	
— EUS	— EUS**	
	— EBUS**	

*In the assessment of the mediastinal lymphatic system in patients with potential indications for surgical treatment, PET-CT is a complementary method (negative PET-CT result with enlarged lymph nodes with > 10 mm in short axis size in the CT requires invasive mediastinal diagnostics, and in the case of smaller dimensions resignation from EBUS/EUS or mediastinoscopy is justified; positive PET-CT result does not mean the presence of metastases and in any case requires histological verification using mediastinoscopy or a US-guided biopsy). In addition, in patients with potential indications for surgical treatment, PET-CT allows more precise assessment of distant organs (especially metastases in the adrenal glands and bones). Suspicion of metastases in mediastinal lymph nodes or in other organs does not relieve the need for a biopsy. PET-CT examination is indicated in cancer staging before the planned surgical treatment and is useful in assessing the extent of disease and in planning radical RT or RCHT in patients with locally advanced NSCLC. PET-CT is an alternative to other imaging studies and bilateral bone marrow trepanobiopsy in the assessment of SCLC stage before planned treatment with a radical intention (I–III stage = LD form). Bone marrow evaluation in patients with SCLC is not necessary in the case of normal LDH activity, absence of bone metastases in scintigraphy, and thrombocytopaenia. MR examination may be helpful in case of diagnostic difficulties in patients with suspected bone metastases and inconclusive results of other imaging examinations.

**Invasive mediastinal assessment (EBUS/EUS) is also recommended in the case of a negative PET-CT or CT result in patients with perihilar or peripheral lung cancer, if one of the following features is present: (i) tumour with a diameter of more than 3 cm, (ii) no uptake or very low uptake in primary tumour, (iii) suspicion of ipsilateral involvement of hilar lymph nodes in PET-CT or CT [14].

CT — computed tomography; MR — magnetic resonance; FNA — fine-needle aspiration; EUS — oesophageal ultrasonography; US — ultrasonography; EBUS — endobronchial ultrasonography; PET — positron emission tomography; LDH — lactate dehydrogenase; RT — radiotherapy; RCHT — radiochemotherapy

Staging

Determination of lung cancer stage includes assessment of primary tumour (T feature), regional lymph nodes (N feature), and organs in which metastases may occur (M feature). In patients qualified for treatment with a radical intention, it is absolutely necessary to determine the size and location of the primary tumour and its relation to the surrounding anatomical structures (chest wall, pleura, diaphragm, heart, large vessels, and oesophagus) and the state of regional lymph nodes. The list of examinations used in the staging assessment is presented in Table 3. On the basis of the combined assessment of T, N, and M features (Table 4), the clinical stage of NSCLC is determined (Table 5). At the diagnosis of NSCLC, the proportion of patients in stages I–II, III, and IV is approximately 25%, 35%, and 40%, respectively.

In assessment of SCLC stage, a simplified classification has been applied so far, which distinguished the stage of limited disease (LD) or extensive disease (ED). The term of a limited disease was defined as a tumour that did not exceed one half of the chest, regardless of metastatic involvement of ipsilateral hilar lymph node and bilateral mediastinal and supraclavicular lymph nodes, not excluding ipsilateral malignant pleural tumour effusion. The presence of tumour lesions outside the mentioned area indicated the diagnosis of extensive disease. Currently, in SCLC — as in NSCLC — the TNM classification is recommended [18, 19].

The frequency of SCLC in I–III and IV stages according to TNM classification is approximately 35% and 65% at diagnosis.

In patients with lung cancer subjected to excision of pulmonary parenchyma and lymph nodes, the final stage is determined on the basis of pathomorphological examination of the surgical material. The "pathological" stage (pTNM) determined in this way is more accurate and reflects the prognosis of patients better than does the clinically defined stage (cTNM) [18].

Recommendations

— NSCLC staging should be made using the principles and criteria for the TNM classification (IV, A).
— If there are two lesions suspected to be primary cancer, they should be assessed separately (III, A).

Table 4. TNM classification of lung cancer (UICC, 2016) [19]

Feature	Characteristics
T	
TX	Primary tumour cannot be assessed or tumour proven by presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour 3 cm in greatest dimension surrounded by lung or visceral pleura without invasion in the main bronchus
T1a(mi)	Minimally invasive adenocarcinoma — solitary adenocarcinoma ≤ 3 cm with a predominately lepidic pattern and ≤ 5 mm invasion in any one focus
T1a	Tumour ≤ 1 cm in greatest dimension (also uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus)
T1b	Tumour >1 cm but ≤ 2 cm in greatest dimension
T1c	Tumour > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumour > 3 cm but ≤ 5 cm or tumour with any of the following features: — involves main bronchus regardless of distance from the carina but without involvement of the carina — invades visceral pleura — associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumour > 3 cm but ≤ 4 cm in greatest dimension
T2b	Tumour > 4 cm but ≤ 5 cm in greatest dimension
T3	Tumour > 5 cm but ≤ 7 cm in greatest dimension or a tumour of any size with infiltration of one of these areas: — chest wall (including the parietal pleura and superior sulcus tumours) — phrenic nerve — parietal pericardium or Associated with separate tumour nodule(s) in the same lobe as the primary tumour
T4	Tumour > 7 cm in greatest dimension or a tumour of any size with infiltration of one of these areas: — mediastinum — diaphragm — heart — great vessels — trachea — recurrent laryngeal nerve — oesophagus — vertebral body — carina or Tumour of any size associated with separate tumour nodule(s) in a different ipsilateral lobe than that of the primary tumour
N	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M	
MX	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

Table 5. Stages of lung cancer (UICC, 2016) [19]

Stage	Characteristics		
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1a(mi), T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a, T1b, T1c	N1	M0
	T2a, T2b	N1	M0
	T3	N0	M0
IIIA	T1a, T1b, T1c, T2a,	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
IIIB	T3, T4	N2	M0
	T1a, T1b, T1c, T2a,	N3	M0
	T2b	N3	M0
IIIC	T3, T4	N3	M0
IVA	Any T	Any N	M1a, M1b
IVB	Any T	Any N	M1c

— In lung cancer patients with mediastinal lymph node involvement found on imaging examinations, while qualifying for possible resection of pulmonary parenchyma, pathomorphological confirmation of the nature of suspicious lesions should be obtained (IV, B).
— In patients before the planned radical treatment, it is advisable — if possible — to obtain a pathomorphological confirmation of the presence of cancer in the single suspected lesions detected in imaging studies in other organs (IV, A).
— In patients with lung cancer subjected to excision of pulmonary parenchyma and lymph nodes, the final stage is determined on the basis of pathomorphological examination of postoperative material (IV, A).

Respiratory and cardiovascular capacity assessment

Before the planned surgical treatment and radical RT or RCHT, assessment of respiratory and cardiovascular capacity, including gasometry (optimally — arterial blood or arteriovenous capillary blood), spirometry, and lung plethysmography should be performed. The tests also include the determination of forced expiratory volume — 1st second (FEV_1), vital capacity (VC), maximum voluntary ventilation (MVV), and diffusing lung carbon monoxide (DLCO), exercise tests (six-minute walk test and "second floor" test) and electrocardiography and echocardiography (in justified situations — exercise electrocardiography and coronary angiography). Before qualifying for surgical treatment, the expected post-operative values of FEV_1 ($poFEV_1$) and DLCO (poDLCO) should be calculated in order to assess the risk of perioperative and pulmonary-cardiac complications [19]. Patients with poFEV1 and poDLCO results higher than 60% of the due value, in the absence of concomitant serious chronic diseases, may be eligible for surgery without additional exercise testing. Management in patients with poFEV1 or poDLCO values of up to 60% of the due value is shown in Figure 3 [20].

Recommendations

— In lung cancer patients, cardiovascular and respiratory capacity assessment is necessary before planned treatment (III, A).
— In all lung cancer patients, comorbidity of other serious diseases should be taken into account before deciding on treatment (III, A).

Treatment

Treatment of patients with lung cancer (general principles — see Figure 4) should be planned by a multidisciplinary team (thoracic surgeon, radiation oncologist, medical oncologist, pneumonologist, specialist in radiodiagnostics, and patologist) and carried out in centres with full access to current diagnostic methods, surgical treatment, RT, and systemic treatment. Such centres should have appropriate experience and condi-

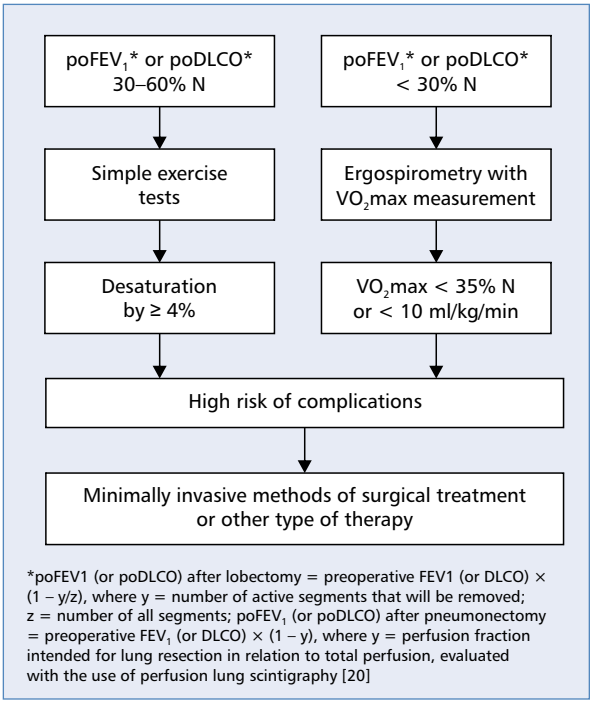

Figure 3. Management of patients with $poFEV_1$ or poDLCO values of up to 60% of the due value when qualifying for surgical treatment. $poFEV_1$ — expected post-operative forced expiratory volume — 1st second; poDLCO — expected post-operative diffusing lung carbon monoxide

tions for the use of combined treatment and appropriate management in cases of complications, which are often inevitable.

Non-small cell lung cancer — treatment in stages I–II and IIIA (potentially operable patients)

Surgical treatment

In patients with NSCLC in stages I and II and in selected patients with stage IIIA (without the N2 feature; in the case of N1 feature before eligibility for resection it is necessary to exclude the N2 feature using EBUS/EUS or mediastinoscopy) the treatment of choice is radical pulmonary parenchyma resection [21]. In patients with stage IIIA with the presence of the N2 feature, the results of primary surgical treatment are bad — resection of pulmonary parenchyma can be considered only in selected patients, provided use of neoadjuvant chemotherapy (CHT) and lymph node response is confirmed in PET-CT and mediastinoscopy [22, 23].

Lobectomy is the method of choice in patients who are eligible for resection. Pneumonectomy is performed only when the lobectomy is not likely to be radical. Both types of resection are routinely accompanied by removal of ipsilateral hilar lymph nodes and mediastinal nodes [21, 24]. The postoperative material should contain at least six lymph nodes from N1 (three lymph nodes) and N2 group (three lymph nodes; always lymph nodes below the tracheal bifurcation — group number 7). The influence of lymphadenectomy extent on the results of surgical treatment has not been definitively established, but a more extensive excision of the lymphatic system allows for a more complete determination of postoperative cancer stage and facilitates qualification for adjuvant treatment [21–23]. In patients with stage I and some patients with stage II lung cancer the recommended method of treatment is videothoracoscopic lobectomy [24–26]. Resection more limited than lobectomy is justified only in patients with significant limitation of respiratory reserves.

If resection is not possible due to significant medical contraindications or lack of patient's consent, the use of radical RT or RCHT should be considered with modern PET-CT-based planning techniques (dose intensity modulation, consideration of respiratory motion, irradiation based on current imaging) with total dose of 60–66 Gy (2.0 Gy per fraction). This treatment can be used in patients in good PS and without significant reduction of respiratory and circulatory capacity. In patients with small size (T1 or T2) peripheral tumour and without metastases in lymph nodes detected in imaging tests (PET-CT) who are not eligible for surgical treatment due to limited respiratory and/or cardiovascular capacity, management of choice is stereotactic RT, which allows a percentage of local cure to be obtained similar to that of surgical treatment. The role of stereotactic RT in perihilar tumours is still under investigation [27].

The value of ablation methods (thermoablation, cryoablation) in patients with reduced circulatory and cardiac capacity requires confirmation in prospective studies, and their routine use is unjustified.

Postoperative radiotherapy

The results of the meta-analysis of randomised clinical trials (RCTs) showed that in patients with pN0 and pN1 features post-operative RT may even worsen treatment outcomes, and in patients with pIIIA it reduces the risk of local recurrence and slightly prolongs overall survival [28]. The main limitations of this meta-analysis are suboptimal RT techniques used in previous clinical trials and inadequate patient selection. The results of the next meta-analysis of RCTs suggest a beneficial effect of modern post-operative RT in relation to local control and survival time in patients in pIII stage [29, 30], which, however, still needs to be confirmed in prospective studies.

Adjuvant RT is indicated when the presence of tumour cells is found in the cut line in post-operative histological examination, but it is not recommended after complete tumour resection (tumour-free surgical

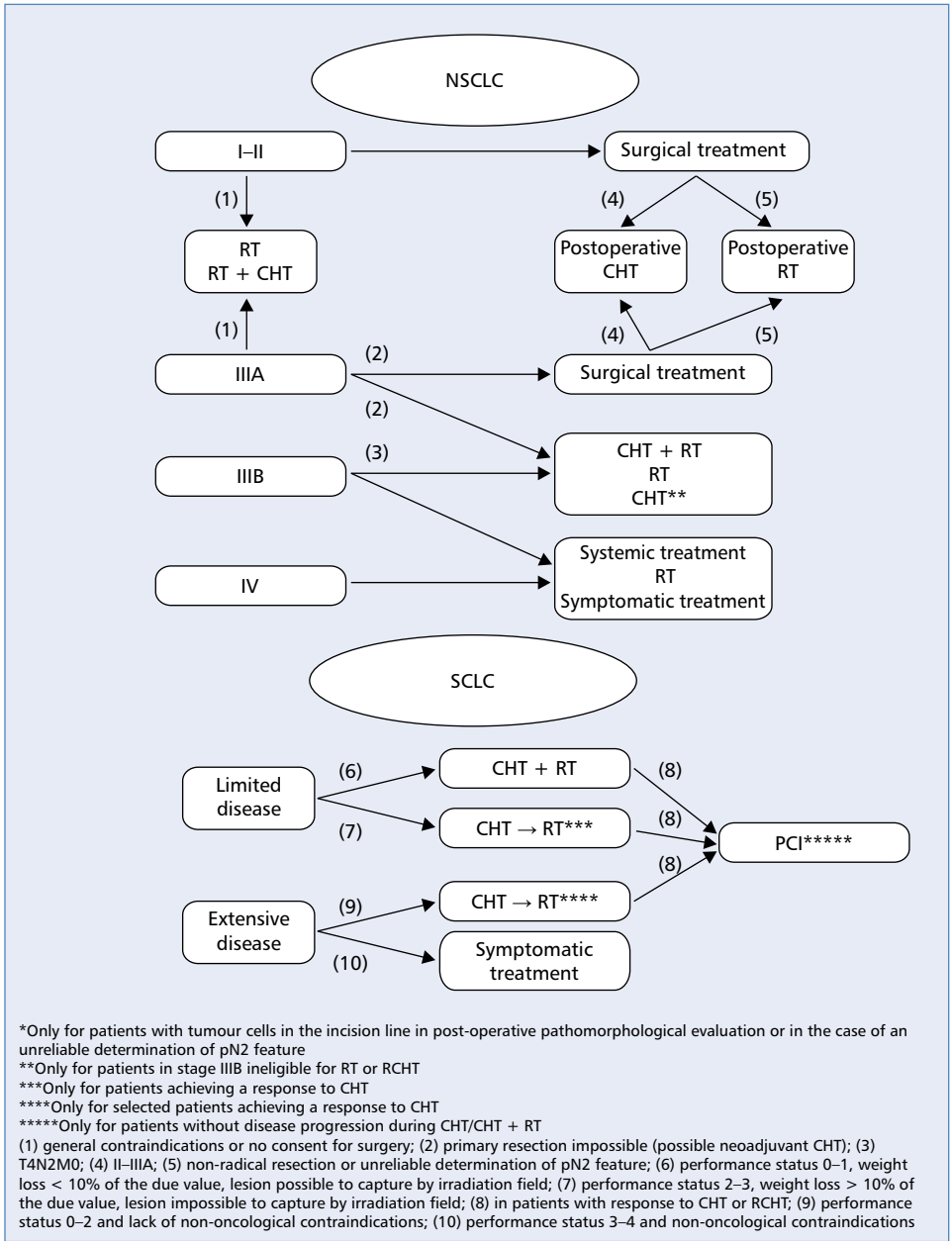

Figure 4. Principles of primary treatment of patients with lung cancer. NSCLC — non-small-cell lung cancer; SCLC — small-cell lung cancer; RT — radiotherapy; CHT — chemotherapy; CHT + RT — chemoradiotherapy; PCI — prophylactic cranial irradiation (elective brain irradiation in patients with response to RCHT or CHT)

margin — R0) and in the presence of pN0 or pN1 features, provided that the pN feature is reliably assessed. Adjuvant RT uses a dose of 60–66 Gy (fractional dose 2.0 Gy per day with conventional fractionation and using a 4–15 MeV megavoltage beam). Treatment should begin within six weeks of surgery.

Postoperative chemotherapy

The results of a meta-analysis of studies with random selection of patients indicate that the use of post-operative CHT improves the five-year survival by approximately 5% [31]. Significant benefits of supplementary CHT apply only to patients in II and IIIA stages (including patients undergoing post-operative RT), but they depend on gender and age of patients as well as histological type of cancer. In patients in stage I, adjuvant CHT does not improve prognosis.

Post-operative CHT should include 3–4 cycles of a regimen with cisplatin 80–100 mg/m^2 on day 1 in combination with vinorelbine at a dose of 25–30 mg/m^2 on days 1 and 8 (frequency every three weeks), whose efficacy is best documented [31]. Post-operative CHT

can be used only in patients in very good or good PS, with full recovery after surgery and without significant co-morbidities and medical contraindications. The risk of adverse reactions during post-operative CHT is higher in patients over 70 years of age and patients after pneumonectomy. In case of simultaneous indications for postoperative RT, it can be started at the same time as CHT. The usefulness of molecular prognostic and predictive factors assessment in the qualification to post-operative CHT has not yet been proven [10].

Preoperative treatment

In previous studies pre-operative CHT was mainly used in selected patients with stage IIIA and pN2 feature, but the optimal treatment strategy has not been definitively determined. In a meta-analysis of randomised controlled trials of 2385 patients in IB–IIIA stages a 13% reduction in relative risk of death was found, which corresponds to the absolute difference in five-year survival at 5% (statistically significant difference) in favour of pre-operative CHT compared with surgical treatment alone [32].

Pre-operative CHT may be considered in patients with pIIIA stage with feasible lobectomy (initial CHT in patients undergoing pneumonectomy does not prolong survival as compared to less aggressive resection), always based on multidisciplinary team decision after reliable determination of mediastinal lymph nodes (imaging and invasive tests — pN2 feature). Treatment includes 2–3 cycles of CHT using a cisplatin-based regimen in combination with vinorelbine, gemcitabine, paclitaxel, or docetaxel. It is necessary to carefully monitor the response and tolerance. Surgical treatment can be carried out after recovery from haematological toxicity during a three-week gap from the last CHT cycle. The condition for qualifying for resection is obtaining a histologically confirmed complete response in the mediastinal lymph nodes [32].

Preoperative RCHT does not improve outcomes, except for patients with superior sulcus tumour *(Pancoast tumour*), in whom simultaneous use of CHT (two cycles of cis-platinum in combination with the second drug) and RT (50–60 Gy) in most cases allows complete resection. Surgery should be performed 4–6 weeks after completion of RCHT [33].

Recommendations

— Resection of the pulmonary parenchyma with removal of hilar and mediastinal lymph nodes is the treatment of choice in patients with non-small-cell lung cancer in I–II and IIIA stages with N1 feature (I, A).
— Lobectomy is the preferred method of pulmonary resection. Pneumonectomy can only be performed if the lobectomy does not ensure complete resection (II, A).
— In patients with non-small-cell lung cancer in stage I and some patients in stage II, the recommended method is videothoracoscopic lobectomy (I, A).
— In patients with non-small-cell lung cancer with T1 or T2 feature and without metastases in lymph nodes, who are not eligible for surgical treatment due to respiratory or circulatory failure, stereotactic radiotherapy is the treatment of choice (II, A).
— In patients in I–IIIA stages, who are not eligible for resection and stereotaxic radiotherapy, radical radiotherapy or chemoradiotherapy should be used (II, A).
— Postoperative complementary radiotherapy in patients with non-small-cell lung cancer with pN0 and N1 features is not justified (I, A) except the patients after incomplete resection (III, B).
— The role of postoperative radiotherapy in patients with pN2 feature is not clearly defined (II, C).
— Postoperative radiotherapy should be started within six weeks of surgery; it can be started simultaneously with chemotherapy (III, B).
— Post-operative chemotherapy (cisplatin and vinorelbine — 3–4 cycles) in patients with non-small-cell lung cancer is recommended for pII and pIII stages (I, A).
— Pre-operative chemotherapy (regimens containing two drugs, including cisplatin) can be used in selected patients with non-small-cell lung cancer in stage IIIA with pN2 feature (I, B).
— Surgery may be offered for patients with non-small-cell lung cancer with the N2 feature only if complete response to chemotherapy, confirmed in positron emission tomography and mediastinoscopy, is achieved (II, B).
— In patients diagnosed with superior sulcus non-small cell lung cancer, potentially qualifying for surgery, pre-operative radiotherapy or chemoradiotherapy should be used (II, A).

Non-small cell lung cancer — treatment in IIIA (inoperable patients) and IIIB stages

Patients with stage IIIA NSCLC, in whom complete resection cannot be performed due to advanced stage of disease or other reasons, should receive RT or RCHT according to the rules referring to stage IIIB. The primary surgical treatment — based on the management principles in patients with stages II–IIIA — may be considered in selected patients with T4N0 or T4N1 stages, whereas patients with T1–3N3 and T4N2–N3 stages are not eligible for resection, and in this group RT or RCHT is the treatment of choice [33–35]. These differences in the procedure justify conducting full diagnostics in order to assess the status of lymph nodes classified as N2 and N3 features. The presence of pleural or pericardial effusion (confirmed by cytological examination of the material obtained by means of puncture or thoracos-

copy) currently qualifies the tumour to grade M1 and constitutes an indication for treatment in accordance with the rules in force in generalised disease.

The results of a meta-analysis of randomised clinical trials indicate that the combination of RT and CHT is more effective compared to the RT alone, and the simultaneous RCHT is more valuable than the sequential use of both methods, but at a higher risk of acute oesophagitis (as of pneumotoxicity and myelotoxicity, but to a lesser extent) [34, 36, 37]. Simultaneous RCHT can be used in specialised centres with available treatment of complications. Chemoradiotherapy — especially concurrent — can only be used in patients with good performance status, without significant (more than 10% of the due value) weight loss, with limited tumour mass and adequate respiratory capacity [34, 36, 37]. In some patients who do not qualify for concurrent RCHT (e.g. due to tumour burden), 2–4 pre-treatment CHT cycles may be considered, with the need to monitor the response to initial systemic therapy. In selected patients over 70 years of age in very good PS, with normal cardiorespiratory capacity and without serious comorbidities, sequential CHT and RT may be used [38]. Irradiation should begin within 2–3 weeks of CHT completion (longer interval reduces the effect of initial CHT). In the case of progression during CHT, it should be terminated and the radical RT should start immediately.

