Expert recommendation on diagnostic--therapeutic management in skin carcinomas

Team of authors:

Piotr Rutkowski[1], Witold Owczarek[2], Dariusz Nejc[3], Arkadiusz Jeziorski[3], Wojciech M. Wysocki[1, 4], Monika Słowińska[2], Monika Dudzisz-Śledź[1], Piotr Wiśniewski[1], Hanna Tchórzewska-Korba[1], Anna Szumera-Ciećkiewicz[1, 5], Hanna Koseła-Paterczyk[1], Dorota Kiprian[1], Tomasz Świtaj[1], Joanna Narbutt[6], Leszek Królicki[7], Dawid Murawa[8], Marcin Zdzienicki[1], Marcin Ziętek[9, 10], Adam Maciejczyk[9, 10], Lidia Rudnicka[11]

[1]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw
[2]Military Institute of Medicine, Central Clinical Hospital of the Ministry of National Defense, Warsaw
[3]Medical University of Lodz, N. Copernicus Provincial Multidisciplinary Centre of Oncology and Traumatology, Lodz
[4]Department of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz-Modrzewski Krakow University, Krakow
[5]Institute of Hematology and Transfusion Medicine, Warsaw
[6]Department of Dermatology, Pediatric Dermatology and Oncology Clinic, Medical University of Lodz
[7]Department of Nuclear Medicine, Medical University of Warsaw
[8]Department of Surgery and Oncology, Faculty of Medicine and Health Sciences, University of Zielona Góra
[9]Lower Silesian Oncology Center, Wrocław
[10]Department of Oncology, Wrocław Medical University
[11]Chair and Clinic of Dermatology, Medical University of Warsaw

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According to the authors and editors, this report contains the best justified principles of diagnostic and therapeutic procedures prepared on the basis of the scientific value of evidence and the category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always

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correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities for reimbursement of individual procedures should be considered.

1. *The quality of scientific evidence*
   I — Evidence from at least one large randomized controlled clinical trial (RCT) of high methodological quality (low risk of bias) or meta-analysis of properly designed RCTs without significant heterogeneity
   II — Small RCTs or large RCTs with risk of bias (lower methodological quality) or a meta-analysis of such studies or RCTs with significant heterogeneity
   III — Prospective cohort studies
   IV — Retrospective cohort studies or case-control studies
   V — Uncontrolled studies, case reports, expert opinions
2. *Strength of recommendations*
   1 — Recommendation based on high-quality evidence on which unanimity has been achieved or a high level of expert team consensus
   2A — Recommendation based on lower-quality evidence on which unanimity was reached or a high level of expert team consensus
   2B — Recommendation based on lower-quality evidence on which moderate expert consensus is achieved

Reviewer: Prof. Grażyna Kamińska-Winciorek

Methodology

Review of all phase II and III clinical trials available in PubMed and published between 1990 and 2021 with the terms: cutaneous carcinoma, skin carcinoma, basal cell carcinoma, cutaneous squamous cell carcinoma, Merkel cell carcinoma, and the current recommendations of ESMO, ASCO, NCCN, and PTOK.

Summary

Diagnostics

— Dermoscopic examination is recommended before possible resection of skin lesions
— If skin cancer is suspected, an excisional biopsy should be performed (in most cases under local anesthesia), with a minimum surgical margin of 1–2 mm, or a skin lesion biopsy for histopathological examination (IV, 2A)

Staging

— Physical examination with a careful assessment of full-body skin (especially the assessment of other suspicious skin lesions, regional lymph nodes, and possible distant metastases)
— In the higher stages, it is recommended to perform ultrasound, CT, and/or PET for proper staging

Treatment — stages I–III (resectable)

— The primary goal of treatment in patients with skin cancers is complete resection of neoplastic tissues (III, 1). Therefore, in the first place, it is necessary to choose methods with the greatest radicality and, at the same time, the lowest risk of local failure. The choice of therapy should be determined by (1) clinical assessment, number and size of skin cancer foci; (2) histological type; (3) the grade of cancer invasiveness, the risk of local and distant recurrence; (4) preservation of organ/body part function and the final aesthetic effect of the treated area; (5) the effectiveness of therapy assessed as relapse rates within 4–6 months and 3–5 years (verified by physical examination, dermoscopy, and histopathology); (6) treatment tolerance (pain, treatment duration, side effects, complication risk); (7) the availability of a given therapeutic method; (8) efficiency of the patient's immune system; (9) and individual patients' preferences
— Local treatment should be according to the Summary of Product Characteristics (SmPC), for example, imiquimod — Bowen's disease, superficial BCC; photodynamic therapy (PDT) using *5-aminolevulinic acid* (*5-ALA*) nanoemulsion — Bowen's disease, superficial BCC; 5-ALA patch — only used in actinic keratosis, 5-FU — Bowen's disease, superficial BCC
— Sentinel lymph node biopsy (SNB) is recommended in patients with Merkel cell carcinoma without metastases detectable clinically or in imaging tests

— Lymphadenectomy is indicated in the case of skin cancer metastases in clinically overt lymph nodes (II, 1). Radiotherapy is recommended as adjuvant treatment (III, 2A)

