Skin carcinomas

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

Table of contents

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

1. The quality of scientific evidence

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

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

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

Introduction

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

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

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

Epidemiology

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

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

Basal cell and squamous cell skin carcinomas

Risk factors

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

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

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

Diagnosis

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

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

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

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

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

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

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

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

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

Evaluation of prognostic factors and staging

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

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

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

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

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

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

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

Treatment

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

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

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

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

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

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

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

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

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

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

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

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

T stage (primary tumour)*

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

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

High-risk factors

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

N stage (regional lymph nodes)

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

M stage (distant metastases)

M0	No evidence of distant metastases
M1	Distant metastases present

→

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

TNM staging

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

Histopathological grading (G)

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

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

T stage (main tumour mass)

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

N stage (regional lymph nodes)

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

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

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

M stage (distant metastases)

M0	No evidence of distant metastases
M1	Presence of distant metastases

TNM staging

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

Histopathological grading (G)

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

Skin cancer treatment — basic methods

Resection with histological evaluation of surgical margins

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

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

Radiotherapy

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

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

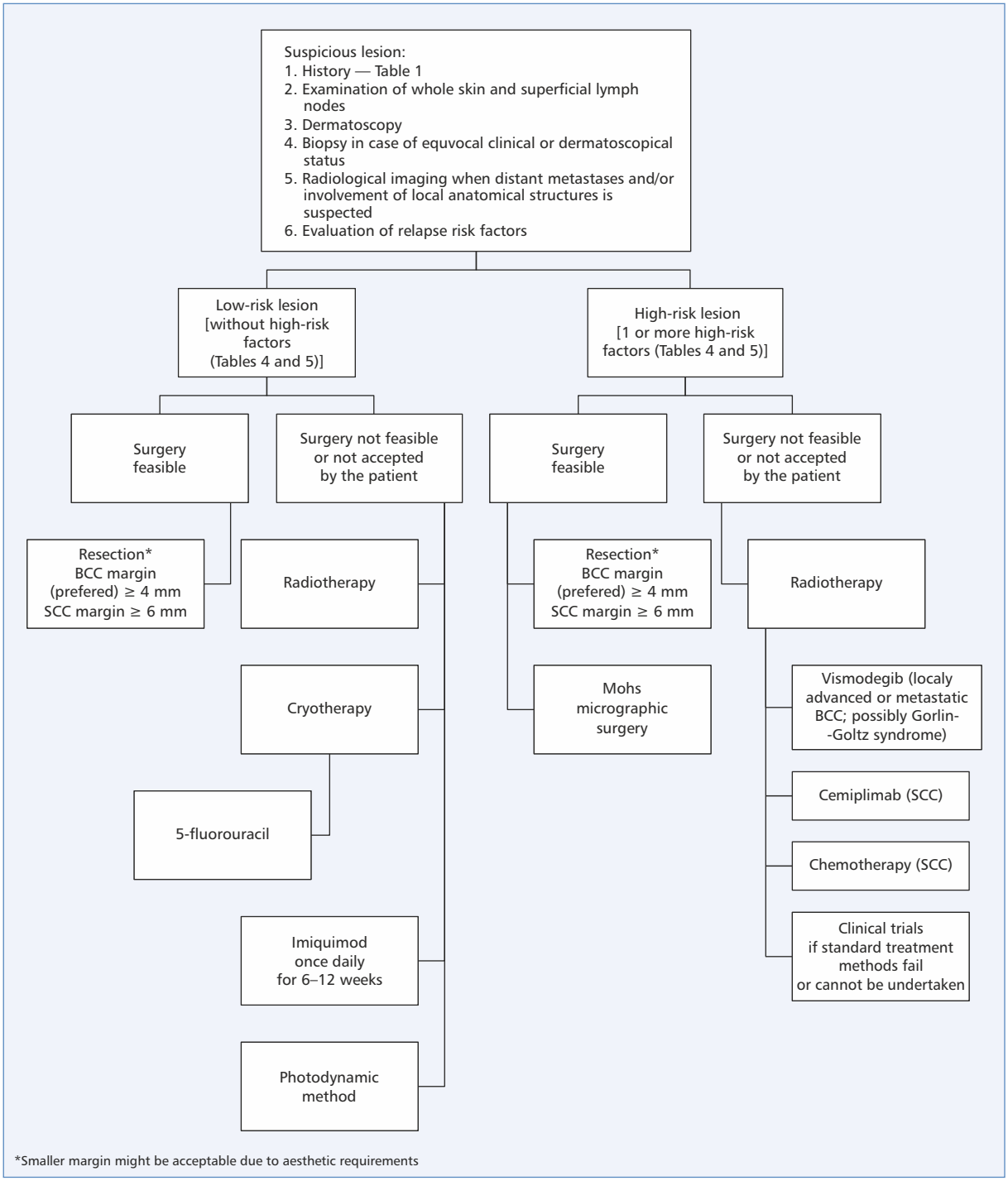

Figure 1. Recommended diagnostic and treatment algorithm in case of skin carcinoma suspicion

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

Contraindications for radiotherapy include:

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

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

Chemotherapy

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

Hedgehog pathway inhibitors

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

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

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

Immunotherapy in the treatment of advanced SCC

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

Clinical trials

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

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

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

External treatment of skin cancer

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

5-fluorouracil (0.5%)

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

Imiquimod (5%)

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

Photodynamic method

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

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

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

Cryosurgery

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

Commentary

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

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

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

Observation after oncological treatment

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

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

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

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

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

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

Skin cancer prevention

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

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

Merkel-cell carcinoma (primary neuroendocrine carcinoma of skin)

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

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

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

Aetiology

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

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

Diagnosis

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

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

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

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

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

Staging and prognosis

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

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

Treatment

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

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

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

Table 8. Staging/prognostic groups

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

Stage I and II

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

Stage III

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

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

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

Stage IV

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

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

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

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

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

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

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

Treatment of local and locoregional recurrence

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

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

Other rare forms of skin cancer

Sebaceous carcinoma

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

Primary cutaneous apocrine carcinoma (apocrine adenocarcinoma)

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

Eccrine carcinoma (also syringoid carcinoma)

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

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

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

Conflicts of interest

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

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