The use of CHT before or after concurrent RCHT (induction or consolidation therapy) does not increase the effectiveness of therapy but is associated with higher incidence of side effects and therefore is not recommended [33–38]. The results of the phase III study showed that the use of consolidation immunotherapy with durvalumab (monoclonal antibody blocking programmed death receptor 1 ligand, PD-L1) in patients with stage III NSCLC with objective response or stable disease following concomitant RCHT decreases by 49% the relative risk of disease progression or death compared to placebo (median duration of progression-free survival — 17 and 6 months, respectively) and has a significant effect on overall survival (reduction of death risk by 32%, median — not reached for durvalumab and 29 months for placebo); two-year survival — 66% and 56%, respectively). The incidence of severe adverse events was similar in both groups of patients [39].The drug is registered in the European Union, but in Poland it is currently not reimbursed.

In a radical RT (alone or in combination with CHT) a dose of 60–66 Gy is applied using a high-energy photon beam with conventional fractionation (1.8–2.0 Gy per day) and conformal planning [33, 34]. Increasing the dose above 66 Gy does not give any clinical benefit [35, 37]. The irradiated volume should cover the area of the primary tumour and involved hilar and mediastinal lymph nodes. It is recommended to use modern RT techniques (planning based on PET-CT, modulation of dose intensity, consideration of respiratory motion, irradiation based on real-time imaging). Irradiation of non-affected groups of lymph nodes, in particular of the opposite mediastinal and supraclavicular areas, does not improve efficacy and increases treatment toxicity.

Radical RT or RCHT are not indicated in patients with impaired performance status (grade 2 or higher according to the WHO scale), presence of pleural effusion, active infection, weight loss over 10% of the value due in the three months preceding the treatment commencement, and coexistence of other serious diseases (e.g. severe cardiovascular or respiratory failure, recent myocardial infarction or stroke, renal failure). In the aforementioned situations, palliative RT or CHT is used.

As part of the simultaneous RCHT (treatment of choice), cisplatin (75–80 mg/m^2 — day 1) is used in combination with etoposide (100–120 mg/m^2 — day 1, 2, and 3) or vinorelbine (30 mg/m^2 — day 1 and 8). In the case of sequential RCHT, regimens consisting of cisplatin and one of the above-mentioned drugs or taxoid (docetaxel 75 mg/m^2 — day 1 or paclitaxel 200 mg/m^2 — day 1) can be used. In patients with contraindications to cisplatin, carboplatin (AUC 6 — day 1) may be used in combination with the mentioned drugs. Subsequent cycles of CHT within the sequential and simultaneous RCHT should be repeated at 21-day intervals [33, 34].

In patients with contraindications to RCHT, only radical RT at a dose of 60–66 Gy (30–33 fractions) can be used. Use of hypofractionated RT in the regimen 66 Gy/22 fractions is also allowed [33]. However, a recent analysis of RCTs indicates that the conditions for the benefit from hypofractionated RT use in combination with CHT in patients who are not eligible for radical RT are good performance status and life expectancy of at least three months [40]. The decision regarding selection of the fractionation scheme should be made on the basis of individual assessment of post-radiation complication risk.

Recommendations

— Surgical treatment (primary or preceded by initial chemotherapy) can only be considered in selected patients with locally advanced non-small-cell lung cancer (II, B).
— The treatment of choice in patients with locally advanced non-small-cell lung cancer is radical chemoradiation or — in the case of contraindications to chemotherapy — radiotherapy alone (in both situations a dose of 60–66 Gy, including primary tumour and ipsilateral hilar and mediastinal lymph nodes) (I, A).
— Patients with locally advanced superior sulcus non-small-cell lung cancer undergo resection — depending on feasibility — followed by chemoradiotherapy or chemoradiation alone (III, A).

— In patients with locally advanced non-small-cell lung cancer, the treatment of choice is simultaneous radiotherapy and chemotherapy, while sequential therapy is acceptable only in the case of a clinically justified inability to conduct simultaneous chemoradiation (I, A).
— The chemotherapy regimens for combined chemoradiotherapy in patients with locally advanced non-small-cell lung cancer should include cisplatin (I, A).
— Consolidating chemotherapy after chemoradiotherapy is not justified (I, A).
— In patients undergoing radical simultaneous chemoradiation with PD-L1 expression on tumour cells, consolidation with durvalumab should be considered (I, A).

Non-small cell lung cancer — treatment in stage IV

Treatment of patients with disseminated NSCLC is of a palliative nature. Depending on the individual clinical situation, the use of CHT or EGFR, ALK, and ROS1 tyrosine kinase inhibitors, immunotherapy, palliative RT, or symptomatic treatment only may be considered. Currently, EGFR first- (erlotinib, gefitinib) or second-generation (afatinib) and third-generation (osimertinib) inhibitors, ALK inhibitor (crizotinib), and PD-1 inhibitors (nivolumab, pembrolizumab, atezolizumab) are available in Poland. The choice of systemic treatment method depends on the histological type (non-squamous- or squamous-cell carcinoma) and molecular features of the tumour. In patients with activating genetic disorders, the treatment of choice is molecularly targeted treatment. The choice of treatment should take into account the patient's age and PS as well as the presence of co-morbidities. In patients with non-squamous cell carcinoma, the possible presence of primary mutations (activating and responsible for resistance) should be determined in exons 18–21 of *EGFR* gene, followed by the presence of *ALK* and *ROS1* gene rearrangements. These tests are best performed within one medical order. Determination of PD-L1 expression using the validated IHC method to qualify patients with squamous- and non-squamous-cell carcinoma for immunotherapy can be carried out using tissue or cell material (in case of non-squamous-cell carcinoma it should be preceded by an assessment of *EGFR* and *ALK* genes status). If, in the case of tumour recurrence, it is not possible to perform a genetic test in archived tumour material, a re-biopsy is recommended. In patients with progression during treatment with EGFR tyrosine kinase inhibitors, it is necessary to re-sample the material for molecular testing in order to evaluate the mechanism of resistance (possible presence of T790M mutation). Firstly, it is recommended to evaluate for this mutation in circulating DNA (cfDNA, liquid biopsy), and if a negative result is obtained — re-biopsy or needle biopsy should be considered. When choosing the procedure, the patient's preferences should be taken into account. In selected patients with single adrenal or cerebral metastases — based on the decision of a multidisciplinary team — surgical treatment including excision of primary and metastatic lesions may be considered.

First-line systemic treatment

Chemotherapy

Numerous randomised clinical studies and meta-analyses showed survival prolongation and quality of life improvement in patients with advanced NSCLC receiving palliative CHT [41, 42].

Palliative CHT in patients with NSCLC in stage IV may be used, if:
— PS is very good or good (WHO category — 0 or 1);
— no body weight loss of no more than 10% is revealed within the three months before starting treatment;
— no serious comorbidities and/or sequelae of previous cancer treatment are found;
— adequate function of the haematopoietic system, liver, kidneys, and cardiovascular and respiratory system is confirmed;
— objective assessment of response to treatment according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria, version 1.1. is possible.

Patients who do not meet all of the abovementioned conditions may receive best supportive care or palliative RT depending on the individual situation. Palliative RT, regardless of lesions in other organs, is the method of choice in patients with troublesome complaints associated with the spread of a tumour in the chest (symptoms of superior vena cava syndrome, obstructive dyspnoea, haemoptysis, dysphagia, pain). Irradiation is also useful in patients with painful or fracture-threatening bone metastases and secondary deposits in the central nervous system (CNS).

In advanced NSCLC, CHT is used according to the regimen containing cisplatin (75–80 mg/m^2 — day 1) in combination with one of the following drugs: etoposide (100–120 mg/m^2 — day 1, 2, and 3), vinorelbine (25–30 mg/m^2 intravenously — day 1 and 8 or 25–30 mg/m^2 intravenously — day 1 and 60–80 mg/m^2 orally — day 8 or 60–80 mg/m^2 orally — day 1 and 8), gemcitabine (1000–1250 mg/m^2 — day 1 and day 8), docetaxel (75 mg/m^2 — day 1), paclitaxel (200 mg/m^2 — day 1), or pemetrexed (500 mg/m^2 — day 1), wherein in combination with pemetrexed the recommended dose of cisplatin is 75 mg/m^2 (day 1 of the cycle). The results of meta-analyses of RCTs showed that the cisplatin-containing regimens compared with carboplatin (especially in combination with taxoids and gemcitabine) result in longer overall survival [43, 44]. The use of carboplatin (AUC 5–6 — day 1) in combination with these drugs may

only be considered in patients with contraindications to the use of cisplatin (gemcitabine and pemetrexed are registered only in combination with cisplatin).

In NSCLC patients with histology other than those with a predominance of squamous-cell carcinoma, the combination of cisplatin and pemetrexed is more effective than other CHT regimens [45].

Patients older than 70 years and in good PS (grades 0–1 in the WHO scale) can receive multi-drug CHT [46].

Regimens without platinum derivatives can be considered only in the case of contraindications to the use of this group of drugs [44]. In the case of absolute contraindications to the use of schemes containing two drugs including platinum derivatives, single-dose CHT (e.g. intravenous or oral vinorelbine) may be considered [47].

The duration of palliative CHT depends on its effectiveness and tolerance, which justifies the assessment of treatment effects not later than after the second cycle. Treatment should not exceed 3–4 cycles in general, but patients with progressive response may use an additional two cycles (a total of six cycles of CHT) [48].

The use of maintenance or consolidation therapy (in Poland not reimbursed) after obtaining an objective response after initial CHT may slightly prolong the overall survival (difference — 1–3 months compared with CHT without further maintenance treatment). In patients with very good or good PS (WHO grades 0–1) without persistent adverse effects after initial CHT and with non-squamous-cell carcinoma, the use of pemetrexed maintenance therapy prolongs time to progression [49]. It was also found that patients with *EGFR* gene mutation and without progression after CHT may benefit from erlotinib maintenance treatment [50]. So far, however, the criteria for selecting patients for the aforementioned procedure have not been defined and maintenance therapy is a subject of controversy.

Molecularly targeted treatment

Numerous RCTs and their meta-analyses indicate that in patients diagnosed with adenocarcinoma and the presence of activating mutations in *EGFR* gene, the use of one of the first- (erlotinib — 150 mg per day or gefitinib — 250 mg per day) or second-generation (afatinib — 40 mg per day) EGFR tyrosine kinase inhibitors may produce higher response rate and longer progression-free survival and is better tolerated compared to CHT [51, 52]. The use of EGFR tyrosine kinase inhibitors is the first choice in the treatment of patients with *EGFR*-activating mutations. These EGFR inhibitors have very similar efficacy, and the differences concern only side effects (e.g. more frequent occurrence of diarrhoea after application of afatinib or abnormalities in liver function during treatment with gefitinib). Previous RCTs showed no significant differences between the anti-EGFR drugs and CHT in terms of overall survival, because the majority of patients who progressed during or after CHT received EGFR inhibitors in the next treatment line. Only for afatinib — in the combined analysis of LUX-Lung 3 and 6 [53] — a significant increase in overall survival compared to CHT was observed in patients with *EGFR* exon 19 deletion (median for afatinib and chemotherapy in LUX-Lung 3 and 6 trials — 33 *vs.* 21 months and 31 *vs.* 18 months, respectively), which was not observed in patients with *EGFR* exon 21 substitution. Treatment with EGFR tyrosine kinase inhibitors should be continued to disease progression or serious side effects.

A phase III clinical trial conducted in an Asian population showed a significant prolongation of progression-free survival and overall survival after dacomitinib (second-generation EGFR tyrosine kinase inhibitor) compared to gefitinib (14.7 *vs*. 9.2 months and 34.1 *vs.* 26.8 months, respectively), with higher toxicity of dacomitinib [54]. This drug is currently being evaluated for registration in the first-line of treatment for patients with advanced NSCLC with the presence of activating *EGFR* mutations in exon 19 or 21.

The phase III study compared the efficacy of first-generation EGFR inhibitors (erlotinib or gefitinib) and osimertinib (a third-generation inhibitor, active in the presence of activating mutations in *EGFR* 19 or 21 exons and T790M resistance mutations in exon 20) in the first- line of treatment [55]. Significant prolongation of progression-free survival was found in osimertinib group (median — 19 and 10 months, respectively). Higher efficacy of osimertinib was found in patients with and without CNS involvement. The influence of osimertinib on overall survival has not yet been evaluated, but the drug is currently registered in the first-line treatment based on the extension of progression-free survival (in Poland so far only reimbursed in the second-line of treatment).

Phase III trial results show some benefits of bevacizumab — a monoclonal antibody directed against vascular endothelial growth factor (VEGF) — in combination with CHT. However, the study excluded patients with squamous-cell carcinoma, haemoptysis, and bleeding disorders or undergoing anticoagulant therapy, as well as metastases in the brain and pharmacologically uncontrolled hypertension. Irrespective of the careful selection of the study group, side effects in patients receiving bevacizumab were more frequent and more severe [56].

Attempts to combine cetuximab with CHT as part of first-line treatment yielded conflicting results (no effect in one study and a slight increase in overall survival in another) [57].

In patients diagnosed with adenocarcinoma and *ALK* gene rearrangement in a phase III trial, it was found that crizotinib (ALK tyrosine kinase inhibitor) used in

first-line treatment reduces the relative risk of tumour progression or death by 55% compared with CHT [58]. The use of crizotinib in the first-line is strongly justified, but currently the drug is reimbursed in Poland only in the second-line treatment. In randomised trials, significantly greater benefits were also found following the use of other ALK inhibitors (ceritinib and alectinib) compared to CHT (the use of crizotinib in first-line treatment and other ALK tyrosine kinase inhibitors is not yet reimbursed in Poland).

In a phase III clinical trial comparing alectinib (a second-generation ALK tyrosine kinase inhibitor) with crizotinib, significant differences were found in favour of alectinib (reduction in the relative risk of disease progression or death by 53%) with better tolerance [59]. The differences concerned the whole population and patients with CNS metastases, which results from better penetration of alectinib across the blood-brain barrier.

The use of crizotinib is also justified in first-line treatment of patients with *ROS1* gene rearrangement [60].

In selected patients with oligopression and with simultaneous response of other lesions during tyrosine kinase inhibitor treatment, their further use after local treatment may be considered (excision or RT — especially stereotactic, provided it can be used).

Immunotherapy

Among immune checkpoint inhibitors, pembrolizumab (PD-1 inhibitor) is of proven value in the first-line treatment. In a phase III clinical trial, a significant prolongation of progression-free survival time and overall survival after pembrolizumab treatment compared to CHT (platinum-derived patterns) was demonstrated in patients with PD-L1 expression in at least 50% of tumour cells (median — 10 *vs.* 6 months and 30 *vs*. 14 months, respectively) [61]. Benefits were reported by patients with both squamous- and non-squamous-cell carcinoma. In the case of another PD-1 inhibitor — nivolumab — no significant benefits have been demonstrated during first-line treatment [62].

Atezolizumab (PD-L1 inhibitor) was evaluated in IMpower-150 trial [63] in first-line treatment in patients with non-squamous-cell carcinoma. This study analysed the value of chemotherapy (carboplatin and pemetrexed) used in combination with bevacizumab with or without atezolizumab (with maintenance treatment in both arms with bevacizumab alone or bevacizumab and atezolizumab). In the group of patients receiving atezolizumab, a significantly better overall survival rate after 12 and 24 months (67% and 43% and 61% and 34%, respectively), and a longer progression-free survival (median of 8.3 and 6.8 months, respectively) was obtained. Severe adverse events were more common in patients treated with atezolizumab (58% *vs*. 50%). The reduction in the risk of death depended on PD-L1 expression.

In a phase III clinical study, the addition of CHT (two-drug regimen) to pembrolizumab in patients with non-squamous-cell carcinoma resulted in a higher 12-month survival rate compared to CHT alone (69% *vs*. 49%) [64]. The benefits of adding CHT to pembrolizumab were independent of PD-L1 expression, but the greatest reduction in the risk of death (58%) was in patients with high expression (50% or more cells). The addition of CHT did not significantly increase the frequency of serious adverse reactions. The combined use of immunotherapy and CHT in first-line treatment is not yet reimbursed in Poland.

Immunotherapy with the use of anti-PD-1 drugs (e.g. pembrolizumab and nivolumab) or anti-PD-L1 (e.g. atezolizumab) may cause side effects (most commonly rash, diarrhoea, liver dysfunction and hypopituitarism, or hypothyroidism). Side effects of immunotherapy usually appear after 2–6 weeks of treatment. Early diagnosis and appropriate management allow most patients to continue treatment [65, 66].

Second-line systemic treatment

Chemotherapy

In selected patients without *EGFR*, *ALK* and *ROS1* gene disorders and with progression after prior palliative CHT, leading to objective response lasting at least three months, the use of docetaxel or pemetrexed in the second-line treatment may be considered [67]. The superiority of multiple-drug CHT over monotherapy in second-line treatment was not demonstrated in RCTs [68]. The effectiveness of other cytotoxic drugs, except docetaxel and pemetrexed, in second-line treatment has not been proven. Second-line treatment can only be used in patients who are in good PS and without persistent complications of previous CHT. Pemetrexed in second-line treatment is slightly more effective than docetaxel in patients with non-squamous-cell carcinoma [67].

Molecularly targeted treatment

The use of EGFR tyrosine kinase inhibitors in second-line treatment after previous CHT is justified only in patients with *EGFR* gene mutation. In the case of patients with *ALK* and *ROS1* gene rearrangement, it is justified to use crizotinib. Molecular disorders should be determined on the basis of reliable tests (optimally simultaneously within one medical order). The duration of treatment should depend on its tolerance and outcomes.

In patients with *EGFR* gene mutation, in whom one of the EGFR tyrosine kinase inhibitors (afatinib, erlotinib or gefitinib) was used as first-line treatment, and the disease progressed after remission, the T790 mutation in exon 20 of *EGFR* gene should be tested (liquid biopsy or re-sampling of tissue material) [69]. Phase III clinical trial in patients with this mutation, showed superiority of osimertinib compared to chemotherapy — median dura-

tion of progression-free survival was 10 and 4 months, respectively (reduction of relative risk by 70%) [70].

In patients with *ALK* gene rearrangement, ALK tyrosine kinase inhibitors are the treatment of choice (this therapy is currently not reimbursed in Poland in the first line).

In patients with *ALK* gene rearrangement and disease progression during the first line of CHT, the use of crizotinib allows prolongation of progression-free survival by five months and a reduction in relative risk of disease progression or death by 51% compared to docetaxel or pemetrexed [71]. In phase III study, crizotinib was compared to brigatinib (ALK tyrosine kinase inhibitor second generation) in patients who had not previously received anti-ALK therapy (27% of patients had previously received CHT). In the group of patients who were previously treated with CHT, the risk of disease progression or death was 65% lower after brigatinib treatment [72]. Brigatinib is registered in the second line treatment for patients with *ALK* gene rearrangement (in Poland this indication is not covered by reimbursement).

In the case of failure of first-line treatment using crizotinib, ceritinib is highly effective [73] (this treatment is currently not reimbursed in Poland).

The efficacy of dabrafenib (BRAF kinase inhibitor) and trametinib (MEK kinase inhibitor) was assessed in phase II study in patients with NSCLC with *BRAF V600E* mutation after failure of previous systemic treatment. The median progression-free survival and objective responses rate were 9.7 months and 63.2%, respectively. Treatment with dabrafenib and trametinib in patients with *BRAF V600E* mutation is currently not reimbursed in Poland [74].

The use of docetaxel in combination with nintedanib (an anti-angiogenic drug) in patients with advanced adenocarcinoma with progression after previous multi-drug CHT with the use of platinum derivatives reduced the risk of death by 25% in comparison with docetaxel monotherapy [75]. The benefits associated with the use of nintedanib and docetaxel were related to patients with so-called early chemoresistance (disease progression on treatment and during the first three months from the end or nine months from the start of CHT).

Immunotherapy

Phase III clinical trial results showed that anti-PD-1 drugs (nivolumab and pembrolizumab) and anti-PD-L1 (atezolizumab) used in second-line treatment for NSCLC patients (both squamous- and non-squamous-cell carcinoma) are more effective than docetaxel. In the case of squamous-cell carcinoma, the use of nivolumab compared to CHT was associated with a 41% reduction in the relative risk of death, regardless of PD-L1 expression [76]. In patients with non-squamous-cell carcinoma, the decrease of relative risk of death compared with docetaxel was 27% with nivolumab [77] and atezolizumab [78] and 33% with pembrolizumab (the difference in favour of pembrolizumab was highest in patients with PD-L1 expression on at least 50% of cancer cells — 47%) [79].

Radiotherapy

In patients with advanced NSCLC and signs and symptoms in chest indicate a good results after palliative RT, which can be used in various regimens (e.g. 20 Gy in five fractions in five days, 30 Gy in 10 fractions in 12 days or 16 Gy in two fractions of 8 Gy with one-week interval).

The indications for palliative RT are also symptomatic metastases in the CNS or bones. In selected cases of airway obstruction due to endobronchial tumour growth, valuable palliative treatment may be endobronchial brachytherapy, resection of the obliterating mass with the use of laser or insertion of endobronchial prosthesis (stent), which can also be used in the case of bronchial outside pressure.

Anti-osteolytic treatment

Bone metastases occur in 30–40% of patients with NSCLC. The results of the phase III trials showed that the use of zoledronic acid [80] or denosumab [81] in patients with advanced NSCLC with bone metastases may prevent or delay bone complications. Analysis of subgroups in a study using denosumab in various cancers, in addition to the anti-osteolytic effect, also showed an increase in survival in a subset of NSCLC patients [81].

Pleurodesis

In patients with recurrent pleural effusion, a good palliative effect gives the use of pleurodesis (especially with the use of talc).

Treatment of patients with a single metastasis

In the case of primary cancer diagnosed together with a single metastasis, treatment with a radical intention may be considered, but it is necessary to carry out a detailed assessment of the extent of the disease using PET-CT.

In patients with a single adrenal metastasis, in whom complete excision of the primary lesion is possible, adrenalectomy may be considered, followed by pulmonary resection (in the case of localisation of lung cancer and adrenal metastasis on the left side, simultaneous excision of both lesions from transdiaphragmal approach during thoracotomy could be performed). Treatment of primary chest changes should be carried out according to the previously presented principles [82].

A similar procedure (excision of metastasis with irradiation of the postoperative area and pulmonary resection in the second stage) may be considered in

patients with a single brain metastasis. If CNS metastasis excision or radical treatment of primary tumour in the chest is not feasible, RT of metastasis (if possible stereotactic irradiation) is indicated in the first step, followed by treatment of the primary lesion according to the previously presented principles [82].

The presence of a single cancer lesion in the second lung (so-called synchronous cancer) — depending on the location and other factors — is not a contraindication to radical treatment (primarily resection).

Recommendations

— In patients with disseminated non-small-cell lung cancer, the choice of treatment method depends on clinical and pathomorphological and molecular characteristics (I, A).
— Patients with disseminated non-small-cell lung cancer with EGFR mutations should receive one of the EGFR tyrosine kinase inhibitors as part of the first-line treatment (I, A).
— Patients with non-small-cell lung cancer with ALK gene rearrangement should receive one of the ALK tyrosine kinase inhibitors in the first-line treatment (I, A).
— Patients with disseminated non-small-cell lung cancer with the presence of PD-L1 expression at 50% or more of the percentage of cells should receive pembrolizumab in the first-line treatment (I, A).
— Patients with metastatic non-small-cell lung cancer without *EGFR* mutation and with PD-L1 expression less than 50% should receive chemotherapy in the first line (regimens containing two drugs including cisplatin or — in justified situations — carboplatin, and monotherapy may be considered only in selected clinical situations) (I, A).
— Patients with metastatic non-small-cell lung cancer the use of bevacizumab or cetuximab in combination with chemotherapy is not justified (I, A).
— The second-line treatment of patients with disseminated non-small-cell lung cancer depends on the clinical-pathomorphological characteristics, the effects of earlier systemic therapy and molecular characteristics. In this group the following therapy modalities should be considered: chemotherapy (docetaxel or pemetrexed), docetaxel in combination with nintedanib, first- or second-generation EGFR inhibitors in patients who have not received these drugs in first line, or osimertinib in patients previously treated with the first- or second-generation EGFR inhibitors, ALK inhibitors (crizotinib in case of *ALK* gene rearrangement), immunotherapy (nivolumab or pembrolizumab), palliative radiotherapy, or symptomatic treatment (I, A).
— In selected patients with non-small-cell lung cancer with a single metastasis, treatment with a radical intention may be considered (III, B).
— In the case of progression in a single area with simultaneous response in other tumour lesions during the treatment with EGFR or ALK inhibitors, continuation of current systemic therapy in combination with local management (resection or radiotherapy) should be considered) (III, B).
— In patients with metastatic non-small-cell lung cancer with bone metastases, zoledronic acid is recommended (I, B).
— In patients with disseminated non-small-cell lung cancer and with chest problems or signs and symptoms related to metastases, palliative radiotherapy should always be considered (I, A).
— In patients with non-small-cell lung cancer with recurrent pleural effusion, it is advisable to perform pleurodesis with talc (II, A).

Small cell lung cancer — primary treatment

Chemotherapy

Chemotherapy is the essential method of treatment for patients with SCLC. The regimen of choice is a combination of cisplatin with etoposide (PE scheme) in various modifications (e.g. cisplatin 80 mg/m^2 — day 1 or 30 mg/m^2 — day 1, 2, and 3 and etoposide 100 mg/m^2 — day 1, 2, and 3, every 21 days) [83]. The limitation for the use of the PE regimen is the coexistence of renal dysfunction — then cisplatin can be replaced with carboplatin (in a dose calculated according to Calvert's formula for AUC 6) [83]. The less effective and currently rarely used regimen is a combination of cyclophosphamide, doxorubicin and vincristine or etoposide (CAV or CAE scheme: cyclophosphamide 1000 mg/m^2 — day 1, doxorubicin 45 mg/m^2 — day 1, vincristine 2 mg — day 1) or etoposide 80 mg/m^2 — day 1–3, every 21 days). Anthracyclin-containing chemotherapy is contraindicated in patients with significant cardiovascular disorders and cannot be used simultaneously with chest X-ray [84, 85].

Standard treatment includes 4–6 cycles of CHT. Unjustified dose reduction and prolonged intervals between cycles should be avoided. There is no justification for the alternate use of different CHT regimens, maintenance therapy, and treatment intensification [85].

The phase III IMpower133 trial compared first-line chemotherapy with carboplatin and etoposide with or without atezolizumab in patients with stage IV SCLC — the overall survival time was two months longer (median — 12.3 and 10.3 months) in the case of treatment with a PD-L1 inhibitor [86]. Atezolizumab in combination with CHT in patients with SCLC is not yet reimbursed.

Radiochemotherapy

In patients with a localised SCLC (stages I–III according to TNM classification), determined on the basis of correctly performed initial diagnosis, it is advisable to use simultaneous CHT (the combination of cisplatin and etoposide is a regimen of choice) and chest irradiation. Simultaneous RCHT compared to the sequential use of both methods increases the chance of cure or long-term remission with prolonged survival, but at the expense of severe acute radiation reactions [87]. If CHT and RT cannot be started simultaneously, it should be attempted to start RT no later than simultaneously with the second cycle of CHT [88]. The use of simultaneous RCHT should not reduce the due intensity of CHT [88, 90].

Only patients in good condition and without other factors that increase the risk of serious complications are eligible for RCHT. Chemo-radiotherapy is not used in patients with pulmonary lymphangiosis and/or pleural effusion and in situations when the lesion could not be encompassed by RT because of its significant dimensions.

The irradiated area includes primary lesion and metastatic local lymph nodes as well as the area of adjacent unchanged lymph nodes. Currently, RT conventionally fractionated at a dose of 60–66 Gy — 30–33 fractions or hyperfractionated (45 Gy in two fractions of 1.5 Gy per day for three weeks, minimum interval between fractions — six hours) is recommended. It is also recommended to use modern RT techniques (similar to NSCLC) [87].

The results of the phase III study show that the use of chest irradiation (30 Gy — 10 fractions) after achieving an objective response to CHT in patients with stage IV SCLC increases the time to disease progression and two-year survival rate (13% *vs*. 3%) [89]. Benefits are observed primarily in patients with cancer dissemination limited to the chest organs. These observations justify the consideration of chest irradiation also in patients with stage IV SCLC after achieving a response to CHT.

In patients with localised (stage I–III) and extensive (stage IV) cancer, who have responded to RCHT or CHT, elective cranial irradiation allows a reduction in the risk of brain metastases and extension of the survival time [90, 91].

Surgical treatment

Surgical treatment in SCLC is used very seldom — it can only be considered in patients with T1N0M0 and in some patients with T2N0M0 cancer (less than 5% of all SCLC patients). Surgical treatment is preceded by a full assessment of tumour burden (including mediastinoscopy). If the diagnosis of SCLC is established intraoperatively and there is a possibility of radical excision of the lesion, the lobe is removed and a radical lymphadenectomy is performed (pneumonectomy is not recommended because extensive surgery make subsequent CHT difficult to use). Surgical treatment should always be completed with full CHT (4–6 cycles), and in the presence of metastases in the lymph nodes, additional RT should be considered. In all cases, elective cranial irradiation is used [92].

Surgical treatment (excision of persistent lesions after a partial response following CHT) is also used in selected patients with a mixed form (SCLC and NSCLC) [92].

Small cell lung cancer — treatment at relapse

The treatment of patients with recurrent SCLC after previous CHT or RCHT depends on the effectiveness of the first-line therapy and performance status.

In patients with relapse of SCLC after at least three months after completion of CHT with objective response, an attempt can be made to re-use the original regimen. In patients who did not respond to first-line treatment or in whom remission lasted less than three months, the chance of achieving a response after second-line treatment (e.g. CAE or CAV regimen after prior use of the cisplatin and etoposide regimen) is low. In patients with good performance status, topotecan monotherapy can be used (1.5 mg/m^2 intravenously — day 1–5, every 21 days) [85].

In case of progression limited to the brain, the choice of treatment method (CHT or RT) depends on the patient's condition, previous treatment, and the intensity of neurological symptoms.

The number of second-line CHT cycles depends on the tolerance of the treatment and the objective benefits obtained. In selected cases palliative RT is used.

Recommendations

— In the majority of patients with small-cell lung cancer in stage I–III, concomitant chemoradiation should be used, or, in the case of contraindications, chemotherapy and radiotherapy should be administered consecutively (I, A).
— In patients with small-cell lung cancer, a chemotherapy regimen consisting of cisplatin and etoposide should be used (I, A).
— Surgical treatment of patients with small-cell lung cancer can only be considered in stage T1–2 N0 (III, A).
— In patients with small-cell lung cancer in stage I–III with response to chemoradiotherapy or chemotherapy, elective central nervous system irradiation should be used (at a dose of 25 Gy in 10 factions, treatment should be started within 2–5 weeks after completion of radiochemotherapy or chemotherapy) (I, A).
— In patients with stage IV small-cell lung cancer, chemotherapy should be used, and if response is achieved, elective irradiation of central nervous system (I, A) and — in selected patients — chest irradiation should be considered (I, B).

— Before the irradiation of the central nervous system, magnetic resonance imaging of the brain is advisable (II, B).
— The management of relapsed small-cell lung cancer patients depends on the clinical characteristics and benefits obtained during the initial treatment (options — second-line chemotherapy, palliative radiotherapy, or symptomatic care) (II, A).

Follow-up after treatment

The aim of observation in patients with lung cancer treated with radical intention is early detection of relapse, complications of treatment, and independent primary cancer. The results of a prospective, randomized study showed no differences in terms of overall survival in patients who after pulmonary resection in stages I–III were monitored using CT scans performed at 3-, 6- and 12-month intervals [93]. There is no indication for active search for asymptomatic metastases in other organs (abdominal cavity, brain, bones) [94]. The schedule of control tests in palliative patients should take into account the individual clinical situation. An interesting solution, potentially increasing the effectiveness of control tests compared to their traditional form, is the electronic reporting of symptoms by patients [95].

Recommendations
— In patients with lung cancer treated with radical intention in the first 24 months after radical treatment, it is recommended to perform a chest CT scan every six months and every 12 months for the following three years (I, B).
— In the remaining patients, the control test schedule should be individualised (III, C).

Malignant pleural mesothelioma

Epidemiological and pathomorphological characteristics

Malignant pleural mesothelioma is the most common primary malignancy originating from submesothelial cells that line the pleura and pericardium. Due to significant diagnostic problems, especially in differentiation, until recently it was difficult to determine the actual incidence of this cancer. Currently the progress of pathomorphological diagnostics (especially the introduction of IHC methods) allows us to establish the diagnosis with greater certainty [97]. Diagnosis and treatment of patients with mesothelioma should be carried out in centres with extensive experience in this field. In recent years pleural mesothelioma has been the cause of approximately 250 deaths in Poland per year [1]. The average age of onset is about 60 years.

Since the introduction of more precise diagnostic criteria, there has been an increase in morbidity (previously, a large proportion of pleural mesotheliomas were considered to be pleural metastases of adenocarcinoma with an undetermined primary lesion location). This tendency also results from the actual increase in incidence, caused by the high exposure to asbestos until now (in the past extensively used in the construction, textile, shipbuilding, and car industries). Direct contact with asbestos can be proven in approximately 70–80% of patients with malignant pleural mesothelioma. The greatest risk concerns people employed in asbestos mines and their families living near mineral deposits, as well as people directly exposed to asbestos during many years of work in the shipbuilding industry [97].

In the histological pattern epithelial and sarcoma components are present. The most common type is epithelioid (about 55%), in which the prognosis is slightly better than in the others. The biphasic type is diagnosed less frequently (about 30%), and the least common (about 15%) is the sarcomatoid type, characterised by an especially aggressive course [98].

Diagnostics

Diagnostics include recognition of pleural lesions, confirmation of their malignant character, differentiation with metastases of another cancer, and burden assessment. For this purpose, close co-operation of the pathologist, radiologist, and clinician is necessary. An appropriate volume of material sample should also be obtained for IHC studies (Figure 5). In the majority of patients, mesothelioma is diagnosed at the local and regional stage (metastases in distant organs are relatively rare).

Medical history

Medical history includes an interview for exposure to asbestos and symptoms associated with the localisa-

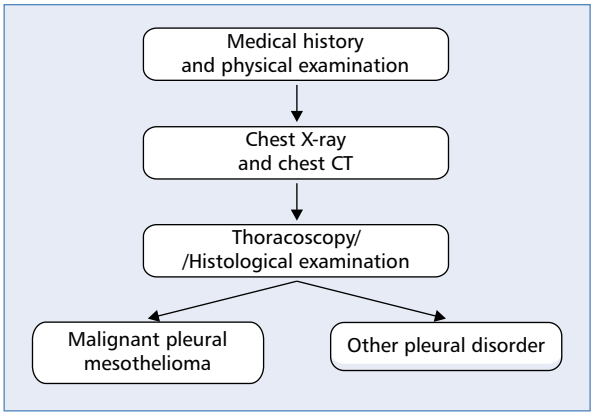

Figure 5. Principles of diagnostic procedures in malignant pleural mesothelioma. CT — computed tomography

tion of primary lesion and local spread along the pleural surface (chest wall pain, dyspnoea, signs of threatening cardiac tamponade).

Physical examination

Physical examination consists in a typical assessment of respiratory system and chest condition.

Imaging examinations

The result of a conventional chest X-ray can only be the basis for mesothelioma suspicion. An absolutely essential method of mesothelioma imaging (especially in the assessment of its extent and degree of chest wall, pericardium, and diaphragm infiltration) is CT scan. In a few patients who potentially qualify for surgery with radical intention, MR may be helpful. The PET-CT examination is not applicable except in situations where treatment with radical intention is considered [98]. Performing earlier pleurodesis significantly hinders the interpretation of the results of the PET-CT examination.

The most common radiographic symptoms include:
— pleural thickening;
— nodular mass on pleural surface;
— pleural effusion;
— infiltration of chest wall;
— pericardium infiltration;
— diaphragm infiltration.

Pathomorphological evaluation

In pathomorphological diagnosis, it is essential to distinguish malignant mesothelioma from benign mesothelial and other malignant tumours, as well as to determine its histological type (epithelioid, biphasic, or sarcomatoid). Diagnosis is based on histological evaluation and IHC assays (assessment of specific protein in mesothelioma cells — calretinin, vimentin, cytokeratin, mesothelin, thrombomodulin, osteopontin), including clinical data [96, 99]. The material for histopathological examination is most often obtained by means of thoracoscopy; during the procedure a lot of excisions from suspicious pleural lesions should be taken. Pleural mesothelioma should not be recognised solely on the basis of cytological examination of pleural effusion or material obtained with fine-needle aspiration [96, 97].

Staging

In the assessment of malignant pleural mesothelioma, the UICC classification from 2017 applies (Table 6, 7) [19].

Treatment

Patients with malignant pleural mesothelioma should be treated only in specialised centres with ex-

Table 6. Staging of malignant pleural mesothelioma (UICC, 2016) [19]

Feature	Characteristics
Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement
T2	Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: — involvement of the diaphragmatic muscle — extension of tumour from the visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: — involvement of the endothoracic fascia — extension into the mediastinal fat — solitary, completely resectable focus of tumour extending into the soft tissue of the chest wall — non-transmural involvement of the pericardium
T4	Locally advanced, technically unresectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: — diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction — infiltration of the rib — direct diaphragmatic extension of the tumour to the peritoneum — direct extension of the tumour to the contralateral pleura — direct extension of the tumour to a mediastinal organ — direct extension of the tumour into the spine — tumour extending through to the internal surface of the pericardium with infiltration of full thickness of the pericardium, with cancer cells in a pericardial effusion or tumour involving the myocardium — infiltration of brachial plexus
Lymph nodes	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastases
N1	Metastases present in one or more ipsilateral intrapulmonary, hilar, or mediastinal lymph nodes
N2	Metastases in the contralateral lymph nodes, ipsilateral or contralateral supraclavicular, and/or area of oblique muscles lymph nodes
Metastases	
M0	No distant metastasis
M1	Distant metastasis present

Table 7. Stages of malignant pleural mesothelioma (UICC, 2016) [19]

Stage	T	N	M
IA	T1	N0	M0
IB	T2, T3	N0	M0
II	T1, T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1, T2, T3	N2	M0
	T4	Any	M0
IV	Any	Any	M1

tensive experience in this field and the possibility of using all methods of diagnosis and treatment (surgery, RT, and CHT).

Radical surgical treatment is possible only in the epithelioid histological type in stages I, II, and III (without N2 feature), after careful qualification including the assessment of performance status, tumour burden, and the coexistence of other diseases (especially cardiovascular diseases). Before qualification for radical treatment, mediastinoscopy is necessary [100, 101]. Radical resection can be achieved with extrapleural pneumonectomy (excision of the lung and pulmonary and parietal pleura) and removal of half of the diaphragm and pericardium with their reconstruction. An alternative procedure is pleurectomy and decortication (resection with lung sparing — removal of the pleura with or without partial excision of diaphragm and pericardium). In both cases, dissection of mediastinal lymph nodes is most often performed. The choice of surgical treatment method is a subject of controversy - extrapleural pneumonectomy seems more justified in patients with lower risk of relapse and with very good or good performance status and absence of other diseases of clinical significance, but it is much more burdensome [101]. In some patients undergoing radical resection, complementary CHT and RT are used, but the value of these methods has not yet been unequivocally verified.

Palliative treatment methods to prevent the accumulation of neoplastic effusion include pleurectomy or pleurodesis (preferably with talc). The results of randomised study showed better local control of pleural effusion with the use of videothoracoscopic pleurectomy, but this procedure has no effect on overall survival [102].

In some patients (particularly with epithelioid type) who are not eligible for resection, moderate prolongation of survival and periodic symptoms alleviation can be achieved after use of palliative CHT. Only patients in good performance status with feasible objective response assessment are eligible for treatment.

The highest efficacy in mesothelioma is demonstrated by some antimetabolites (pemetrexed, gemcitabine, and raltitrexed) and cisplatin, doxorubicin, and vinorelbine. The most effective one is a regimen composed of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) — both drugs on the first day of the cycle repeated every three weeks [103]. Assessment of CHT effectiveness requires the use of modified RECIST criteria, which results from the plane character of changes in the mesothelioma and the frequent coexistence of pleural effusion. Selected patients (good performance status, lack of persistent effects of earlier treatment) may have a short-term benefit from the second-line CHT (e.g. vinorelbine, doxorubicin, gemcitabine) [104].

The results of randomised trials indicate that the addition of anti-angiogenic drugs — bevacizumab [105] or nintedanib [106] — increases the effectiveness of CHT with the use of cisplatin and pemetrexed. Neither drug is reimbursed in Poland for the treatment of patients with pleural mesothelioma.

Radiotherapy in mesothelioma is used:
— as post-operative treatment in patients in stages I–III (postoperative RT), but in some patients in combination with CHT;
— as palliative treatment to reduce the symptoms associated with locally advanced tumour.

The development of RT techniques, in particular the introduction of intensity modulated radiation therapy (IMRT), increased the precision and safety of treatment and enabled the use of higher doses. As a result, this led to a reduction in the risk of local tumour recurrence after surgery and a slight improvement in survival rates. The use of modern RT can be considered as part of combined treatment (postoperative RT and CHT) [107].

In patients who are not eligible for CHT, symptomatic management is warranted.

Follow-up after treatment

Depending on treatment assumption, observation of patients includes medical history and physical examination and — due to the risk of local recurrence — chest CT scan.

Recommendations
— Standard imaging study for suspected malignant pleural mesothelioma is chest computed tomography (IV, A).
— The basis for diagnosis of malignant pleural mesothelioma should be the result of histological examination of the material (numerous sections) sampled during thoracoscopy and immunohistochemical assays of markers specific for mesothelioma (IV, A).
— If malignant mesothelioma is diagnosed, it is necessary to determine the histological type (IV, A).
— In patients with malignant pleural mesothelioma in stages I–III, after exclusion of N2 feature, the possibility of complete resection should be considered.

If this is not feasible, the surgical procedure should be aimed to control the accumulation of pleural effusion (pleurodesis or decortication) (II, B).
— In patients with advanced mesothelioma, chemotherapy should be considered (a regimen containing cisplatin and pemetrexed) (I, A).
— In selected patients with advanced mesothelioma, the use of second-line chemotherapy may be considered (II, B).
— In patients with malignant pleural mesothelioma, radiotherapy should be considered as part of combined treatment involving surgery and chemotherapy. Radiotherapy can also be considered in palliative treatment (II, B).

Mediastinal malignant tumours

Epidemiological characteristics

Mediastinal tumours are rare (less than 1.5% of all cancers) [1]. In adults, thymoma and thymic carcinomas are most common, and in children the neoplasms of neural origin. The organ origin of mediastinal tumours determines their location (adults — most often in anterior part; children — in posterior part).

Mediastinal lymphomas are discussed in detail in the part of the diagnostic-therapeutic guidelines dedicated to lymphomas.

Many lesions located in the mediastinum are benign, and among malignant tumours more often are metastases from other locations. It is always necessary to carry out detailed diagnostics (histological evaluation and staging).

Primary thymic tumours

Primary thymic tumours originate from epithelial cells and are characterised by T-lymphocyte proliferation of different intensity. Thymic tumours — in contrast to lymphomas and germ-cell tumours — are usually characterised by relatively slow development. Approximately half of the patients have general symptoms (usually paraneoplastic syndromes) [108]. The most common is myasthenia gravis (about 30% of patients), less frequently aplastic anaemia, neuropathy, and disorders of the immune system. Thymomas with symptoms of myasthaenia are characterised by a better prognosis (probably due to earlier diagnosis) [109, 110].

Thymic tumours show a tendency to infiltrate adjacent structures (lung, pleura), while metastases in distant organs are rare.

Diagnostics

Diagnostic goals include establishing the diagnosis and determining the extent of the disease. The complexity of mediastinal tumours makes it necessary to cooperate with many specialists (specialist in radiodiagnostics, pathomorphologist, pneumonologist, thoracic surgeon, oncologist, and — in the case of myasthenia gravis — a neurologist).

In addition to medical history and physical examination (including assessment for paraneoplastic symptoms), CT scan should be performed (radiographs of anterior mediastinum usually show a circular or oval opacity with clear borders). In addition, serum markers (AFP — alpha-fetoprotein and beta-HCG — the beta subunit of human placental gonadotropin) should be assessed to differentiate from embryonal tumours. Due to the low incidence of metastases in distant organs, PET-CT scan are of limited usefulness [110].

Pathomorphological diagnosis

The need to perform a biopsy depends on the results of imaging tests and clinical status (e.g. characteristic changes in CT scan qualifying for radical excision in patients with myasthaenia do not require a preliminary biopsy; in other cases the material should be sampled) [111].

The current WHO classification includes thymic epithelial cell morphology and the number of T lymphocytes, and distinguishes six types of thymomas with different prognoses [112]:
— A — thymoma with no nuclear atypia, and accompanied by few, if any, non-neoplastic lymphocytes;
— AB —type A thymoma admixed with foci rich in non-neoplastic lymphocytes;
— B1 — thymoma with features of functional thymus with large numbers of cells that have an appearance almost indistinguishable from normal thymic cortex;
— B2 — thymoma with scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of non-neoplastic lymphocytes;
— B3 — thymoma predominantly composed of epithelial cells that have a round or polygonal shape and that exhibit no or mild atypia;
— C — thymic carcinoma.

The prognosis for patients with type A, AB, and B1 thymomas is significantly better compared to the other types, with radical excision being the decisive factor in all types.

Staging

The most frequently used classification of thymic cancer includes the degree of infiltration and the presence of metastases (Table 8–10) [112].

Treatment

Treatment of patients with thymic tumours should be carried out in specialized centres with documented experience and all therapeutic options available. The primary method of treatment in stages I and II is

a complete resection, which in selected patients can be supplemented with RT and/or CHT [113]. In patients with myasthenia before surgery, the neurological status should be assessed (the risk of myasthenic crisis).

Surgical treatment consists of complete macroscopic and microscopic excision of the thymus and adipose tissue of the anterior mediastinum via sternotomy approach and cervical incision (less invasive methods — e.g. videothoracoscopy — are less effective). Patients after complete resection of the thymomas in stage I do not require additional RT or CHT. Postoperative RT should be considered in thymomas in stage IIB and histological type B2 or B3 (other patients in II stage do not require RT). Post-operative RT is routine management in thymomas in advanced stage III and IVA and in the case of non-radical resection. The total dose of RT is 45–50 Gy after complete excision and 50–54 Gy after incomplete excision, with dose escalation (boost) up to 60–66 Gy in the area with probable presence of persistent cancer. The irradiated area should include a thymic lodge with an appropriate margin. In thymic carcinoma complementary RT (50–54 Gy with boost up to 60–66 Gy in the area at risk of recurrence) is used in stages II–IVA [113, 114]. It is recommended that modern RT techniques be used — similar to those in lung cancer.

At the locally advanced stage (stages III and IVA) combined treatment is recommended, including initial CHT, resection (then possible in 50–70% of patients), and post-operative RT [113, 115]. In patients who do not qualify for a complete resection, RCHT is used [115].

Table 8. The Masaoka-Koga Stage Classification for Thymic Malignancies [112]

Stage	Characteristics
I	No capsular invasion
IIA	Microscopic capsular and fatty tissue invasion
IIB	Macroscopic capsular invasion
III	Macroscopic invasion of neighbouring organs
IVA	Pleural or pericardial dissemination
IVB	Distant metastases outside chest

Table 10. Stages of thymic tumours (UICC, 2016) [19]

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any	N1	M0
	Any	N0, N1	M1a
IVB	Any	N2	M0, M1a
	Any	Any	M1b

Table 9. TNM classification of thymic tumours (UICC, 2016) [18]

Feature	Characteristics
Primary tumour	
T1	Encapsulated tumour or extending into the anterior mediastinal fat; possible infiltration of mediastinal pleura
T1a	Tumour with no infiltration of mediastinal pleura
T1b	Tumour with infiltration of mediastinal pleura
T2	Invasion to the pericardium (both parietal and full pericardial thickness)
T3	Tumour infiltrating at least one of the following structures: lung, brachiocephalic vein, superior vena cava, diaphragmatic nerve, chest wall, extrapericardial pulmonary veins, or pulmonary artery
T4	A tumour infiltrating at least one of the following structures: aorta, aortic arch vessels, intrapericardial pulmonary veins, or pulmonary artery
Lymph nodes	
NX	Metastases in lymph nodes cannot be assessed
N0	No metastases in lymph nodes
N1	Metastases in anterior (perithymic) lymph nodes
N2	Metastases in deep intrathoracic or cervical lymph nodes
Metastases	
M0	No distant, pleural, or pericardial metastases
M1	Distant or pleural or pericardial metastases
M1a	Pleural or pericardial metastases
M1b	Distant metastases (including lungs)

Thymomas show relatively high chemosensitivity (70–100% of objective responses) — CHT is used in combination with local treatment or alone [116]. The following regimens are most often used:

— CAP — cisplatin 50 mg/m^2 IV — day 1
doxorubicin 50 mg/m^2 IV — day 1
cyclophosphamide 500 mg/m^2 IV — day 1
cycles every 21 days
— ADOC — cisplatin 50 mg/m^2 IV — day 1
doxorubicin 40 mg/m^2 IV — day 1
vincristine 0.6 mg/m^2 IV — day 3
cyclophosphamide 700 mg/m^2 IV — day 4
cycles every 21 days
— PE — cisplatin 60 mg/m^2 IV — day 1
etoposide 120 mg/m^2 per day IV — day 1, 2, and 3
cycles every 21 days

Follow-up after treatment

In patients undergoing radical treatment (resection with or without adjuvant therapy) for stage I or II thymic tumour, the first CT scan should be performed after three months, followed by every 12 months for the first five years and then every two years. For patients treated for stage III or IVA thymomas and for thymic cancer, CT scans should be repeated every six months for two years and then every 12 months. Observation is recommended for at least 10 years [113].

Other mediastinal tumours

Germinal neoplasms of the mediastinum in 90% concern men, and they are divided into seminomas and non-seminomas (in women germinomatous and non-germinomatous germ-cell tumours, respectively). Most often they are located in anterior mediastinum (this is the most common — apart from the gonads — localisation of germ-cell tumours). Symptoms of germinal tumours of the mediastinum occur earlier than in thymomas. Prognosis of patients with germ-cell mediastinal tumours is worse than in the same tumours located in the gonads. The treatment of choice is CHT (regimens with cisplatin) and resection of persistent lesions; in some patients diagnosed with seminoma RT is also used [118, 119].

Neoplasms of nervous system origin occur primarily in the posterior mediastinum and most often come from peripheral nerves and ganglia of the vegetative system (malignant nature in 20–30% of cases). Management is based on surgical treatment (RT and CHT are of limited use).

The primary treatment method of mediastinal mesenchymal tumours is also surgical resection [119].

Recommendations

— The standard imaging test for suspected mediastinal neoplasm is chest CT scan (IV, A).
— The basis for diagnosis in mediastinal tumours is a histological examination of material taken through core needle biopsy supplemented with immunohistochemical tests (IV, A).
— The management of thymic tumours depends on the possibility of complete resection (IV, A).
— The indication for postoperative radiotherapy in thymic tumours is clinical stage IIB and histopathological type B2 and B3, as well as stage III and IVA and non-radical resection (IV, A).
— The indication for postoperative radiotherapy in thymic cancer is stage II or higher (IV, A).
— In locally advanced thymic tumours, pre-operative chemotherapy or chemotherapy in combination with radiotherapy should be considered (IV, A).
— Chemotherapy is used for generalised thymic tumours and mediastinal germ-cell tumours (IV, A).
— The management of mediastinal germ-cell tumours consists of the use of chemotherapy and resection of persistent lesions (radiotherapy in some cases should also be considered) (IV, A).

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REVIEW ARTICLE

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Management of brain metastases in melanoma

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ABSTRACT

Melanoma is the third malignant cancer after breast and lung cancer in terms of the incidence of brain metastases. Currently, brain metastases are diagnosed in asymptomatic patients using radiological examinations as a part of the follow-up or qualification for systemic treatment. Treatment of melanoma patients with brain metastases is currently one of the biggest challenges in caring for advanced melanoma patients. The aim of this paper is to provide a multidisciplinary guide to diagnostic and therapeutic management of this group of patients. Treatment of melanoma patients with brain metastases includes local treatment and/or systemic therapy as well as symptomatic treatment, depending on the clinical situation. Therapeutic decisions should be made in teams, which should include at least a clinical oncologist, neurosurgeon, and radiation oncologist.

Key words: melanoma, brain metastases, immunotherapy, neurosurgery, radiotherapy, targeted therapy

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Introduction

Melanoma is the third malignant cancer after breast and lung cancer in terms of the incidence of brain metastases. It is estimated that in the course of advanced melanoma, about 50–60% of patients develop cerebral metastases (about 75% of them are initial diagnosis multiple metastases, often asymptomatic). At the time of diagnosis of melanoma, cerebral metastasis are present in 7% of patients. In 3% of patients with metastasis of melanoma in the brain the primary tumour cannot be found. It should be noted that only in 8–46% of melanoma patients metastases to the brain are found intravitally; however, in the autopsy material they are detected in about 75% of cases. In the latest cancer staging system, the eighth edition according to the American Joint Committee on Cancer (AJCC), brain metastases are separated as a last category in stage IV — M1d [1]. The risk of metastasis to the brain increases with the disease stage [2]. Currently, there are no unequivocal prognostic factors in determining the risk of metastases to the central nervous system (CNS) in melanoma patients. Nevertheless, it is known that certain factors are associated with greater risk of CNS metastases (primary focus in the head and neck area, elevated lactate dehydrogenase [LDH], primary tumour ulceration, mutations in the *BRAF*, *NRAS*, and *PTEN* genes) [3]. The presence of brain metastases worsens the prognosis. Brain metastases contribute to death in 20–50% of patients, and symptomatic tumours are the direct cause of death in about 90% of patients. Historically, median overall survival (OS) after diagnosis of brain metastasis was 5–7 months, in symptomatic patients undergoing whole brain radiotherapy (WBRT, currently rarely used) median OS was 2–5 months, and in patients undergoing surgical treatment or stereotaxic radiotherapy (SRS, stereotactic radiosurgery)/radiosurgery was twice as long [4].

The aim of this paper is to present multidisciplinary guidelines on diagnostic and therapeutic management in melanoma patients with brain metastases. This is currently one of the biggest challenges in caring for advanced melanoma patients.

New therapies introduced to everyday clinical practice mean that the current way of proceeding in cases of metastatic melanoma has little in common with clinical practice from five years ago. Increasingly, brain metastases are diagnosed in the asymptomatic stage using routine magnetic resonance imaging (MRI) and/or computed tomography (CT) of the brain as part of the follow-up or staging evaluation before systemic treatment. Advanced SRS techniques have come to the forefront in local treatment. In the last five years, 10 new drugs have been registered in Europe for advanced melanoma treatment: vemurafenib, dabrafenib, trametinib, cobimetinib, binimetinib, encorafenib, ipilimumab, nivolumab, pembrolizumab, and talimogene laherparepvec (T-VEC). In Poland, as part of drug programs, seven novel drugs are currently available within therapeutic (drug) programs — vemurafenib, cobimetinib, dabrafenib, trametinib, ipilimumab, pembrolizumab, and nivolumab. The median OS in the whole group of patients with metastatic melanoma with the presence of *BRAF* mutation treated with pembrolizumab/nivolumab or combination therapy with BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi), based on data from clinical trials, is now around two years (about four times longer than it was five years ago). Perhaps the best results could be achieved with the use of dual immunotherapy (anti-CTLA-4 and anti-PD-1, as indicated by preliminary results) or other combination therapies (e.g., T-VEC + pembrolizumab) or even combinations of BRAFi, MEKi, and anti-PD-1 or anti-PD-L1. It is obligatory to test the *BRAF* mutation in the fixed tissue in each case of confirmed brain metastases (if not done previously) [5, 6].

The basic and applicable rule in the situation of finding brain metastasis from melanoma should be management carried out under multidisciplinary teams whose members have experience in the diagnosis and treatment of melanoma. Such teams should include at least a neurosurgeon, radiation oncologist, and clinical oncologist [7].

Diagnostics

Signs and symptoms of brain metastases can be subtle and difficult to diagnose. They depend among others on the number, size, and location of metastases. Metastases are most often localised in the cerebrum, less often in the cerebellum (15%) and in the brainstem (5%). The most common symptoms include headaches, sometimes with accompanying nausea and/or vomiting, epileptic seizures, speech, comprehension, and vision disorders, numbness, and movement disorders. Occurrence of clinical symptoms related to brain metastases is associated with worse results of treatment. In patients with melanoma in stage I and II, the risk of developing brain metastases is smaller than in patients with stage III and IV [8]. In younger patients, the risk of late development of brain metastases in the case of thicker primary lesions is higher [9]. Based on analysis of data from the S0008 retrospective large multicentre study, the risk of brain metastases in melanoma stage IIIB and IIIC was 15%; they were found mainly during the first three years after surgery [10]. The time from primary tumour treatment can be relatively long — up to 3.4 years (median) [11].

Therefore, in patients with melanoma stage III and IV it is important to detect the brain metastases in the absence of clinical symptoms by using imaging technics. Brain MRI should be the standard of care within the staging process in patients diagnosed with stage IV melanoma. In asymptomatic patients with stage IIIC melanoma and higher, brain CT or brain MRI should be considered [6]. In patients with signs and/or symptoms, including even minor intensities, indicating the possibility of the presence of lesions in the brain it is advisable to perform an MRI scan [12]. Magnetic resonance imaging is the most sensitive test to detect brain metastases and has advantages over contrast-enhanced CT. However, it is less available and more expensive. Therefore, in patients with brain metastases confirmed on CT, MRI can be considered as a complementary test to obtain information necessary to determine further management (number and/or location of lesions). This examination is necessary in the case of clinical symptoms and simultaneous absence of changes in contrast-enhanced CT scan [13]. It should be noted that melanoma brain metastases have a tendency to be multiple and are associated with a high risk of intratumoral bleeding [14].

Therapeutic management

Therapeutic management depends on the clinical situation and includes systemic treatment, local treatment (radiotherapy and/or surgery), or symptomatic treatment. In the treatment of melanoma brain metastases, in addition to clinical symptoms, the numerous parameters related to the disease and patient, such as number, size, and location of metastases, presence and control of extracranial disease, previous melanoma treatment and treatment results, presence of *BRAF* gene mutation, general condition of the patient, age, and co-morbidities and treatment, play an important role. In the symptomatic treatment of brain metastases anti-oedematous drugs are used, including primarily glucocorticoids, but also diuretics (loop diuretics, mannitol) and possibly hypertonic fluids. In the case of an epileptic seizure, anti-epileptic treatment should be

Table 1. Prognostic score RPA (recursive partitioning analysis, n = 1200) [15]

	Class I	Class II	Class III
KPS (points)	≥ 70	≥ 70	< 70
Primary lesion	Controlled	Active	Active
Age	< 65	< 65	Any
Extracranial disease	No	Yes	Yes
Incidence	15%	65%	20%
Overall survival (median)	7.1	4.2	2.3

KPS — Karnofsky Performance Status

Table 2. Prognostic assessment of the survival of melanoma patients with brain metastases — DS-GPA scale (diagnosis-specific Graded Prognostic Assessment) [16]

KPS (points)	< 70	70–80	90–100
Number of brain metastases	> 3	2–3	1
Points	0	1	2

Based on the sum of the number of points awarded for KPS and the number of metastases:

DS-GPA	0–1.0	1.5–2.5	2.5–3.0	3.5–4.0
Median overall survival (months)	3.4	4.7	8.8	13.2

KPS — Karnofsky Performance Status

initiated, remembering about interactions with other medicines used in the patient, including glucocorticoids.

Tables 1 and 2 summarise data on two prognostic scales in patients with brain metastases; the recursive partitioning analysis (RPA) scale refers to all neoplasms, and the DS-GPA (diagnosis-specific graded prognostic assessment) scale exclusively to melanoma patients. However, it must be remembered that these scales were developed before the introduction of new therapies systemic in the treatment of generalised melanoma.

The algorithm of management of melanoma patients with brain metastases is presented in Figure 1.

Local treatment of melanoma brain metastases

In the case of symptomatic melanoma brain metastases, the expected survival without treatment is 2–3 months, and only in 13% of patients OS will be longer than one year (more favourable prognosis in the group of patients below 65 years of age and with Karnofsky scale performance status [KPS] score > 70 points). The removal or irradiation of all metastatic foci has an impact on the prognosis. Leaving one of several lesions means that prognosis is the same as in the case of no treatment [16].

There are still no unambiguous prognostic factors of occurrence of melanoma brain metastases. It is known, however, that certain factors are associated with an increased risk. These include:

— primary focus within the head and neck;
— elevated LDH;
— ulceration of the primary tumour;
— molecular changes in *BRAF*, *NRAS*, and *PTEN* [3].

In patients with brain metastases, *BRAF* mutation occurs in 24–58% of cases, and *NRAS* mutation in 23% of cases.

Surgical treatment

Eligibility criteria for surgical treatment of melanoma brain metastases (EBM [evidence-based medicine], 2010, level 1);

— newly identified, single lesions up to four;
— the size of the lesion precluding SRS (above 3 cm);
— location of the lesion available surgically;
— symptomatic tumours:
  • causing neurological deficits and/or
  • symptoms of increased intracranial pressure due to its volume and / or with an accompanying haemorrhagic focus and/or secondary to obstruction of fluid pathways, leading to hydrocephalus (lesions located in the back bottom of the skull);
— KPS > 70, age < 65 years;
— progression after prior stereotactic radiotherapy.

The goals of surgical treatment

The goals of surgical treatment are as follows:

— histological verification;
— radical excision of all lesions, which has an impact on OS (no justification for performing a biopsy) — it is possible to use hybrid therapy in the case of multiple metastatic tumours — resection of large surgically available lesions in combination with SRS for smaller tumours located in deep brain structures;
— improvement or stabilisation of the neurological condition (occurrence of new neurological deficits shortens OS by four months);
— enabling further oncological treatment;
— resection of symptomatic radionecrotic lesions after SRS.

Irradiation

Stereotactic radiotherapy

Stereotactic radiation consists of delivering a biologically high radiation dose to a precisely defined small volume with a significant decrease of the dispersed

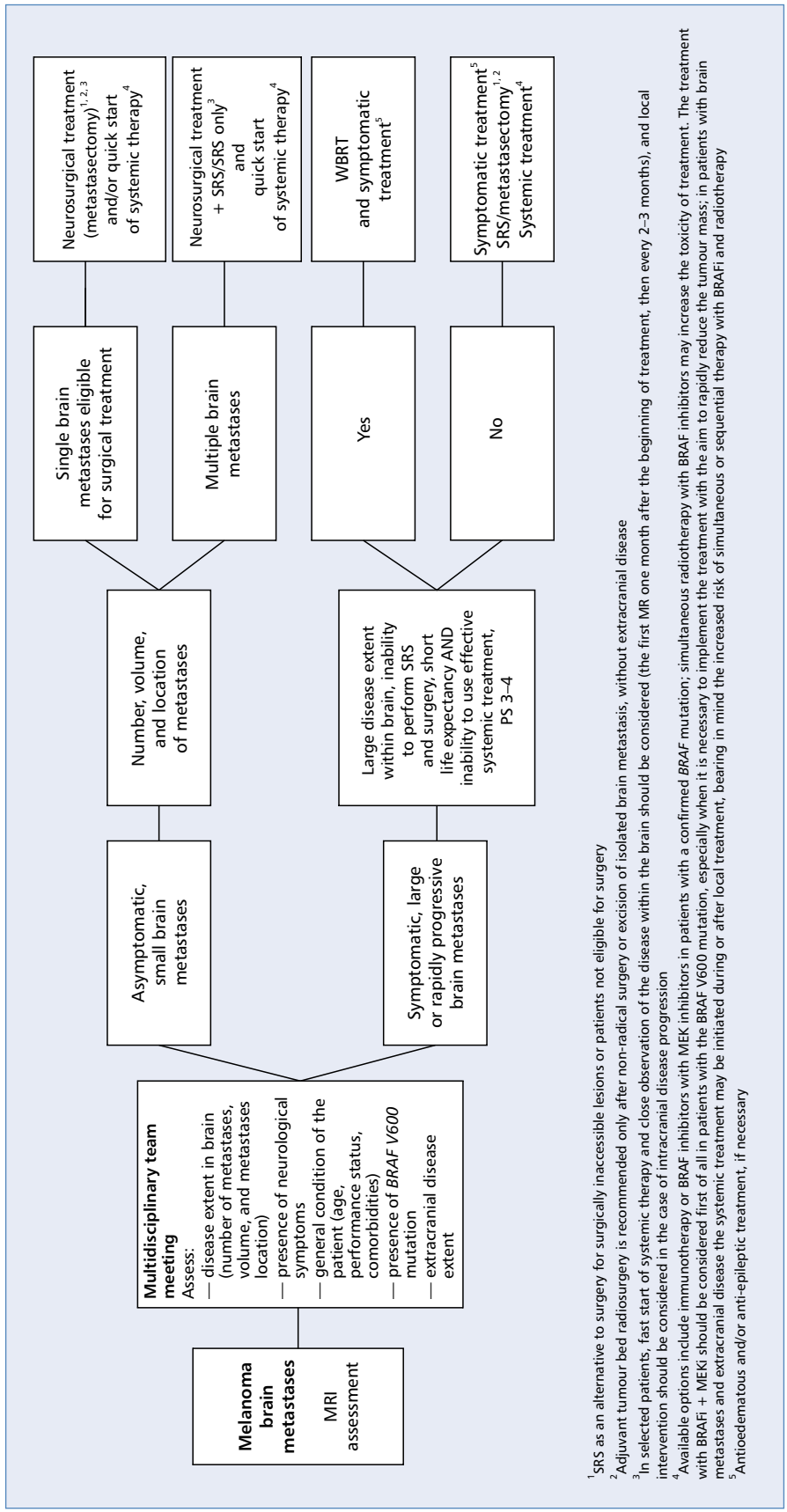

Figure 1. Algorithm for management of patients with melanoma brain metastases

dose outside the target volume. Treatment can be implemented with one fractional dose (radiosurgery) or 3–5 fractions (fractionated stereotactic radiation therapy). Irradiation can be done using several types of equipment dedicated to such treatment (GammaKnife, CyberKnife, EDGE) as well as conventional linear accelerators equipped with high-resolution multi-leaf collimators. The prescribed total dose and the selection of the fractionation regimen depends on the location of the metastatic lesions and their volume. In order to obtain high local efficacy of treatment the aim should be to give the total dose, the value of which, after conversion into a biologically equivalent dose (BED), will be higher than 100 Gy. SRS efficacy in the treatment of small melanoma metastases to the brain has been confirmed in many studies and is similar to that obtained through metastasectomy. Correct qualification of patients for treatment is essential and should be done in multidisciplinary teams.

Qualification for SRS:

— general condition of the patient 0–2 in the scale of the World Health Organisation (WHO);
— single metastasis with a diameter < 3 cm;
— number of metastases > 1, when the total volume of irradiated healthy brain with a dose of 12 Gy does not exceed 10 cm^3;
— no extracranial progression or situation when potentially effective systemic treatment is available;
— irradiation of the post-operative bed [17, 18];
— possible repeated local irradiation in the case of progression;
— life expectancy > 6 months.

Recently, the indications for SRS have been extended, which was originally reserved for patients with one to three brain metastases [22–24]. Optimally the number of lesions should not be greater than five, none of which is more than 3 cm in diameter; however, cautious qualification of patients who do not met such criteria is possible [19]. Currently, the number of metastases is of less importance, and the limitation to stereotactic irradiation has become the volume of all lesions and the volume of the brain that receives the total dose of 12 Gy [25, 26]. It has been proven that the volume of healthy tissue above 10 cm^3 receiving a dose of 12 Gy is associated with a high risk of radionecrosis. In such clinical situations, reducing the therapeutic dose or disqualifying the patient from stereotactic radiotherapy should be considered, as well as qualifying the patient to WBRT, especially in the presence of numerous metastases. With appropriate qualifications local efficacy of SRS (no progression in irradiated volume) can be achieved in 90–95% of melanoma patients [20, 21]. In addition, in half of patients a radiologically significant tumour response has been observed [20]. The local efficacy is closely related to the lesion location and its size.

Whole brain radiotherapy

Melanoma is considered to be a tumour resistant to radiation and sensitive only to higher fractional doses. The fractionation regimens used at WBRT (5 × 4 Gy, 10 × 3 Gy) do not provide an adequate biological dose allowing long-term control of the disease within the CNS. Irradiation of the whole the brain is associated with neurological toxicity. Cognitive function impairment is mainly responsible for the deterioration of the quality of the patient's life [27, 28].

Whole brain radiotherapy should be reserved exclusively for patients:

— with a predicted short survival time;
— in poor condition: WHO 3–4;
— disqualified from surgery and SRS;
— with a large volume of neoplastic lesions within the CNS;
— with their rapid progression and lack of possibility to conduct effective systemic treatment;
— with leptomeningeal metastases, in good general condition.

Patients in very poor general condition (performance status WHO 4) with symptoms of brain oedema that do not yield to anti-oedematous treatment should be disqualified from any form of radiotherapy. Proceeding the choice is to provide symptomatic treatment, such as: effective anti-oedema treatment and antiepileptic, as well as fighting the symptoms often accompanying progression within the CNS.

Systemic treatment

Systemic treatment is the basis of the management of patients with disseminated, including patients with brain metastases. As in the case of molecular targeted therapy (BRAFi and MEKi), the use of immunotherapy, including anti-CTLA4 and anti-PD1 drugs, significantly improves the prognosis of melanoma patients with metastases to the CNS. More and more often long-term remissions in patients who respond to immunotherapy are observed [29]. Depending on previously used treatment, the presence of *V600 BRAF* mutation, and the patient's condition and his clinical situation, the appropriate systemic therapy should be implemented, in the majority of cases supplemented by local treatment. In a situation of a few small metastases in the CNS exclusive systemic treatment remains an option.

Molecular targethed therapy

The efficacy of molecularly targeted drugs (BRAFi/MEKi) in patients with metastatic skin melanoma with brain metastases has been proven in

several prospective clinical trials. In the first clinical trials conducted exclusively in this group of patients the effectiveness of BRAFi monotherapy was assessed. In the largest of them, including as many as 172 patients with asymptomatic metastases, the efficacy of dabrafenib (study phase II BREAK-MB) was assessed. The patients participating in the study were divided into two groups based on the previous local treatment due to brain metastases (without prior local treatment vs. progression after prior local treatment). The intracranial response rates were 39.2% and 30.8%, respectively. The median OS in both groups was over eight months [2]. In a similar clinical trial on the use of vemurafenib in 146 patients with skin melanoma with brain metastases (phase II trial) the intracranial response rate was 18% regardless of previous local treatment. Median OS was about nine months [30]. If we take into account the response assessment done by an independent committee (IRC, independent review committee), the rates of intracranial responses in both these studies were very similar (around 18%). In both studies a high rate of disease control has been shown (about 70–80%). This is due to the fact that the reduction of metastatic lesions in the brain was observed in the majority of patients, but only in some of them were the criteria of partial response met.

A difficult clinical situation is the occurrence of symptomatic brain metastases. This stage of disease is associated with a particularly poor prognosis (median OS 3–4 months). The only clinical trial including only this group of patients concerned the use vemurafenib in monotherapy [31]. This was a small study, including 24 patients not eligible for neurosurgery, after previous treatment due to brain metastases, and requiring the use of glucocorticoids to control symptoms. The percentage of intracranial responses was 16%, and the median OS was 5.3 months. During treatment, a reduction in pain symptoms was observed, improvement of patients' performance status, and reduction of the demand for glucocorticoids. Unfortunately, the treatment effect was short-term, and the disease progressed quickly.

Improvement in the results of targeted treatment has been achieved with combination therapy with BRAFi and MEKi. The only prospective clinical trial evaluating the activity of this therapy in patients with brain metastases is the phase II COMBI-MB study with dabrafenib and trametinib [32]. A total of 125 patients with performance status 0–2 according to the Eastern Cooperative Oncology Group (ECOG) with or without prior local treatment due to brain metastases were enrolled. Intracranial response rate was 56–59% regardless of the previous local treatment and presence of symptomatic metastases. Longer duration of response was observed in patients with asymptomatic brain metastases. The median duration of the response was, however, considerably shorter than that observed in phase III clinical trials without the participation of patients with brain metastases (about 6 months *vs*. 12–14 months) [33–35]. However, no significant differences in treatment tolerance were reported. The most common were fever and gastrointestinal disorders.

The results of the studies mentioned above confirm the activity of BRAFi/MEKi in patients with brain metastases. The response to treatment appears quickly, and the reduction in tumour lesions occurs in the majority of patients. This is not only important for improvement of OS in this group of patients with poor prognosis, but also to improve the quality of life. In particular, this applies to patients with symptomatic brain metastases. Unfortunately, the above data also indicate a short-term therapeutic effect of targeted treatment. Resistance appears faster than in patients without brain metastases. From here, attempts are being made to combine BRAFi/MEKi with other kinase inhibitors or immunotherapy to improve treatment outcomes. Results of studies with BRAFi/MEKi in melanoma patients with brain metastases are presented in Table 3.

Radiotherapy in combination with targeted therapy

High initial BRAFi/MEKi activity in patients with melanoma with brain metastases has slightly changed the approach to the use of radiotherapy. Increasingly used, SRS gives a high rate of local disease control. However, it has not been proven to protect against further disease spreading within the CNS. Therefore, with the exception of patients with isolated metastases to the brain, SRS has little effect on the OS. Therefore, radiotherapy is often used only during BRAFi/MEKi treatment. Data on the purposefulness of combining medicines from the BRAFi group with simultaneous irradiation are contradictory. On the one hand, the potential benefits of such a strategy in the form of sensitisation of melanoma cells to radiotherapy after BRAFi administration has been emphasised, as described in *in vitro* studies [36]. On the other hand, the radiation-sensitising BRAFi action can lead to increased side effects, which has been confirmed by several described case studies of significant skin toxicity during simultaneous use of a combination of irradiation with these drugs, also WBRT. So far no similar radiosensitising effect has been described while using BRAFi with MEKi. There is no clear evidence of increased risk of neurotoxicity, haemorrhage, or radiation necrosis for the combination of targeted treatment with radiotherapy [37–39]. Combination of targeted therapy with radiosurgery to the CNS area gives fewer side effects compared to conventional radiotherapy. In the case of conventional radiotherapy the most common side effect is skin toxicity (more severe when using vemurafenib) [40].

Table 3. Trials dedicated to the evaluation of the efficacy of molecularly targeted therapies in the treatment of melanoma patients with brain metastases

Study	Patients' characteristics	Number of patients	PFS (median, months)	OS (median, months)
II phase study [30] (NCT01378975) vemurafenib	Previously untreated brain metastases	90	3.7	8.9
	Previously treated brain metastases	56	4.0	9.6
Pilot study [31] (NCT01253564) vemurafenib	Previously treated, symptomatic brain metastases	24	3.9	5.3
II phase study BREAK-MB [2] (NCT01266967) dabrafenib	Previously untreated brain metastases	89	~4[a]	~8[a]
	Progression after previous local treatment	83	~4[a]	~8[a]
II phase study COMBI-MB [32] (NCT02039947) dabrafenib + trametinib	Asymptomatic brain metastases without previous local treatment ECOG PS 0–1	76	5.6	0.8
	Asymptomatic brain metastases after previous local treatment ECOG PS 0–1	16	7.2	24.3
	Asymptomatic brain metastases with/without previous local treatment ECOG PS 0–1	16	4.2	10.1
	Symptomatic brain metastases with/without previous local treatment ECOG PS 0–2	17	5.5	11.5

[a]Median for patients with *BRAF V600E* mutation
PFS — progression-free survival; OS — overall survival; ECOG PS — Eastern Cooperative Oncology Group performance status

Irradiation during targeted therapy increases the risk of grade 2 and 3 dermatitis. Its severity depends on the dose of irradiation; therefore, doses ≥ 4 Gy are not recommended in the case of conventional radiotherapy. It is currently recommended that use of BRAFi and MEKi be stopped at least three days before the beginning of radiotherapy and taking the drugs be resumed at the earliest three days after radiotherapy completion [37]. The exception is SRS OUN, in which case a sufficient break in the use of BRAFi and MEKi before and after radiotherapy is one day.

Immunotherapy

Immunotherapy is the main option of treatment in patients with melanoma with CNS metastases in the absence of the *V600* mutation of the *BRAF* gene. In patients with the *BRAF* mutation the decision regarding the choice of using immunotherapy or treatment with BRAFi and MEKi depends on the clinical situation.

In an open-label, phase II clinical trial with ipilimumab (NCT00623766) the highest response rates were observed in asymptomatic patients who did not receive steroids. Based on IRR criteria (immune related response), median intracranial progression-free survival (PFS) was 1.9 months in the asymptomatic group *vs*. 1.2 months in a group requiring glucocorticosteroids due to clinical symptoms of brain metastases, and OS, respectively, 7.0 *vs*. 3.7 months [41]. In the CheckMate 204 study (NCT02320058) with nivolumab and ipilimumab which enrolled patients with melanoma and asymptomatic brain metastases (0.5–3.0 cm) who were not receiving steroids, the primary endpoint was the intracranial clinical benefit (combined endpoint including complete response [CR], partial response [PR], and stable disease [SD] for over six months). The intracranial objective response rate (ORR) was 55% and was CR was 21%. Extracranial responses were similar to those observed in the CNS, and the PFS rate at six months of treatment was 67%. The results of this study confirm that, as in the case of treatment of extracranial disease, in patients with brain metastases it is possible to achieve a similar response to treatment of lesions in the CNS [41]. Similarly, in the Australian ABC study (NCT02374242), in which the efficacy of nivolumab versus nivolumab plus ipilimumab in melanoma patients with brain metastases (n = 79) was investigated, the efficacy of immunotherapy was demonstrated, including the advantage of dual therapy in melanoma patients with asymptomatic brain metastases. In this study, the patients were assigned to three cohorts: cohort A (n = 36,

Table 4. Studies on the effectiveness of immunotherapy in the treatment of patients with melanoma with CNS metastases

Treatment	Patients	Patients' characteristics	IC DCR	IC ORR	IC DOR (months)	mPFS (months)	mOS (months)
IPI: CA184-042 [41]	51 (A) 21 (B)	Asymptomatic Symptomatic	24% 10%	16% 5%	–	1.4 1.2	7.0 3.7
IPI + fotemustine: NIBIT-M1 [43]	20	Asymptomatic	50%	40%	30.3	4.5	12.7
Pembrolizumab: (NCT02085070) [44]	18	Untreated or progressive brain metastases	44%	22%	–	–	NR
NIVO: ABC; CA209-170 [42] (NCT02374242)	27 (B) 16 (C)	Asymptomatic brain metastases without previous local treatment Previously treated or symptomatic	20% 19%	20% 6%	NR NR	2.5 (intracranial) 2.3 (intracranial)	18.5 5.1
NIVO + IPI: ABC; CA209-170 [42]	36 (A)	Asymptomatic brain metastases without previous local treatment	57%	46%	NR	NR	NR
NIVO + IPI: CheckMate 204 [45] (NCT02320058)	75	Asymptomatic, previously treated, ≤ brain metastases	60%	55%	NR	NR	–

IPI — ipilimumab; NIVO — nivolumab; NR — not reached; IC DCR — disease control rate, intracranial disease; IC DOR — duration of response, intracranial disease; IC ORR — objective response rate, intracranial disease; mPFS — median progression-free survival; mOS — median overall survival

a group of asymptomatic patients without local treatment due to brain metastases, receiving ipilimumab with nivolumab); cohort B (n = 27, group of asymptomatic patients without local treatment due to metastases to the CNS, receiving nivolumab); and cohort C (n = 16, patients after local treatment due to brain metastases failure and symptomatic patients with brain metastases and patients with leptomeningeal disease, receiving nivolumab). Complete responses to treatment were observed in 17% of patients in cohort A, 12% in cohort B, and none in cohort C [42]. In the CheckMate 204 study and in the ABC study, grade 3 and 4 treatment-related adverse events in patients receiving dual therapy occurred in 52% and 54% of patients, respectively.

In the situation of the availability of combination therapy with anti-PD-1 plus anti-CTLA-4 (nivolumab with ipilimumab) and in the case of good performance status of the patient this combination is the treatment of choice for asymptomatic melanoma patients with brain metastases.

The results of clinical studies with immunotherapy in patients with melanoma brain metastases are summarised in Table 4.

Combination of radiotherapy with immunotherapy

There are more and more reports related to beneficial effect of combining radiotherapy with immunotherapy. The works published so far have shown an increased incidence of abscopal effect (response of untreated lesions to local treatment of other lesions) after adding radiotherapy to immunotherapy [46]. This is explained by the local stimulation of the immune system and the enhancement of the antigenic effect, where dendritic cells probably play a large role. There are many clinical trials ongoing in which radiotherapy and immunotherapy are combined with each other. There are no contraindications for combining SRS/WBRT with immunotherapy; the decision should be taken at the multidisciplinary meeting individually for each patient. Attention should be paid to the accompanying radiotherapy prophylactic anti-oedema treatment in the form of high doses of glucocorticoids that can reduce the efficacy of immunotherapy. According to current recommendations, indications for glucocorticoids use as part of anti-oedema treatment during SRS are significantly limited.

It seems that combining immunotherapy or molecularly targeted therapy with SRS is generally well tolerated, as demonstrated in the previously conducted clinical trials and analysis. In 2016, the results of the retrospective analysis done in the subgroup of patients participating in two prospective studies with nivolumab for unresectable or metastatic disease were published [47]. Twenty-six patients treated due to melanoma and undergoing SRS due to brain metastases were included in this analysis. The analysis included patients in whom brain metastases were diagnosed and treated with SRS within six months after treatment with nivolumab (before, after, or during immunotherapy). In total 73 lesions

in the CNS were identified in these patients. The primary endpoint of the analysis was treatment tolerability, and secondary endpoints were intracranial disease control and extracranial disease control as well as OS. Most of the metastases were treated using single-fraction radiosurgery, and only 12 lesions in CNS were subjected to fractionated SRS. Grade 2 headaches that resolved after using steroids were observed in one patient. No other neurological complications related to the treatment were observed. In the case of eight lesions in the CNS (11%) the failure of treatment in the form of an increase of lesion volume of by at least 20% was observed. Local control rates after six and 12 months were, respectively, 91% and 85%. The median OS was 12.0 months from the beginning of treatment with nivolumab and 11.8 months from SRS.

In 2017, a systematic review was published dedicated to the assessment of the tolerability of combination treatment with immunotherapy or targeted therapy and SRS. In the overview six retrospective studies and two case studies of patients treated with SRS and ipilimumab were included. Based on the analysis of these data, combination therapy with ipilimumab and SRS for intracranial lesions can be considered as a safe method of treatment [48].

New systemic therapies for melanoma brain metastases

In relation to often short-term or insufficient response to systemic treatment of melanoma in patients with metastases to the CNS, with the use of immunotherapy or molecularly targeted therapy, there are currently attempts to combine BRAFi/MEKi with other kinase inhibitors or immunotherapy to improve the treatment results. An example of such a study is the TRIDeNT study with the use of nivolumab in combination with dabrafenib and/or trametinib in melanoma patients with metastases to the CNS and patients with melanoma with leptomeningeal metastases (NCT02910700) [49].

Surveillance of patients after local treatment of brain metastases and treatment options after progression

Patients undergoing surgical treatment or SRS should be monitored with magnetic resonance imaging of the brain to enable early detection of disease progression. The first MRI scan should be done within one month of surgery/SRS and then every 2–3 months. The imaging test results should be interpreted cautiously, especially in patients undergoing immunotherapy due to the possibility of pseudoprogression and changes after treatment, which can be difficult to distinguish from disease progression. The occurrence of brain metastases from melanoma increases the risk of new metastases in the CNS; therefore, in patients after treatment due to brain metastases from melanoma more frequent brain MRIs are recommended [6]. In about 50% of patients new metastases or progression within previously treated lesions will be detected (recurrence in the lodge, progression after SRS/WBRT) [50]. However, these are not situations disqualifying from further therapy; it is usually possible to use one of the rescue methods of local treatment (surgery, SRS, WBRT) after discussing the patient's case at a multidisciplinary meeting [51–53]. After confirming the progression of lesions in the CNS after SRS or radiotherapy, while retaining the previously described eligibility criteria for neurosurgical treatment, surgical treatment remains the therapy of choice. It can be difficult to distinguish, despite the introduction of modern neuroimaging techniques, whether observed progression is secondary to active cancer or secondary to radionecrosis. In doubtful situations, the treatment of choice should be resection of the lesion because, as well as oncological indications, the removal of necrotic tissues has an antioedematous impact.

Leptomeningeal metastases

The prognosis in this group of patients is bad; survival usually does not exceed a few weeks. Data on the effectiveness of novel systemic treatment in the case of meningitis are limited, and there are no evidence-based treatment standards. Recently published results of retrospective analyses indicate that molecular-targeted therapy and immunotherapy may improve the prognosis in these patients [54, 55]. A phase I clinical trial is being conducted (NCT03025256) with intravenous and intrathecal nivolumab in patients with leptomeningeal disease.

Data on the systemic use of interleukin 2 are encouraging: 1-, 2-, and 5-year survival rates in 43 patients, were 36%, 26%, and 13%, respectively. However, due to the high toxicity of interleukin 2 this is not considered to be the standard of management [56].

WBRT including meninges up to C2 level is a palliative treatment and should be used only in the selected group of patients (good performance status, active systemic treatment).

Summary

The main and valid principle in the situation of brain metastases from melanoma should be multidisciplinary management within the team that includes at least

a neurosurgeon, a radiation oncologist, and a clinical oncologist experienced in melanoma and brain metastases from melanoma treatment. There are no unambiguous risk factors for brain metastases in melanoma patients. The diagnosis of brain metastases is associated with poor prognosis; metastasis to the brain are the cause of death in 20–50% of patients, and symptomatic tumours are the direct cause of death in about 90% of patients. Historical data indicated the median OS after the diagnosis of brain metastases was between five and seven months. Currently, more brain metastases are diagnosed at the asymptomatic stage using routine brain imaging as part of the patient's follow-up and staging evaluation before systemic treatment. Treatment of melanoma patients with brain metastases includes local treatment and/or systemic therapy as well as symptomatic treatment depending on the clinical situation. Advanced SRS techniques have come to the forefront in local treatment. In the last five years 10 new drugs have been registered in Europe for advanced melanoma treatment. Thanks to the introduction of modern systemic therapies the median OS based on clinical trial data has significantly increased. In the situation of the availability of dual anti-PD-1 and anti-CTLA-4 (nivolumab with ipilimumab) blockade and good patient condition, this is the treatment of choice for asymptomatic patients with melanoma brain metastases. In the presence of the *BRAF* mutation and asymptomatic brain metastases from melanoma BRAFi and MEKi systemic treatment can be the first-choice treatment.

Summary of management of patients with brain metastases from melanoma is shown in Figure 1.

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VIA MEDICA

REVIEW ARTICLE

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Odd correlation: Parkinson's disease and melanoma. What is the possible link?

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder, characterised by depletion of dopamine in the striatum and loss of melanin-positive, dopaminergic neurons in the substantia nigra. Melanoma is a skin neoplasm arising from epidermal melanocytes. The epidemiology of melanoma focuses on well-known risk factors such as light skin and hair colour, gender, eye pigmentation, and ultraviolet (UV) exposure. Many studies have suggested an association between Parkinson's disease and melanoma. The mechanism underlying the possible connection between PD and melanoma is not clear and has aroused lots of interest. More interesting is that the link between these two diseases runs both ways. What is the underlying cause of this reciprocal association? Is it due to Parkinson's treatment? Is levodopa the reason for increased incidence of melanoma in people with the neurodegenerative condition? Are there any genetic, immune system irregularities or environmental risk factors that serve as the common denominator between these two conditions? Should we consider melanoma comorbidity with Parkinson's disease and *vice versa*? Some hypotheses include pigmentation changes in melanin and/or melanin synthesis enzyme like tyrosinase hydroxylase, autophagy deficits, disturbed form of metabolically controlled cell death, and changes of PD-related genes such as Parkin or α-synuclein. Learning more about the relationship between PD and melanoma may lead to a better understanding of each disease and contribute to more effective treatments of both.

Key words: Parkinson's disease, melanoma, melanin, dopamine

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease of the central nervous system (CNS), the second most frequent after Alzheimer's disease [1]. Its essence is the loss of substantia nigra in the brain, which is the area responsible for synthesis of dopamine, neurotransmitter necessary for proper functioning of the nervous system. Dopamine deficiency leads to neurotransmission disorders and the occurrence of typical symptoms, including: general slowness of movement, leaning forward, trembling hands (less commonly legs or headaches), problems with movement initiation, difficulty with standing up and performing everyday life activities such as washing, eating, or dressing [2]. The cause of the disease is not fully understood. It probably involves genetic and environmental factors, and the risk of developing the disease increases with age [3]. Epidemiological and toxicological studies emphasise the influence of environmental factors on the development of PD, and genetic studies show the role of specific gene mutations. Parkinson's disease affects up to 1% of the population over 60 years of age. It is a progressive disease that leads to increased dementia, mortality, and risk of death with decreased risk of cancer, except melanoma.

Only symptomatic treatment of PD is possible — it is aimed at improving the patient's quality of life and prolonging surviving for as long as possible in the best physical and mental form. Pharmacological treatment is introduced when the symptoms start to impact the patient's daily functioning. The therapy consists of simulating the function of dopamine as a transmitter (dopaminergic receptor agonists) or its supplementation (levodopa); however, it does not significantly increase patients' overall survival [4].

Melanoma is a malignant tumour from pigmented skin cells — melanocytes — that originate from neural

cells located in body integuments. Melanocytes produce an endogenous pigment melanin that protects the skin against the harmful carcinogenic effects of ultraviolet radiation. Melanocytes are found in the skin and additionally in the eye, mucosal epithelium, and the meninges. Skin melanomas are divided based on the melanocyte transformation site. They account for over 90% of all melanomas (3.7% of melanocytic tumours are localised in the eye, and 1.4% in the mucous membranes) [5]. In recent years, the incidence of melanoma has been constantly increasing worldwide. The annual increase in incidence of this cancer is about 3–7% [6]. The peak of incidence is, on average, at 52 years of age. In Poland, the number of melanoma cases in the last thirty years has increased threefold. Annually over 3000 new cases are found and 1500 people die from this disease [7].

The main risk factors include genetic factors, a fair phototype of the skin, excessive exposure to ultraviolet radiation from solar and artificial radiation, sunburn at an early age, and individual predispositions [6]. Early identification of the primary tumour (excision biopsy of primary lesion) and potential metastases to regional lymph nodes (sentinel lymph node biopsy) give a unique opportunity to cure patients with non-advanced skin melanoma, evaluated in Breslow metric scale in terms of depth of dermis infiltration below 1 mm. In about 80% of patients, melanoma is a localized lesion at diagnosis, 15% of patients present with regionally advanced stage, and in 5% of patients have the disease in disseminated stage at presentation [7].

Parkinson's disease is diagnosed with a frequency of 10–50 people per 100,000 population per year. The disease occurs in 100–300 people per 100,000 individuals in the population [1]. This frequency increases with age, especially after 60 years of age. The relationship between PD and melanoma was noticed about half a century ago. The first suspicions concerned the drug levodopa, which was used to treat PD [8]. Subsequent observations did not confirm this relationship because the increased incidence of PD in people with melanoma is unrelated to dopaminergic therapy [9]. Many publications in prestigious journals and meta-analyses confirm the existing relationship between PD and melanoma, and emphasise not only the role of genetic and immunological factors, but also the common origin of embryonic melanocytes and neurons [10, 11]. Although the correlations themselves seem to be confirmed, new hypotheses are still being proposed in an effort to explain them. The aim of this article is to review the most interesting hypotheses.

Numerous epidemiological studies and meta-analyses support the relationship between PD and melanoma [10, 11]. The researchers also point out that this link is bi-directional and that melanoma also increases the risk of PD. Recent reports based on large samples have shown that people with PD are four times more likely to develop melanoma, in contrast to other malignancies of internal organs related to, for example, smoking [12]. Also, in people with melanoma, there is a four-fold greater risk of developing PD [10]. The reasons for this interaction remain unexplained.

Pathogenesis of Parkinson's disease

The essence of the disease is the irreversible progressive loss of dopamine-producing neurons containing neuromelanin in the substantia nigra (hence the name) with the presence of eosinophilic protein inclusions, termed Lewy bodies (LBs), in their cytoplasm [3]. Lewy bodies result from accumulation of aggregated form of α-synuclein (α-Syn) protein. The loss and degeneration of dopaminergic neurons translates into a significant deficiency of dopaminergic transmission and associated neurological disorders (motor and mental retardation, resting tremor, muscle stiffness). Intravital diagnosis of Parkinson's disease is based on clinical symptoms and neurological differential diagnosis, which in the early stages of disease is difficult and in the advanced phase does not translate into any therapeutic benefits [4]. Degeneration and loss of dopaminergic neurons is a progressive process, with no effective treatment so far.

The following are considered as the main factors involved in neurons damage:

— oxidative stress, because it intensifies the enzymatic and non-enzymatic oxidation of dopamine;
— mutations of genes from the *PARK* family;
— abnormal deposition and aggregation of cytoplasmic proteins, especially α-Syn that accumulates in the form of Lewy bodies;
— mitochondrial dysfunction;
— apoptosis disturbances;
— improper autophagy process;
— mechanism of cell death through ferroptosis.

Physiological production of dopamine involves the formation of numerous intermediates that are highly reactive and generate oxidative stress in neurons (Figure 1) [13]. Dopamine itself does not accumulate in the cytosol of dopaminergic neurons and is protected in synaptic vesicles VMAT-2 because it is a highly reactive compound that damages the cytoplasmic and mitochondrial proteins of the dopaminergic neuron. Parkinson's disease occurs in older age, perhaps due to the depletion of mechanisms that counteract reactive oxygen. Post-mortem brain examinations of patients with PD show signs of damage to dopaminergic neurons due to oxidative stress [1, 3]. Clinical and experimental studies also indicate the effect of oxidative stress associated with gene mutations: α-Syn or parkin [13].

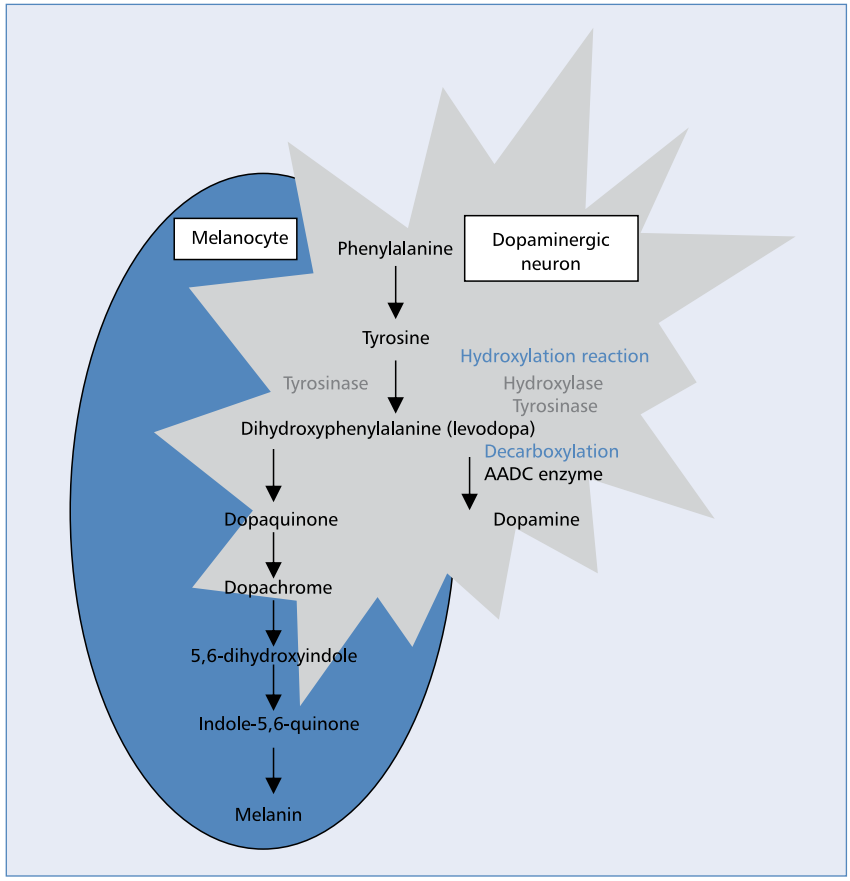

Figure 1. Steps of melanin and dopamine synthesis (in simplified form). Dopaminergic neurons use both dopamine and neuromelanin synthesis pathways, whereas melanocytes utilise a synthetic pathway directed exclusively to melanin. AADC — amino acid decarboxylase

The aetiopathogenesis of PD also highlights the shortage of physiological antioxidants and free radical scavengers, as demonstrated for uric acid [4].

Melanin and neuromelanin

Melanin is the main determinant of skin and hair colour in humans, and its type and quantity determine the skin phototype [14]. Melanin exists in neurons in the substantia nigra and is called neuromelanin. It is a protective factor for neurons against oxidative stress during neurotransmitter production, i.e. dopamine [13]. Melanin disorders in the skin can lead to development of various skin cancers, including melanoma, while Parkinson's disease correlates with neuromelanin abnormalities, suggesting that this pigment is a key link between both diseases [13, 14].

Melanin in the epidermis protects melanocytes and adhering keratinocytes from the harmful effects of UV radiation on cellular DNA, but in the case of transformed melanocytes its increased expression inversely correlates with overall survival and disease-free survival in patients with advanced melanoma (grade III and IV), accelerating tumour progression [14]. In light of new research, the photoprotective role of melanin is not as unambiguous as it was previously thought. It transpires that melanin under the influence of accumulated energy from UVA radiation secondarily damages melanocyte DNA under oxidative stress conditions and paradoxically promotes carcinogenesis of these cells after cessation of the sun's action [15]. During the so-called dark phase, after cessation of UVA action on the skin, energetically excited and oxidised melanin passes from melanosomes, in the form of monomers, to the cell nucleus and induces the formation of pyrimidine dimers of cytosine, damaging the double helix of DNA [16]. DNA damage is greater in the presence of oxygen radicals also formed under UVA influence [17]. Moreover, sunlight affected reddish yellow melanin, e.g. pheomelanin, generates — by its synthesis — the formation of reactive oxygen species (ROS), which increase theirs harmful effect on DNA, proteins, and cell organelles. The harmful effect of UVA on melanocyte DNA is therefore increased by melanin and ROS during solar exposure and sustained afterwards despite sun exposure cessation. Inhibition of

melanin synthesis and the use of free radical scavengers as well as nitric oxide synthase (NOS) and NADPH oxidase (NOX) inhibitors prevents the formation of pyrimidine dimers of the DNA strand [15]. In summary, melanin, in particular reddish yellow pheomelanin, does not effectively protect against the sun, but promotes DNA mutations and carcinogenesis the more the skin is exposed to UVA radiation in combination with free oxygen radicals [16]. The results of these experimental studies explain the epidemiological data that fair phototypes have an increased risk of melanoma after sunburn in their clinical history [18].

A strong electron stimulation of melanin occurring under the influence of UV and free oxygen radicals, called chemiexcitation, was first found in mammals and just in melanocytes. It is analogous to the chemical reaction used by fireflies in the production of light [19]. Chemical excitation of melanin by reactive electrons generates a new important source of genome instability and theoretically can occur everywhere where melanin exists and ROS are generated. This theory, by analogy, does not exclude dopaminergic neurons producing neuromelanin and generating large amounts of reactive oxygen species in the substantia nigra from similar pathogenic phenomena. However, this is just speculation and there is no such research in PD, although oxidative stress is mentioned as the main factor responsible for the irreversible damage and loss of dopaminergic neurons [4].

Neuromelanin also has a dual role. On one hand, it protects dopaminergic cells against oxidative stress, and on the other hand, it damages them in PD, as has been shown by numerous studies [13]. Neuromelanin, like melanin, is a pigment with two faces. With age, its amount is accumulated in cytosol of dopaminergic neurons, and in the embryonic period and at birth it is practically absent. Perhaps the expression of neuromelanin is regulated by factors related to maturation of these cells, dopamine itself and environmental factors influence, as it is in skin melanocytes. Under physiological conditions neuromelanin protects neurons from harmful effects of dopamine and its oxidised derivatives. It converts quinones and semiquinones, which are formed in the dopamine synthesis process and are potentially toxic to cells, into stable and non-reactive polymers. Quinones modify the structure of cytoplasmic proteins and are involved in the formation of insoluble filamentous aggregates similar to α-Syn. Another harmful effect of quinones is inhibition of NADPH reductase in the mitochondria, which increases oxidative stress. These effects are counteracted by neuromelanin. The pigment also binds with high affinity and sequesters heavy metals, which have a proven neurodegenerative effect, such as iron, copper, zinc, lead, or aluminium. Iron associated with neuromelanin inhibits chemical reactions in which ROS are generated.

Under favourable circumstances, however, neuromelanin can become toxic to dopaminergic neurons. This happens in cases of heavy metal poisoning, when its ability to sequester metal ions is depleted. The iron-saturated neuromelanin paradoxically oxidises dopamine and transforms it into harmful and highly reactive derivatives damaging protein structures in neurons. What is more, it supports reactions generating free radicals. Neuromelanin released from damaged neurons induces and inflammation in the substantia nigra in the substantia nigra by microglial cells activation. Heavy metals released from the neuromelanin, additionally damage *de novo* the neuronal cells. Microglial cells with phagocytic properties being activated by neuromelanin presence start to produce neurotoxic inflammatory mediators, i.e. tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and nitric oxide, which together with free oxygen radicals sustain and intensify destructive processes in the substantia nigra.

There is no doubt the role of neuromelanin is very complex, and its final effect depends on the influence of environmental factors, dopaminergic, mitochondrial, and inflammatory processes generated by microglial cells, and translates into oxidative reactions, playing a role in the pathogenesis of PD [13]. It cannot be ruled out that the electron flow from highly reactive oxygen species and neuromelanin oxidation also occurs in the substantia nigra similarly as it is in the skin, under the influence of impaired dopamine synthesis pathways or deficiencies of natural antioxidants, as demonstrated by a current meta-analysis on decreased concentration of uric acid in PD [4].

Also, changes in activity of enzymes involved in the synthesis of melanin and neuromelanin, such as tyrosinase and tyrosine hydroxylase (Figure 1), respectively, play an important role in altered susceptibility to melanoma and PD. The tyrosine hydroxylase catalyses in the presence of oxygen the hydroxylation of tyrosine to dihydroxyphenylalanine, from which the neurotransmitter dopamine or neuromelanin is formed in the substantia nigra [20]. In melanocytes, tyrosinase catalyses the formation of dark eumelanin and reddish yellow pheomelanin. In the course of these reactions, dopaquinones and other free radicals are formed, which have potential toxic effects on cells. In fact, in substantia nigra they lead to neuronal damage, while in the skin they damage the genetic material, increasing the risk of carcinogenesis [21].

Drugs used in Parkinson's disease and melanoma

The synthesis of dopamine and melanin occurs in the common pathway (Figure 1), in which levodopa is a substrate for enzymes and melanin synthesis, which is why it was suspected that levodopa increases the incidence of

melanoma [22, 23]. The probable relationship between levodopa and the development of melanoma was first described in 1972 [8]. Opponents of this theory argue, however, that exogenous L-dopa is not possible to be utilized by melanocytes and moreover toxicity of L-dopa against melanocytes has been demonstrated *in vitro* [24]. Subsequent randomised, prospective studies have also not confirmed this hypothesis. This theory is strongly supported by the fact that the increased incidence of melanoma occurred prior to the diagnosis of Parkinson's disease and levodopa introduction [9, 12]. There is also information in the literature about increased incidence of non-melanoma (a standardised SIR risk index of 1.95) skin cancers in people with PD, with an SIR index of 1.37 for basal cell carcinoma and 1.15 for squamous cell carcinoma, in a Danish patients registry, which also excludes levodopa as the cause that links both diseases [12, 25, 26]. Other cancers in patients with PD, apart from the most common melanoma, include breast and prostate cancers [9, 26, 27]. Unrelated to the treatment of PD and confirming the genetic basis of both diseases is the fact that these diseases are also diagnosed in close family members [27].

Other agents used to treat Parkinson's disease, such as selegiline and CEP-1347, also have no effect on the relationship between PD and melanoma [28].

Genetic basis of Parkinson's disease and melanoma

There are population based studies indicating the risk of PD increases with fair colour of hair. An interesting hypothesis is the linking of the gene polymorphism determining red hair colour as an explanation of the correlation of both diseases, namely variant *R151C* of melanocortin 1 receptor gene (*MC1R*), which accounts for a fair skin phenotype with reduced UV protection, contributing to an increased risk of melanoma development with a simultaneously increased incidence of PD [29]. In this variant, arginine at position 151 is replaced with cysteine, and in the case of homozygote of the *R151C*, Cys/Cys allele, only melanin conditioning the red hair colour is formed [29]. This melanin, called pheomelanin, plays the key pro-oxidative role as a final product of the *MC1R* gene.

MC1R is present on nerve cells in the brain and is thought to play a neuroprotective role, depending on the genetic variant in which it occurs. A similar relationship was found in the Spanish population for the *R160W MC1R* variant, but subsequent studies did not confirm the significance of this variant in the genetic background of PD [29].

Neuromelanin, in addition to reddish yellow (pheomelanin) and black (eumelanin), is the third type of human melanin synthesised in dopaminergic neurons of the substantia nigra. In fact, it is a combination of these two types in the right proportions; its core is pheomelanin, covered on the surface by eumelanin. In red-haired people, the thinning or even lack of eumelanin in neuromelanin may determine the sensitivity of dopaminergic neurons to neurodegenerative processes associated with oxidative reactions or sensitivity to dopaminergic toxins, i.e. 6-OHDA or MPTP [30].

Interestingly, skin cells collected from red-haired patients show gene defects reported in neurodegenerative disorders, i.e. Parkinson's disease, Alzheimer's disease, and Huntington's disease [31], which indirectly links the reddish yellow melanin phenotype with neurodegenerative processes. Interestingly, in vivo imaging studies show a relationship between the fair skin phenotype and increased echogenicity of substantia nigra in the brain.

In the substantia nigra neurons in mice, the expression of MC1R is localised in the cytoplasm and overlaps the expression of tyrosine hydroxylase involved in dopamine synthesis, which may indicate their functional association [30]. And it seems to be so because the mouse model has shown that the "red-haired" variant of the *MC1R* gene reduces the production of dopamine in the substantia nigra and increases the sensitivity of brain cells to harmful dopaminergic substances. The phenotype of the "red-haired" variant of the *MC1R* gene associated with decreased dopamine production is more evident with mice aging, which also confirms the age factor in PD in humans [1].

This study is the first to show the direct impact of the red-haired variant of the *MC1R* gene associated with melanoma on the survival of dopaminergic neurons in the brain and may provide evidence for targeting *MC1R* as a new therapeutic strategy for PD [29, 30]. At present, the efficacy of *MC1R* agonists in acute phototoxic reactions, depigmentation diseases and erythropoietic protoporphyria is being assessed in clinical trials. Perhaps the use of such strategy in PD will prevent the neurodegeneration processes associated with the inactive homozygous "red-haired" *MC1R* allele.

Other genes that are considered in the aetiopathogenesis of both diseases include mutated *PARK2* [32, 33], α-synuclein (*SNCA*) [34, 35], *DJ-1* [36, 37], or *LRRK2*, which is a homologous equivalent to mutated BRAF kinase in melanoma cells [27, 30].

The autosomal recessive germinally mutated *PARK2* gene determines PD at an early age. The gene is located in the fragile part of chromosome 6, in *locus* 6q25-q27, where other numerous tumour suppressor genes are located, that are susceptible to easy deletion, which promotes the development of tumours, especially of the breast and ovary [32]. Mutations of *PARK2* gene encoding ubiquitin E3 ligase, which belongs to tumour suppressor genes, are found in neurons of the juvenile genetic variant of Parkinson's disease, glioblastoma multiforme, as well as colon and lung cancer [33]. The loss of *PARK2* heterozygosity was also found in melanoma cells [27].

Another common gene for PD and melanoma is *SNCA* coding for α-synuclein. Its mutated forms promote disturbed degradation and accumulation of filamentous aggregates in Lewy bodies [34] and the development of neurodegenerative diseases leading to dementia. Overexpression of α-synuclein inhibits the phosphorylation of both enzymes involved in the synthesis of dopamine, tyrosine hydroxylase, and L-dopa amino acid decarboxylase (AADC) converting L-dopa into dopamine, which inhibits the synthesis of the neurotransmitter (Figure 1).

Melanocytes also contain α-Syn, which is regulated by a transcription factor, a product of *MITF* (microphthalmia-associated transcription factor) gene. *MITF* regulates the expression of genes required for melanin synthesis, i.e. tyrosinase and tyrosinase-like proteins, and *MITF* mutation leads to melanocyte transformation and melanoma development. In the primary and metastatic melanoma, significantly increased expression of α-Syn protein is observed [35]. Currently, we cannot explain the role of α-Syn in cutaneous melanocytes and melanoma pathogenesis.

DJ-1 is a highly conservative common gene. Similarly to the *PARK2* gene, its mutations were found in a genetically conditioned, autosomal recessive type of PD manifesting at an early age and sporadic variant. It was originally called *PARK7* [36]. *DJ-1* plays an important role in the regulation of oxidative stress and is located in cytoplasm, cell nucleus, and in the mitochondria. Loss of its function promotes damage to substantia nigra neurons as a result to oxidative stress, and its concentration increases in cerebrospinal fluid (CSF) in patients with advanced PD. Increased levels of circulating *DJ-1* are also found in patients with melanoma [37].

Another interesting issue is the observation that patients with melanoma without concomitant Parkinson's disease have a 10 times greater risk of death due to metastatic melanoma compared to patients with melanoma co-existing with PD [10]. It suggests that PD pathomechanism can inhibit melanoma progression and the ability to create metastases. Perhaps an abnormal activation of the innate and adaptive immunity in PD, responsible for inflammatory neurodegenerative processes may indirectly inhibit the activity of transformed melanocytes in the progression of melanoma.

Autophagy deficit

Interesting theories include the deficit of autophagy or "cellular recycling mechanism". Autophagy disorders lead to accumulation of damaged organelles and deposition of pathogenic protein aggregates in Lewy bodies, which has a proven relationship with neurodegenerative diseases leading to dementia [38, 39]. The clearance of neuronal α-Syn in PD is impaired for two reasons: α-Syn mutation and its resistance to the catabolic effects of autophagy, and impaired autophagy associated with the deficit of regulating chaperone proteins (hsc70) and lysosomal LAMP2A. Under physiological conditions, the half-life of α-Syn is 46.5 hours. In PD, its accumulation and pathological aggregation is observed, which promotes the degeneration of dopaminergic neurons [38].

In neoplastic transformation, there is a disturbed presentation of antigens, a decrease in autophagy, and thus the escape of the tumour from immune surveillance [40, 41]. The reduced *DJ-1* regulated autophagy capacity was found in prostate, breast, and lung cancer cells in which the expression of the DJ-1 protein is high. So the mutant form of *DJ-1* (*PARK7*) described in the pathogenesis of PD promotes tumour formation and inhibits the activity of p53 anti-oncogene [40].

Smoking in melanoma and Parkinson's disease

Many publications showed an inverse relationship between the incidence of melanoma and smoking, as well as for Parkinson's disease [1]. After considering other factors in control studies (age, sex, race, skin type, and history of sunburn) former smokers have a 60% lower risk of melanoma in comparison to non-smokers, and in current smokers the risk is reduced by 35% [42]. A similar inverse relationship exists between smoking and PD, which is explained by the protective effect of smoking on dopaminergic neurons and the antioxidant properties of nicotine [1, 12]. Nicotine and hydroquinone found in cigarette smoke have also been shown to inhibit α-Syn aggregation, which plays a role in the aetiopathogenesis of PD and dementia.

Olfactory (odorant) receptors

Interesting new cognitive abilities in the aetiopathogenesis of melanoma and PD offer olfactory/odorant receptors (OR) present on pigmented skin cells and the dopaminergic nerves [43]. The olfactory receptors regulate melanogenesis in melanocytes and neurons of the substantia nigra. They are the largest family of all known receptors in vertebrates, with over 391 types described in humans. In PD their expression is reduced, which may favour neurodegenerative processes.

There are interesting hypotheses supported by experimental data that olfactory receptor agonists, which include specific chemical and fragrance substances, may have a beneficial effect on the disturbed functioning of melanocytes and dopaminergic neurons in melanoma and PD [44]. In melanoma increased OR51E2 recep-

tor expression was observed, and its stimulation with a specific ligand inhibited the proliferation and migration of melanoma cells, while inducing apoptosis in them [45]. The authors of the abovementioned study suggest that the family of olfactory receptors may offer an interesting and easily available topical therapeutic intervention in melanoma, as well as a preventive one via nasal airway in PD.

Disorders of ferroptotic programmed cell death

Another interesting phenomenon combining melanoma with degenerative brain diseases, including PD, is recently identified ferroptosis [46]. It is programmed cell death that is morphologically, biochemically, and genetically different from apoptosis, necrosis, and autophagy. While the physiological role of ferroptosis is not explained, its aetiology results from the imbalance of iron-regulated oxidation processes leading to lipid peroxidation toxic to the cell and disturbed metabolic processes [47]. Cells in which oxidation processes are constantly taking place and ROS are activated, are susceptible to ferroptosis, such as melanocytes and neurons of the substantia nigra due to the synthesis of melanin and dopamine. Ferroptosis is induced by inhibition of cysteine uptake that reduces intracellular glutathione levels (GSH) and the antioxidant status of cells [48].

An important aspect from the oncological point of view seems to be the fact that non-apoptotic forms of cell death may facilitate the selective elimination of specific cancer cells. Recently, it has been reported that resistant mesenchymal tumours depend on the GPX4/lipid peroxidase pathway, which allows ferroptosis to be avoided [49]. This observation gives an importance to ferroptosis in the new strategy of anticancer drugs [50]. In addition, drugs that induce a suicidal cell death process through ferroptosis may be used to treat de-differentiated melanoma cells that have lost the ability to die in this mechanism. Further studies in patients with grade IV melanoma are warranted if the induction of impaired ferroptosis improves the efficacy of immunotherapy and anti-BRAF targeted therapy [51].

Ferroptosis is also involved in neurodegenerative diseases because it has been shown that ferrostatin and iron chelators are effective in the Parkinson's disease model [52]. Recent evidence suggests that iron is an interesting therapeutic target for PD. Application of the iron chelator, i.e. deferiprone in neural cell cultures and mouse model, reduces oxidative stress and increases the availability of dopamine, which consequently improves the existing motor disorders and prevents their deterioration [53].

The issue of using ferroptosis in the treatment of melanoma or neurodegenerative disease creates interesting and new possibilities for further research of another phenomenon that links transformed melanocytes with degenerating neurons in the substantia nigra of the brain.

Summary

We do not know the exact correlation between Parkinson's disease and melanoma, or it is so complicated that we do not fully understand it. Undoubtedly, both diseases relate to dendritic cells with the same embryonic origin, melanocytes producing melanin and neurons producing dopamine and neuromelanin. Although these cells differ in localisation and function, they have common embryo-determined genetic material, as confirmed by numerous studies on similar gene expression and mutations [1, 3].

It is known now, that melanin itself plays an important role in the malignant transformation of melanocytes in addition to UV radiation, especially its reddish yellow variety with free oxygen radicals [16]. It could be similar in the case of neuromelanin, which under certain conditions intensifies oxidation processes, inhibits reducing reactions, damages dopaminergic neurons, and generates inflammation induced by phagocytic cells of microglia [13]. Current knowledge shows that the development of both diseases is influenced by complex genetic background, environmental factors, and oxidative stress [27], which is also confirmed by the last study investigating the role of melanocortin 1 receptor gene (*MC1R*) in the "red-haired" variant in substantia nigra in mice [29]. The genetic basis of both diseases is presented extensively in the review paper by Inzelberg et al. [54] and summarised in Table 1.

More information on the relationship between Parkinson's disease and melanoma may lead to a better understanding of these diseases and provide a basis for further research, as in the case of ferroptosis [51]. Such studies may influence the findings of new therapeutic strategies and molecular targeted therapies, thus contributing to more effective treatment of both diseases in the future. There are currently some indications that the use of antioxidants and free radical scavengers may have a neuroprotective effect and protect against the development of melanoma, but only theoretically, because supporting clinical trials do not exist [4, 15].

It is also worth considering the introduction of screening tests for the early detection of melanoma in patients with nervous system diseases. There are currently no guidelines for recommending regular screening of patients with PD towards melanoma and vice versa. It is worth emphasising the need to raise awareness about the ongoing correlation among doctors, patients, and their families [9]. Unfortunately, PD cannot be

Table 1. Abnormal genes and disorders found in dopaminergic pigmented cells of the nervous system in Parkinson's disease (PD) and melanocytes in melanoma (MM)

Gen/gene product/ /phenomenon	Parkinson's disease	Melanoma
SNCA/α-synuclein	Mutation in AD variation of PD α-synuclein aggregates in Lewy bodies Overexpression inhibits the synthesis of dopamine	α-synuclein present in MM and nevi
Parkin	Mutation in AR variation of PD and sporadic PD	Expression in MM
PARK2/ubiquitin ligase E3	Mutation in AR variation of PD	Loss of heterozygosity of *PARK2* in MM
DJ-1 (*PARK7*)	Mutation in AR variation of PD and sporadic PD	Inhibits apoptosis and autophagy phenomena in MM Increased serum concentration in MM patients
LRRK2	Mutation in AD variation of PD	Mutated *BRAF* in MM is an analogue
MC1R/melanocortin receptor 1	Red hair, a fair phenotype associated with an increased risk of PD The dark variant has a neuroprotective effect	"Fair skin" variant increases MM risk
Variant *R151C MC1R*	PD risk increase No or trace amount of eumelanin in neuromelanin	Hyperactivation of pheomelanin under the influence of UVA and ROS damages DNA of melanocytes
Odorant receptors (OR)	Decreased expression in PD	Increased OR51E2 expression in MM Regulation of proliferation, migration and apoptosis in MM
Ferroptosis (metabolic programmed cell death)	Increased ferroptosis	Resistance to ferroptosis
MITF	Regulates the activity of enzymes in dopamine synthesis	Mutation in MM
The effect of nicotine	Smoking correlates inversely with PD risk	Smoking correlates inversely with MM risk

AD — autosomal dominant; AR — autosomal recessive

prevented or cured effectively [4]. Early diagnosis based on clinical examination and neurological experience is difficult and imperfect in PD. Melanoma, on the other hand, is a cancer that is virtually completely cured when it is detected early enough [7]. Nevertheless, it is still recognised too late. In Poland, unfortunately, the mortality rate due to melanoma according to the National Cancer Registry is 20% higher than the average for the European Union; therefore, all activities that increase vigilance towards this cancer are justified.

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VIA MEDICA

CASE REPORT

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A paraplegic patient with fever and leucocytosis: not always what it seems

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ABSTRACT

A 54-year-old obese woman with a history of spina bifida was admitted to the hospital with malaise and fever accompanied by leucocytosis, thrombocytosis, and hypercalcaemia. As treatment for neurogenic bladder dysfunction she had a suprapubic catheter. Diagnostic workup for osteomyelitis revealed an unknown mass originating from the urinary bladder on MRI of the pelvis. Further diagnostic analyses showed that the mass was a squamous-cell carcinoma (SCC) with laboratory abnormalities as paraneoplastic phenomena mediated by PTH-related peptide and cytokines released by the SCC. Despite radiotherapy the patient died within two months after initial diagnosis. Squamous-cell carcinoma of the bladder is rare in western countries. In unresectable or metastatic disease survival rates are low due to low responsiveness to standard chemotherapy. Concurrent chemoradiotherapy might be an alternative in unresectable or locally advanced disease; however, evidence to support this is lacking. The poor survival in these patients raises the question of whether high-risk groups for SCC of the bladder, like paraplegic patients or patient with neurogenic bladder dysfunction, should receive screening even though the ideal starting point and frequency are still unknown.

Key words: suprapubic catheter, squamous-cell carcinoma suprapubic tract, neoplastic phenomena

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Introduction

Patients with neurogenic bladder dysfunction can be treated with a suprapubic catheter. Here we present a case of a patient with a squamous cell carcinoma (SCC) of the bladder around the suprapubic catheter tract and consequentially three paraneoplastic phenomena, mimicking infection. Written, informed consent was obtained from a legally authorised representative for anonymised patient information to be published in this article.

Case report

A 54-year-old obese (BMI = 48.9 kg/m^2) woman was admitted to the hospital with malaise and fever. She was known with a history of smoking, type 2 diabetes mellitus, and spina bifida. The latter was accompanied by paresis of both legs and neurogenic bladder dysfunction for which she had had a suprapubic catheter for the last 30 years ago with follow-up by her general practitioner. Physical examination at admission was normal except for two ulcers: one stage IV pressure ulcer at the tailbone and one ulcer at the entrance of the suprapubic cystostomy tract. Laboratory findings revealed a thrombocytosis, neutrophilic leukocytosis, and increased CRP (Tab. 1). Both urine analysis and chest radiography were unremarkable.

An MRI-scan of the pelvis was made to rule out ischial tuberosity osteomyelitis beneath the stage IV pressure ulcer. The MRI showed no signs of osteomyelitis, but an unknown mass originating from the urinary bladder around the suprapubic catheter extending to the entrance of the suprapubic cystostomy (Fig. 1). A biopsy revealed a moderately differentiated invasive squamous cell carcinoma (SCC). CT-scan of the chest, abdomen, and pelvis showed no distant metastases.

Table 1. Laboratory test results at admission and after two weeks

	Reference	Hospital admission	After two weeks
Haemoglobin [mmol/L]	7.5–10.0	5.5	5.1
Haematocrit [L/L]	0.35–0.45	0.28	0.26
Thrombocytes [/nL]	150–400	510	600
Leukocytes [/nL]	4.0–10.0	43.5	54.9
Neutrophilic leukocytes [/nL]	1.5–7.5	40	–
Lactate dehydrogenase [U/L]	122–222	254	–
Alkalic phosphatase [IU/L]	33.0–98.0	181	–
Creatinine [μmol/L)]	50–100	54	65
Urea [mmol/L]	2.5–6.4	3.6	3.4
Creatinine clearance [MDRD, ml/min]		> 60	> 60
Natrium [mmol/L]	135–145	136	137
Potassium [mmol/L]	3.5–5.0	3.4	3.5
Calcium, corrected [mmol/L]	2.10–2.55	2.55	3.43
Albumin [g/L]	35–50	31	28
Magnesium [mmol/L]	0.75–1.0	0.61	0.6
PTH-related protein [pmol/L]	< 0.6	–	2
PTH [pmol/L]	1.6–6.9	0.94	–
25-OH vit D [nmol/L]	> 50	34	26
1,25 di-OH vitamine D [pmol/L]	47–130	–	45
Monoclonal immunoglobulins [g/L]		Positive, IgG lambda: < 2	Urine: negative
TSH [mIU/L]	0.27–4.2	1.6	–
Vitamin A [μmol/L]	0.7–2.1	1.1	–
Thrombopoietin [IE/ml]	4–32	130	–

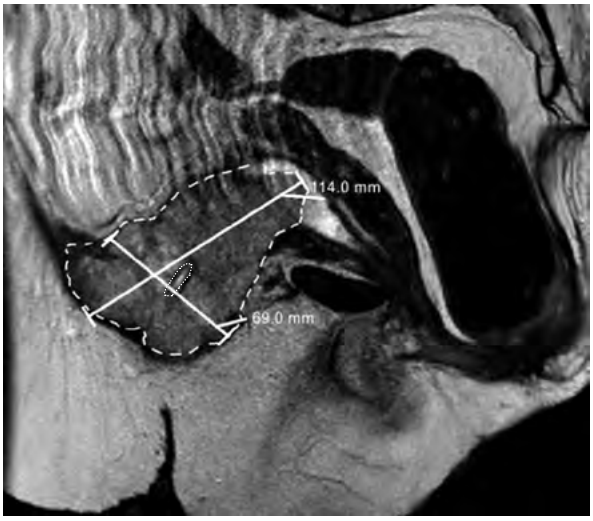

Figure 1. MRI showing a squamous-cell carcinoma (large dashed line) around the suprapubic catheter (small dotted line)

Initially, intravenous antibiotic treatment with ciprofloxacin and flucloxacillin was started to treat a potential underlying infection. Treatment was stopped after two weeks due to lack of clinical benefit, multiple negative blood cultures, and persistent leucocytosis and fever. In addition, a progressive hypercalcaemia of 3.43 mmol/L was found, which was unlikely to be explained by common causes like immobilisation, osteolytic metastases, or dehydration because the patient had already been immobilised for many years, osteolytic metastases were absent, and hydration did not improve calcium levels. The concomitant suppressed parathyroid hormone (PTH) of 0.94 pmol/L was probably a normal physiological reaction and suggested another mediator responsible for the hypercalcaemia. Closer investigation showed an elevated PTH-related protein of 2.0 pmol/L. Likewise, an elevated thrombopoietin of 130 IE/ml was found as a mediator for the thrombocytosis (Tab. 1).

The final diagnosis was a squamous cell carcinoma of the bladder (cT4N1M0) accompanied by a paraneoplastic syndrome of fever, leukocytosis, thrombocytosis, and hypercalcaemia. The patient was ineligible for radical cystectomy and concurrent chemoradiation based on a WHO performance status of 2. Therefore, treatment was started with bisphosphonates and radiotherapy (51 Gy in 17 fractions). This treatment normalised calcium levels and stopped the fever. After six weeks

of hospitalisation the patient was discharged to strengthen at home. Unfortunately, one week after discharge she was readmitted due to a deteriorating condition. A CT-scan of the chest and abdomen showed new pulmonary metastases, and in consultation with the patient supportive care was started. The patient died within two weeks in a hospice.

Discussion

Squamous cell carcinoma (SCC) of the bladder consists of two subtypes: the bilharzial-associated SCC (B-SCC) and non-bilharzial-associated SCC (NB-SCC). The B-SCC is mainly found in regions where schistosomiasis is endemic, representing 30–50% of bladder cases in these areas [1, 2]. In western countries the NB-SCC subtype is more common, which accounts for 2–5% of bladder neoplasms [1–3]. Important risk factors for NB-SCC are smoking, recurrent urinary infections, and the use of chronic indwelling urinary catheters causing reactive chronic inflammatory and proliferative pathologic changes of the bladder [1, 4, 5]. The incidence of NB-SCC in paraplegic patients is therefore 16–28 times higher.

Paraneoplastic syndromes are well known in pulmonary SCC. These syndromes have also occasionally been reported in SCC of the bladder [6–9]. In this case, the patient presented with a progressive hypercalcaemia and elevated PTH-related peptide (PTH-rP), also known as "humorally mediated hypercalcaemia of malignancy". This is caused by cancer cells producing PTH-rP with an almost identical structure to PTH, which is therefore able to bind bone and renal PTH-1 receptors. This enhances renal reabsorption and osseous release of calcium [10, 11]. Besides the hypercalcaemia, PTH-rP might also be responsible for the leukocytosis and thrombocytosis. PTH-rP is able to stimulate interleukin-6 (IL-6) secretion from osteoblasts, aside from possible IL-6 secretion by the malignancy itself, which has been described in SCC. IL-6 enhances production of haematopoietic growth factors like granulocyte-colony stimulating factor (G-CSF) and thrombopoietin, resulting in leukocytosis and thrombocytosis [11].

Although we did not measure G-CSF or cytokines, the elevated levels of thrombopoietin and PTH-rP combined with the excessively high neutrophilic leukocytes in the absence of positive blood cultures or steroids suggest that all three phenomena were neoplastic.

Substantial evidence for standard guidelines to treat NB-SCC are lacking since the incidence is low. The main treatment for non-metastatic NB-SCC is radical cystectomy. Preoperative radiotherapy might reduce local recurrence and improve survival [3, 4]. However, despite radical cystectomy and radiotherapy, the prognosis of non-metastatic NB-SCC remains poor with a five-year survival of 34–50%, which is mainly related to failure of locoregional control [1, 3, 4]. Even though distant metastases are infrequent (8–10%), the presence of metastases or unresectable malignancy reduces the survival dramatically. The reasons for this poor outcome is that NB-SCC shows only low responsiveness for chemotherapy commonly used in urothelial cancer. One study demonstrated some response to treatment with ifosfamide, paclitaxel, and cisplatin with a median survival of 8.9 months, although conclusions are hampered by the small sample size [3, 12]. An alternative treatment for unresectable or locally advanced disease might be concurrent chemoradiotherapy. However, evidence to support this is scarce. Recently, immunotherapy targeting the PD-1 pathway showed promising results. Both atezolizumab in patients previously treated with platinum based therapy and pembrolizumab in patients ineligible for platinum-based regimes have demonstrated an effect in metastatic urothelial cancer [13, 14]. The use of immunotherapy in metastatic squamous cell carcinoma is still unknown and is currently being investigated in a clinical trial using durvalumab and tremelimumab (Clinicaltrial.gov: NCT03430895).

To prevent NB-SCC it is important to reduce the use of chronic indwelling urinary catheters in long-term paraplegic patients. In addition, early discovery with surveillance cystoscopy and urine cytology might be considered in high-risk groups with neurogenic bladder dysfunction, like spina bifida. However, screening on NB-SCC is still under debate because the ideal starting point and frequency are unknown [1, 5, 15, 16].

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VIA MEDICA

CASE REPORT

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Nivolumab in treatment of renal cell carcinoma during renal replacement therapy

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ABSTRACT

The prolongation of overall survival of advanced RCC patients requires the use of modern therapies including tyrosine kinase inhibitors and immune checkpoint inhibitors. Although these drugs have different pharmacokinetics, preclinical studies rarely indicate significant renal clearance. To date there has been a lack of prospective studies evaluating their efficacy and safety in end-stage renal disease patients undergoing dialysis.

This case study describes second-line treatment of RCC with nivolumab in a dialysed patient following bilateral nephrectomy.

Key words: kidney cancer, nivolumab, dialysis

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Introduction

Renal cell carcinoma (RCC) and commonly performed nephrectomy are associated with the risk of a decrease in glomerular filtration rate (GFR) [1], which may affect future oncological treatment. In patients with pre-existing chronic kidney disease or in rare cases when bilateral nephrectomy is necessary it could result in end-stage renal disease. Hence, it requires implementation of renal replacement therapy. Due to inclusion criteria that usually do not allow patients with severely impaired renal function to participate in clinical trials, this group of patients is deprived of access to modern therapies. This paper presents the case of a patient with disseminated clear cell RCC (CCRCC) after bilateral nephrectomy.

Case report

In 2016, a 57-year-old female patient with disseminated RCC was admitted to the Department of Oncology of the University Hospital in Krakow; the patient was receiving chronic dialysis due to bilateral nephrectomy and therefore was not eligible for the standard treatment.

In 1990, the patient was treated for cancer of the left kidney. A total left nephrectomy was then performed, and clear cell RCC was diagnosed. The patient remained under observation for 19 years. In 2009, she reported for control because of increasing, unproductive cough. In the computed tomography (CT) examination oncologically suspicious lesions were found in the right lung. After consultation of a thoracic surgeon, in March 2009 non-anatomical, wedge resection was performed. Histopathological examination confirmed the presence of clear cell RCC (CCRCC). The CT scan of the other anatomic regions performed at that time did not reveal other pathologies. After a further four years of follow-up, a CT scan detected two tumours in the right kidney (66 × 44 mm and 20 × 16 mm) and suspected regional lymph nodes. Considering the size of tumours and previous left-sided nephrectomy, in October 2013, partial right-side nephrectomy (nephron-sparing surgery — NSS) with lymphadenectomy was performed. The histopathological examination confirmed the presence of clear cell carcinoma reaching the cut line (R1).

A CT scan performed three months after the surgery showed the presence of metastatic, non-regional lymph nodes. During this period, the patient did not require dialysis. The patient was qualified for treatment with sunitinib in a standard dose of 50 mg/d on days 1–28, with a 14-day break (28 days on/14 days off). The patient started therapy in February 2014. The treatment was poorly tolerated, the patient complained about the symptoms of *palmar-plantar erythrodysesthesia* (PPE or hand-foot syndrome, HFS), clinically significant asthaenia, and increasing peripheral oedema. In subsequent studies, a decrease in platelet levels and deterioration of renal parameters was observed. There was also drug-induced hypothyroidism requiring levothyroxine supplementation. Taking into consideration the above circumstances, the dose of sunitinib was reduced to 37.5 mg/day, leading to resolution of the reported adverse effects and improvement of quality of life. The therapy was administered until September 2015, for a total of 19 months.

A follow-up CT examination performed after this period showed the presence of a nodular mass in the initial section of the right ureter (8 × 8 × 8 mm) and widening of the ureter up to 14 mm. The patient was referred for urological consultation. Due to the increasing widening of the ureter, a JJ catheter was implanted. There was also an unsuccessful attempt to collect material for histopathological examination from the lesion described in CT. The patient remained under observation until March 2016, at which point tomography described a tumour of the right renal hilus with dimensions 61 × 67 × 71 mm, with additional infiltration of the lower renal pole and shaping of the pyelocaliceal system. Numerous enlarged local lymph nodes were also described. In this situation the decision was made to perform a complete right-sided nephrectomy with removal of the tumour thrombus from the inferior vena cava (IVC). During the operation, which was carried out in March 2016, tumour infiltration into the liver parenchyma was observed. In the postoperative period there was serious bleeding into the abdominal cavity, which required reoperation. From that moment on, the patient was chronically dialysed. Renal cell carcinoma recurrence was confirmed in histopathological examination.

Until November 2016, the patient remained under observation, despite evident disease progression in imaging studies. Due to end-stage renal failure and dialysis, the patient was not eligible for second-line treatment under the drug program.

In November 2016, the patient was in good general condition (performance status, PS = 1). The patient was treated for hypothyroidism, probably associated with previous sunitinib treatment, and mild hypertension, presumably associated with chronic dialysis. Clinically the patient did not present symptoms associated with neoplastic disease, although the CT scan performed at that time revealed the presence of pathologic masses (57 × 36 × 72 mm) in communication with the IVC and aorta, as well as dissemination to the abdominal, mediastinal, liver, and lung lymph nodes.

Because nivolumab was available in the Oncology Clinic of the Jagiellonian University Medical College in Krakow as part of an extended access program (EAP), a sponsor was asked to agree to inclusion of the patient in the treatment, despite not meeting the formal recommendation for creatinine concentration. This request was supported by available literature data. The sponsor agreed, and from November 22, 2016 the patient started treatment with nivolumab in a standard dose of 3 mg/kg every two weeks.

The patient was treated for five months until April 2017. The therapy was well tolerated. There were observed fluctuations in TSH concentration requiring levothyroxine dose adjustment and a flat, slightly reddish, exfoliating rash of moderate intensity (G1). The CT follow-up performed in February 2017 showed the enlargement of metastatic lesions and the appearance of a new small lesion in the liver. However, due to the clear clinical benefit, they were considered a potential pseudoprogression, and a decision was made to continue treatment subject to an earlier CT scan after six weeks.

One month later, the patient reported an unplanned visit due to worsening general condition, severe dyspnoea at rest, and worsening of the rash to grade G2. X-ray examination did not show lesions in the lungs, saturation on admission was 79% in the atmospheric air. There were also mild peripheral oedemas of the upper and lower limbs and the face. The patient did not have a fever and denied any cough. Due to the clinical suspicion of interstitial autoimmune pneumonitis, the patient was referred for urgent hospitalisation and steroid therapy — prednisone was included at the dose of 1 mg/kg/day.

Due to ambiguities regarding the aetiology of oedema of the upper body, an angio-CT examination was also performed after the admission, which revealed a massive thrombosis of the entire superior vena cava (SVC) on the inserted dialysis catheter. This study showed no inflammatory or interstitial lesions in the lungs. Due to this, steroid therapy was terminated and unfractionated heparin was included in a continuous infusion, which after a few days was changed to treatment with low-molecular-weight heparin under the control of anti-Xa activity. After finishing the initial period of treatment of thrombosis, the patient was discharged home in good general condition.

A CT scan performed after the end of treatment showed further enlargement of metastatic lesions, which ultimately forced the discontinuation of nivolumab therapy. Due to the lack of other available therapeutic

options, the patient was treated symptomatically and died in early 2018.

Discussion

This report presents a patient who due to bilateral nephrectomy was deprived access to standard therapy. Tomography performed before inclusion in the treatment with nivolumab showed rapid progression of the disease and the risk of invasion of aorta and inferior vena cava. The use of immunotherapy allowed a 14-month survival, and the most serious complication — superior vena cava thrombosis — in the opinion of treating physicians, was not directly related to the therapy. It should also be noted that the occurrence of sudden dyspnoea with an uncharacteristic result of imaging examinations during treatment with PD-1 inhibitors may result from other reasons, such as heart failure, pulmonary embolism, or superior vena cava syndrome.

Currently there are no guidelines for the treatment of kidney cancer in patients with end-stage renal disease, because they are usually excluded from clinical trials. It should be noted that patients in this group are usually burdened with accompanying diseases, which may increase treatment-related risk. Except for the pazopanib program, all current drug programs of the National Health Fund require normal kidney function (defined as the value of estimated glomerular filtration rate [eGFR] > 30 mL/min or creatinine serum level < 1.5–2 × ULN [upper limit of normal]). These indications correlate with the inclusion criteria for relevant clinical trials, although they are not fully reflected in pharmacokinetic data.

Nivolumab, a human IgG4 monoclonal antibody directed against the receptor of programmed cell death 1 (PD-1), is registered in the second line of treatment for generalised renal cancer, based on the Checkmate 025 study. In this study, the drug was compared to everolimus in a group of 821 patients who had previously received anti-vascular endothelial growth factor receptor (VEGFR) treatment. It resulted in an increase in the median overall survival (25 months *vs.* 19.6 months; hazard ratio [HR] 0.73; 98.5% CI [confidence interval] 0.57–0.93; p = 0.002), as well as objective response rate (ORR) (25% *vs*. 5%, HR 5.98, 95% CI 3.68–9.72, p < 0.001). The differences in progression-free survival (PFS) between the study arms were not statistically significant, which is characteristic for immune checkpoint inhibitors, and the median PFS was 4.6 months [2]. The CheckMate 025 study did not address the clinical situation of patients during dialysis. The nivolumab Summary of Product Characteristics (SmPC) indicates that dose adjustment is not necessary in patients with mild to moderate renal impairment, and that there are no data available for the group of patients with severe renal impairment. Pharmacokinetic analysis in populations of patients previously receiving nivolumab in clinical trials showed no significant effect of eGFR on drug clearance in patients with mild (eGFR > 60 mL/min) and moderate (eGFR 60–30 mL/min) renal failure. The lack of this relationship is consistent with the physical properties of the drug, because its large molecule (144 kDa) is unlikely to be filtered in the glomerulus [3].

Available literature data do not include any prospective studies on the safety and efficacy of nivolumab in populations of patient during dialysis, and only a few case reports are available that do not allow safe recommendation of this treatment. However, due to the increasing number of patients in this clinical situation, it is necessary to take action to determine the optimal treatment regimen for patients with renal cell carcinoma with end-stage renal disease, both in the field of immunotherapy and the use of tyrosine kinase inhibitors. The lack of such data may result in the deprivation of treatment of patients who objectively require this form of therapy.

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VIA MEDICA

CASE REPORT

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Long-term survival after surgical resection of locoregional gastric adenocarcinoma recurrence — a case report

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ABSTRACT

Introduction. Recurrence is the leading cause of death of gastric cancer patients after curative resection. This report describes a 44-year-old woman with gastric adenocarcinoma and surgically resected locoregional recurrence, who has survived for more than 13 years after diagnosis.

Case report. A 33-year-old woman was admitted to the Gastroenterology Clinic with an episode of epigastric pain and minor weight loss. Two years earlier she had been diagnosed with gastric adenocarcinoma G2 of the antrum, pT2N1M0 (IIA) stage. She had undergone total gastrectomy with D2 lymphadenectomy and Roux-en-Y anastomosis followed by postoperative chemotherapy. Further diagnostic investigation after two years revealed the presence of metastatic cancer in the gastric bed. An explorative laparotomy was performed, and the surgeons successfully excised the enlarged lymph node. Post-operative pathologic examination proved gastric cancer metastasis. Since April 2007 the patient has stayed recurrence-free, and there have been no signs of recurrence on either US or CT scan, as of April 2018. This patient represents a rare case of long-term survival of recurrent gastric adenocarcinoma successfully treated with surgery despite particularly poor prognosis.

Conclusions. Surgery for gastric cancer recurrence is a valuable treatment in chosen patients, provided it is performed by a team of specialised surgeons.

Key words: gastric carcinoma, locoregional recurrence, surgical resection

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Introduction

Gastric cancer is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths [1]. Gastric adenocarcinoma comprises 95% of malignant tumours of the stomach. While its incidence is gradually decreasing, the prognosis for the patients after curative gastrectomy is still poor. Recurrent tumour develops in most cases and often makes gastric cancer incurable [2–4]. Recurrences after curative resection for gastric carcinoma have been categorised as locoregional recurrence, peritoneal recurrence, and distant (including haematogenous) metastasis [5]. Although there is no clear consensus on the treatment of choice for recurrent gastric cancer, there have been a few reports on the relative effectiveness of surgical treatment in selected patients [6]. Here, we present a rare case of long-term survival (over 11 years after secondary resection of locoregional recurrence) of gastric adenocarcinoma.

Case report

A 33-year-old woman reported to the Oncology Centre with an episode of abdominal pain and minor weight loss. On examination she was in good overall condition, without lymphadenopathy, and the abdomen was tender and painless, with no abnormal masses. Ultrasound re-

vealed a tumour in the gastric bed. Fine-needle biopsy confirmed the presence of metastatic adenocarcinoma in a lymph node located around the pancreatic head.

The patient had a relevant medical history. Two years earlier, in 2004, she had undergone a total gastrectomy due to gastric cancer. Back then, she had presented with similar symptoms of unabating epigastric pain. Endoscopic findings had revealed an exophytic mass with central ulceration spreading over the lesser curvature and the anterior gastric wall, and the diagnosis of gastric adenocarcinoma G2, mixed type by Lauren classification, had been confirmed on histopathologic examination. On November 11, 2004, a total gastrectomy with D2 lymphadenectomy had been performed (R0 resection), with Roux-en-Y reconstruction of the gastrointestinal tract continuity. Pathologic examination revealed that the tumour was pT2N1M0 stage (clinical stage IIA) with two positive out of 30 excised lymph nodes. The patient had then received postoperative chemotherapy in the form of four cycles of FAM regimen (Fluorouracil-Adriamycin-Mitomycin).

Having considered the available treatment options, the surgeons decided to perform an exploratory laparotomy and the malignant lymph node was excised 28 months after the primary resection. She has not received perioperative chemotherapy. Both the serum carcinoembryonic antigen (CEA) and the carbohydrate antigen 19-9 (CA 19-9) levels were within the normal range immediately after the surgery and at follow-up. Post-operative examination of the excised lymph node proved gastric cancer metastasis (Fig. 1 A–C). Since April 2007 the patient has remained recurrence-free, and there have been no signs of recurrence on either US or CT scan, as of April 2018.

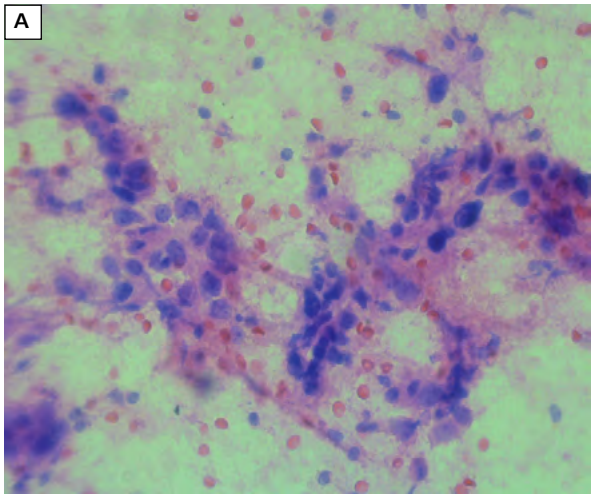

Figure 1A. Hematoxylin and eosin stain (H&E). Cytology. Lymph node metastasis

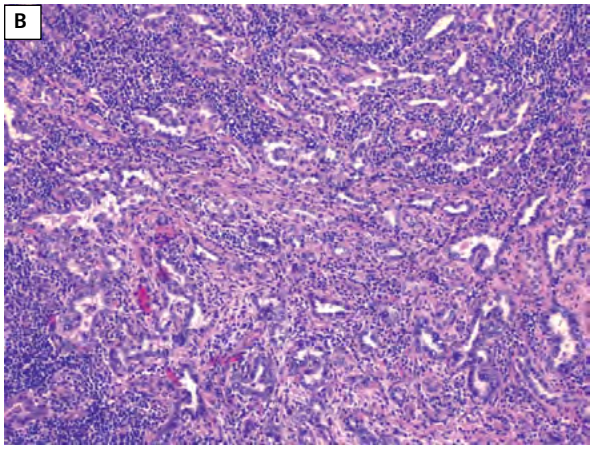

Figure 1B. Hematoxylin and eosin stain (H&E). Glandular structures of gastric cancer in the metastatic lymph node

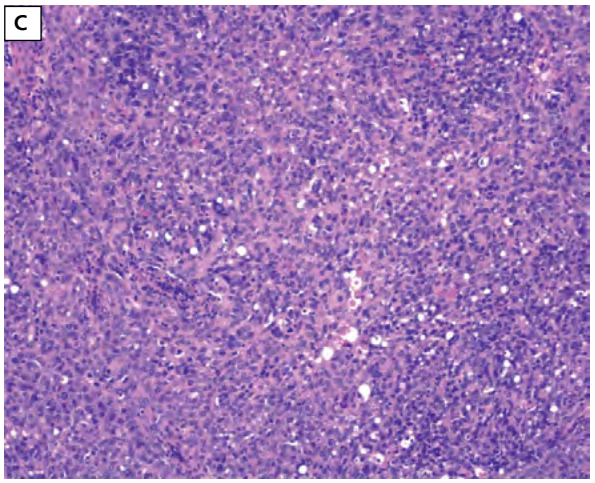

Figure 1C. Hematoxylin and eosin stain (H&E). Solid nests of gastric cancer in the metastatic lymph node

Discussion

Despite the improvements in diagnosis and surgical techniques, the prognosis and survival of gastric adenocarcinoma patients are significantly dependent on the stage of disease at the time of diagnosis. According to the American Joint Committee on Cancer (AJCC) survival data, for a cancer staged as in our case, treated with surgery and perioperative therapy, three-year and five-year survival are, respectively, 54.8% and 46.3% [1]. One major problem is that no effective therapy for recurring gastric cancer exists at present. Numerous studies try to evaluate the patterns and pre-operative predictive factors of recurrence. It seems that valid strategies to prevent postsurgical recurrence are curative resection, standard lymphadenectomy, and perioperative chemotherapy. Current ESMO recommendations include perioperative chemotherapy for patients with ≥ stage IB gastric cancer and adjuvant

therapy only if no chemotherapy was administered preoperatively [7]. The mean time to recurrence for locoregional recurrence was reported to be 26.4–28.1 months [8, 9]. In the presented case, it was 27 months after the primary surgery when the recurrence was detected.

While locoregional recurrence accounts for around 25% of all recurrences, the most common recurrence pattern is peritoneal recurrence (around 40% of cases). Haematogenous metastasis is the third most common pattern, with liver being a typical location [2]. Locoregional recurrent gastric cancer is commonly treated with chemotherapy only. Recurrences are rarely treatable with surgery and there are no proper indications for those patients. There are no predictive clinicopathological indicators for surgical resection, other than resectability [2, 8, 10]. However, when surgical resection is performed, the expected five-year survival rate was reported to be 20%, and the prognosis is even better if the resection was complete [2, 3, 8]. Our patient has experienced over 11 years recurrence-free.

Kong et al. found the two-year cumulative survival rates to be significantly better for resection of the recurrence plus chemotherapy than for chemotherapy only (23.8% *vs.* 1.2%, $p < 0.001$) [2]. Other studies also report generally longer survival time when surgery is performed along with chemotherapy [5, 6]. For any given patient, appropriateness of extensive resection should be assessed by a multidisciplinary assessment team. If the perioperative risk is low, surgery seems justified because no other therapy is effective enough. There are also numerous reports of long-term survival after surgery of recurrent gastric cancer with liver metastasis. Kiyasu described a case of over 18-year survival after gastric adenocarcinoma resection and subsequent liver metastases resection 30 months later [11]. Ambiru et al. reviewed the cases of six patients who survived longer than five years after curative excision of the stomach and liver [12].

Conclusions

Surgery for gastric cancer recurrence is a valuable treatment in chosen patients, provided it is performed by a team of specialised surgeons. Considering the high mortality and ineffectiveness of other therapies for recurrent gastric cancer, standardised indications for surgery should be elaborated. Further studies assessing the validity and effectiveness of this method are also needed.

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Immunotherapy in the treatment of advanced gastric cancer — more limitations than potential

It is obvious that the introduction of modern immunotherapy has significantly changed oncological practice. Despite the fact that immunotherapeutic drugs have become the standard care in several types of cancer, for most solid tumours the change is limited. In some cancers, such as pancreatic ductal adenocarcinoma, currently used immune checkpoint inhibitors (ICIs) have no activity. For other cancer types, such as colon cancer, the benefit of ICIs is limited to a particular, well defined sub-population (patients with microsatellite instability). A few cancer types, such as melanoma and lung cancer, are especially susceptible to ICIs, and here the immunotherapy is a real breakthrough. From this perspective, gastric cancer can be seen as a specific entity. The last decade brought limited improvement in gastric cancer treatment (limited mostly to the introduction of ramucirumab, a VEGF2 inhibitor, for second-line treatment and development of trifluridine/tipiracil combination as a salvage therapy). Simultaneously, despite promising results of phase I and II trials [1], which led to registration of pembrolizumab for the treatment of patients with advanced gastric cancer by the Food and Drug Administration (FDA), available phase III trial data are disappointing. On the one hand, it is clear that ICIs possess some activity in the treatment of gastric cancer (with 10–20% response rate achieved with ICIs monotherapy). On the other hand, there is only a single positive phase III trial, which assessed activity of nivolumab as a salvage treatment of gastric cancer in an Asian population. Two other phase III trials, which evaluated pembrolizumab and avelumab, are negative. The question regarding the role of ICIs in the treatment of gastric cancer remains open. Nevertheless, available phase III data will provide a base for further research, which justifies more detailed analysis.

The first of the aforementioned trials was published on 6th October 2017 by Kang et al. [2] in "The Lancet". ATTRACTION-2 was a randomised, double-blinded, phase III trial that compared nivolumab with placebo as a salvage treatment for patients with advanced gastric cancer. The trial included 493 patients from Japan, South Korea, and Taiwan, randomised in a 2:1 ratio to nivolumab or placebo, respectively. The primary end-point was overall survival (OS), and the secondary end-point was progression-free survival (PFS). Patients recruited to the trial had very good or good performance status (ECOG 0 or 1) and progressed after at least two lines of systemic treatment. After a median follow-up of 8.87 months in the nivolumab arm and 8.59 months in the placebo arm, the primary end-point was met. The achieved median OS was significantly longer in patients receiving nivolumab, reaching 5.26 months (95% confidence interval [CI] 4.60–6.37) compared to 4.14 months (95% CI 3.42–4.86) in patients receiving placebo. The hazard ratio (HR) for the OS difference was 0.63 (95% CI 0.51–0.78; $p < 0.0001$). The achieved effect was independent of the length of nivolumab treatment and remained significant in most of the analysed sub-groups. Additionally, the secondary end-point of PFS was also met, with median PFS of 1.61 in the nivolumab arm (95% CI 1.52–2.30) and 1.45 in the placebo arm (95% CI 1.45–1.54), which resulted in an HR of 0.60 (95% CI 0.49–0.75; $p < 0.0001$). The objective response rate was also in favour of nivolumab (11.2% *vs.* 0%). Rates of all adverse events (91% *vs.* 84%), all treatment-related adverse events (43% *vs.* 27%), grade 3 and 4 treatment-related adverse events (10% *vs.* 4%), serious adverse events (10% *vs.* 5%), and adverse events that led to death (2% *vs.* 1%) were numerically higher in the nivolumab arm compared to the placebo arm. The OS benefit associated with nivolumab was independent of programmed death-ligand 1 (PD-L1) expression, but these results were not available for all patients. The described trial led to the registration of nivolumab in the treatment of patients with advanced gastric cancer in several Asian countries (including Japan). Because pre-clinical data suggest that gastric cancer presents more immunogenicity in non-Asian patients, the trial raised high expectations for similar results in different populations.

The outcomes of the next study, KEYNOTE-061, were published on 4th June 2018 in "The Lancet" by Shitara et al. [3]. KEYNOTE-061 was a randomised, non-blinded, phase III trial that compared pembrolizumab with paclitaxel in the second-line treatment of advanced gastric cancer. The study included patients

after progression on platinum-based first-line treatment from both Asian and non-Asian countries. Patients were randomised in a 1:1 ratio to either pembrolizumab or paclitaxel, with primary end-points of OS and PFS assessed in patients with PD-L1 combined positive score (CPS) equal to or higher than 1. Altogether, 592 patients were recruited, from whom 395 had PD-L1 CPS equal to or higher than 1. After median follow-up of 8.5 months in the PD-L1 CPS-positive population, the study failed to meet its primary endpoints of both OS and PFS. Median OS in the pembrolizumab arm reached 9.1 months (95% CI 6.2–10.7) compared to 8.3 months (95% CI 7.6–9.0) in the paclitaxel arm, with HR equal to 0.82 (95% CI 0.66–1.03; one-sided p = 0.0421). OS results were consistent in all analysed sub-groups, with a more pronounced benefit from pembrolizumab seen in patients with very good performance status (ECOG 0) and in patients with primary tumour arising from the gastro-oesophageal junction (GEJ). Similarly to other trials comparing immunotherapy with chemotherapy, survival curves were better for chemotherapy during the first six months of the trial and then crossed favouring immunotherapy. This was confirmed by 12-month and 18-month survival rates (respectively, 40% and 26% in the pembrolizumab arm and 27% and 15% in the paclitaxel arm). In the subgroup of patients with PD--L1 CPS lower than 1 OS was 4.8 months (95% 3.9–6.1) in the pembrolizumab arm and 8.2 months (95% CI 6.8–10.6) in the paclitaxel arm (HR 1.20; 95% CI 0.89–1.63). Median PFS in the CPS-positive population was 1.5 months (95% CI 1.4–2.0) in patients receiving pembrolizumab and 4.1 months (95% CI 3.1–4.2) in patients receiving paclitaxel, with HR of 1.27 (95% CI 1.03–1.57). Similarly as with OS, patients with PD-L1 CPS lower than 1 receiving pembrolizumab had worse PFS than patients receiving paclitaxel (HR 2.05; 95% CI 1.50–2.79). Response rates achieved in patients with PD-L1 CPS equal to or higher than 1 were similar in both arms (16% in the pembrolizumab arm *vs*. 14% in the paclitaxel arm). In post-hoc analysis of patients with microsatellite instable tumours, pembrolizumab was associated with significantly higher response rate (47% *vs.* 17%), noticing low numbers of such patients. The rate of treatment-related adverse events was 53% among patients receiving pembrolizumab and 84% in patients receiving chemotherapy, with grade 3–5 adverse events rates of, respectively, 14% and 35%. The rate of adverse events that led to treatment discontinuation was 3% in the pembrolizumab arm and 5% in paclitaxel arm. Treatment-related deaths occurred in three patients (1%) in the pembrolizumab arm and in one patient (< 1%) in the paclitaxel arm. About 10% of patients in the paclitaxel arm received ICIs in subsequent treatment lines. Unfortunately, the published results did not include a quality-of-life comparison between arms. It more than obvious that the results of the KEYNOTE-061 trial were, and still are, a considerable disappointment for immunotherapy enthusiasts. Despite the limitation of primary end-point analysis to the subgroup of patients with higher probability of response to immunotherapy, pembrolizumab was not superior when compared with paclitaxel as a second-line treatment for advanced gastric cancer. At the same time, available data from the population with low PD-L1 CPS, albeit numerically limited, suggests superior results achieved with standard chemotherapy in this subgroup. This result strongly suggests that proper selection of patients will be crucial for ICI success in the treatment of gastric cancer.

Data from the last of the mentioned trials were published on 24th July 2018 by Bang et al. [4] in "Annals of Oncology". JAVELIN Gastric 300 was a randomised, open-label phase III trial that compared avelumab with the investigators' choice of chemotherapy (either irinotecan or paclitaxel in monotherapy) or best supportive care (BSC) in the third-line treatment of advanced gastric cancer. The trial included 371 patients, randomised in a 1:1 ratio to both arms, with a primary end-point of OS. In the control arm, only three patients (1.6%) received BSC instead of chemotherapy. PD-L1 expression, defined as the presence of immunohistochemical staining on at least 1% of cancer cells, was present in 29.3% of patients in the avelumab arm and 24.4% of patients in the chemotherapy arm. After a median follow-up of 10.6 months, the study failed to meet its primary end-point. Median OS was 4.6 months (95% CI 3.6–5.7) in the avelumab arm and 5.0 months (95% CI 4.5–6.3) in the chemotherapy arm, with an HR of 1.1 (95% CI 0.9–1.4; p = 0.81). The lack of difference in OS was consistent in all analysed subgroups. No difference was seen between patients assigned to paclitaxel and irinotecan. Median PFS was 1.4 months (95% CI 1.4–1.5) in patients receiving avelumab and 2.7 months (95% CI 1.8–2.8) in patients receiving chemotherapy (HR 1.73; 95% CI 1.4–2.2; p > 0.99), with results in favour of chemotherapy in all analysed subgroups. The achieved response rate was low in both arms, with only 2.2% response rate in the avelumab arm and 4.3% response rate in the chemotherapy arm. Treatment-related adverse events occurred — 48.9% of patients receiving avelumab and 74% of patients receiving chemotherapy, with grade 3 and higher in, respectively, 9.2% and 31.6% of patients. Only seven patients (3.8%) in the avelumab arm and nine patients (5.1%) discontinued the treatment due to adverse events. No deaths due to adverse events were noted in the avelumab arm. However, a significant difference in the rate of infusion-related adverse events was seen — 21.2% in the avelumab arm and only 2.8% in the chemotherapy arm. Subsequent treatment with immunotherapy was reported in two patients (1%) receiving avelumab and eight patients

(4.3%) receiving chemotherapy. Results of JAVELIN Gastric 300 trials was, just as results of KEYNOTE-061, a disappointment. Avelumab activity in the third-line treatment of gastric cancer was marginal, and clinical outcomes were numerically inferior to conventional chemotherapy. Therefore, despite a favourable toxicity profile, it is difficult to recognise avelumab as a valuable treatment option.

The results of the three described phase III trials define the current role of immunotherapy in the clinical management of advanced gastric cancer. The ATTRACTION-2 trial confirms the benefit from nivolumab as a salvage treatment after failure of standard chemotherapy in an Asian population. However, considering the difference in tumour biology and drug metabolism in other populations, these results cannot be extrapolated to non-Asians. For European and North American patients, pembrolizumab might be more appropriate option, as approved by the FDA in September 2017. Nevertheless, it should be stressed that pembrolizumab cannot be considered as the standard of care in second and subsequent lines of treatment, but only as a potential option for selected patients (with PD-L1 CPS equal to or higher than 1). This is probably one of the reasons why the European Medicines Agency (EMA) have not yet registered pembrolizumab in this indication. As evidence of nivolumab activity cannot be translated to the European population, with limited benefit of pembrolizumab and marginal activity of avelumab, it seems that the concept of ICI monotherapy for advanced gastric cancer has failed. Despite promising ICI activity, monotherapy is not enough to induce significant clinical benefit. ICIs are currently under intensive evaluation, mostly in early treatment lines and in combinations. Combining ICIs with chemotherapy can prevent early treatment failure, allowing the patient to achieve long-term benefit from immunotherapy. Unfortunately, the question of whether this assumption is correct or not will remain unanswered for many months or years.

Adjuvant treatment for biliary tract and gallbladder cancers — one vote "yes", one vote "no"

Biliary tract cancers are relatively uncommon and responsible for only one per cent of all cancer cases. It is quite a heterogenic group, which includes typical biliary tract cancers (intrahepatic and extrahepatic cholangiocarcinoma and sometimes separated subtypes of perihilar and distal common bile duct cancers) and, traditionally included in this group, gallbladder cancer. Despite the anatomical proximity of all these cancers, they form few completely separate molecular subtypes, which impedes conduction of clinical trials. Unfortunately, most cases are inoperable at the point of diagnosis, with only 20% of cases amendable with surgery. Even with optimal surgical treatment, the prognosis remains poor, with five-year survival rates lower than 15%. As a result of lack of good quality data regarding adjuvant chemotherapy, many patients receive adjuvant treatment based on fluoropyrimidine compounds or gemcitabine. This may change because last year brought early results from randomised phase III trials that compared adjuvant chemotherapy with observation. Strikingly, the available results lead to completely different conclusions.

The most mature data came from PRODIGE 12-ACCORD 18-UNICANCER GI trial and were published in the Journal of Clinical Oncology on 1st February 2019 by Edeline et al. [5]. The ACCORD study was a randomised, non-blinded, phase III trial that compared six months of chemotherapy (gemcitabine and oxaliplatin) with sole observation. GEMOX chemotherapy consisted of gemcitabine administered at a dose of 1000 mg/m^2 on day 1 of each cycle and oxaliplatin at a dose of 85 mg/m^2 on day 2 of each cycle, with cycles repeated biweekly. Patients were recruited within three months after both microscopically radical (R0) and non-radical (R1) procedures. The primary end-point was relapse-free survival (RFS) and time to definitive deterioration (TDD) of health-related quality of life. OS was one of the secondary end-points. The trial included 196 patients, randomised in 1:1 ratio to both arms. After a median follow-up of 46.5 months, the study failed to meet its primary endpoints. Median RFS was 30.4 months (95% CI 15.4–43.0) in the GEMOX arm and 18.5 months (95% CI 12.6–38.2) in the observation arm, which resulted in an HR of 0.88 (95% CI 0.62–1.25; p = 0.48). The rate of distant relapses were similar in both arms (75% in the GEMOX group and 71% in the observation group). There was no significant difference in TDD of health-related quality of life (log-rank p = 0.39) or in OS (median OS was 75.8 months [95% CI 34.4 to not reached] in the GEMOX arm *vs.* 50.8 months [95% CI 38.0 to not reached] in the observation arm, with an HR of 1.08 (95% CI 0.70–1.66; p = 0.74)). Any analysed subgroup derived benefit from chemotherapy, with significantly better results with observation in patients with gallbladder cancer. Safety analysis showed significantly higher risk of adverse events in the chemotherapy arm (p < 0.001 for grade 3 and 4 adverse events), but no difference in mortality within the first six months was seen (three deaths in the GEMOX arm *vs.* two deaths in the observation arm).

Initial analysis of the BILCAP trial, available only as an abstract from 2017 Congress of American Society of Clinical Oncology published by Primrose et al. [6], can lead to different conclusions. The trial included 447 patients after R0 and R1 resection of biliary tract and gallbladder cancers, randomised in a 1:1 ratio to either six months of capecitabine (eight cycles of capecitabine 1250 mg/m^2 twice per day for 14 days of each 21-day cycle) or sole observation. Primary end-point was overall survival (OS). Initial results of intention-to-treat analysis failed to meet the primary end-point, with median OS in the capecitabine arm of 51 months (95% CI 35–59) compared to 36 months (95% CI 30–45) in the observation arm (HR 0.80; 95% CI 0.63–1.04; p = 0.097). However, per-protocol analysis showed statistically significant benefit from adjuvant chemotherapy (median OS 53 months in the capecitabine arm [95% CI 40 to not reached] *vs.* 36 months in the observation arm [95% CI 30–44], with HR of 0.75 [95% CI 0.58–0.97; p = 0.028]). Full results have not yet been published due to data immaturity.

Currently, we dispose one full report of the negative ACCORD trial and one primary report of the positive BILCAP trial. Strictly according to evidence-based medicine (EBM) methodology, we should recognise that no adjuvant chemotherapy should be used in biliary tract and gallbladder cancers until full data from the BILCAP trial are published. Simultaneously, from a purely practical perspective, it is difficult to resign from adjuvant treatment in all patients, considering their poor prognosis. The more contradictory the evidence, the more important is honest discussion with the patient – understandable description of treatment options, limited evidence in favour of chemotherapy and unfavourable prognosis. Patients' preferences are an additional, case-specific factor that can support or dismiss the idea of adjuvant chemotherapy and support decision-making.

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