Treatment — stage III unresectable and stage IV, as well as locoregional unresectable lesions

— In patients with metastatic disease, treatment in clinical trials is the most appropriate treatment
— In the systemic treatment of patients with basal cell carcinoma, the use of Hedgehog pathway inhibitors (vismodegib), squamous cell carcinoma — immunotherapy (cemiplimab), Merkel cell carcinoma — immunotherapy (avelumab) is indicated (II, 1). Assessment of PD-L1/PD-1 expression in cancer tissue is not required to initiate immunotherapy (III, 2A)

Follow-up after treatment completion

— Patient education regarding skin and lymph nodes self-examination and compliance with photoprotection requirements
— History and physical examination, including the full-body skin evaluation (dermoscopy), especially around the scar after cancer and regional lymph nodes resection (examination every 3–6 months for the first 2–3 years, then every 3–12 months up to 5 years and once a year after 5 years)
— The frequency and type of examinations, as well as the duration of the observation period, should depend on the individual risk of relapse

Introduction

Skin cancers, mainly basal cell carcinoma (BCC) and squamous cell carcinomas (SCC), account for 98% of skin cancers and are the most common malignant neoplasms among people with light skin color. Skin cancers, referred to in the Anglo-Saxon literature as "non-melanoma skin cancers" (NMSC), account for approximately 1/3 of all recorded human cancers.

Although they rarely lead to metastases and patient death, they constitute a very important clinical problem. These cancers are characterized by infiltration of surrounding tissues and destruction of adjacent structures such as bone and cartilage, resulting in, *inter alia*, aesthetic defects, and a quality-of-life (QoL) deterioration; they are also responsible for significant morbidity. On the other hand, among high-risk patients (i.e. people undergoing chronic immunosuppression, with a genetic predisposition to developing skin cancer induced by UV radiation), these cancers are aggressive and can lead to death. It should be emphasized that patients with skin cancer more often suffer from other skin neoplasms, including melanoma, than the general population.

It should be noted that this study does not cover preneoplastic conditions (including actinic keratosis) or squamous cell or basal cell carcinomas located within the genital organs and the oral cavity [1–13].

Epidemiology

Skin cancers account for over 30–50% of all diagnosed malignant neoplasms. The lifetime risk of developing skin cancers (in Caucasians) exceeds 20%. The incidence tends to increase with the age of patients (most cases are recorded in the 8th decade of life). In 2017, 14 180 new cases were registered in Poland (6795 in men and 7388 in women), which corresponds to the incidence of 8.1% and 8.5%, respectively [14]. Unfortunately, in this group of cancers, one should expect a significant degree of underestimation resulting from incomplete reporting to the National Cancer Registry.

The most common skin cancer is basal cell carcinoma (BCC), which accounts for 80% of skin cancers, followed by squamous cell carcinoma (SCC) — 15–20% of cases [10, 13]. Other forms of skin cancers are significantly less frequent [1–13].

Basal cell and squamous cell cutaneous carcinoma

Risk factors

The rapidly increasing incidence of BCC and SCC is caused by excessive exposure to ultraviolet radiation.

The main factors responsible for the increasing incidence of BCC and SCC include lifestyle, way of dressing, tan "fashion", migrations of people with I, II, and III skin phototypes to the regions in the world with high sun exposure, living in mountainous regions or low latitude geographical areas, the use of lamps emitting UV radiation (so-called sunbeds). An important factor in the development of BCC and SCC is occupational exposure to UV radiation in people who work outdoors and do not use any form of photoprotection [1–11]. Table 1 shows the risk factors for skin cancer development.

Table 1. Risk factors for the development of skin cancer [1, 2]

Risk factors for the development of skin cancer		SCC	BCC
Environmental factors	Cumulative UV dose		×
	Intensive intermittent sunbathing	×	
	Ionizing radiation	×	×
	Exposure to chemicals *	×	(×)
	HPV infections	×	
	Smoking	×	
Genetic factors	I skin phenotype	×	×
	Xeroderma pigmentosum	×	×
	Oculocutaneous albinism (OCA)	×	(×)
	Epithelial papillary dysplasia	×	
	Bullous epidermal detachment	×	
	Ferguson-Smith disease (FSD)	×	
	Muir-Torre syndrome	×	(×)
	Bazex syndrome		×
	Rombo syndrome		×
	Gorlin-Goltz syndrome		×
Chronic skin diseases	Chronic non-healing ulcers	×	
	Long-lasting: — cutaneous lupus erythematosus — erosive lichen planus (ELP) — lichen sclerosus (LS)	×	
	Porokeratosis	×	
	Sebaceous nevus		×
Immunosuppression	Status after organ transplantation	×	(×)
	Other types of immunosuppression, e.g. AIDS syndrome, HPV infection	×	

*Arsenic, mineral oil, coal tar, soot, nitrogen mustard, aromatic polycyclic compounds — biphenyl derivatives, 4,4'bipyridyl, psoralen (with UVA) [1–11]; BCC — basal cell carcinoma; SCC — squamous cell carcinoma; HPV — human papillomavirus

Hedgehog (Hh) pathway activation is found in most patients with BCC, mainly in the form of PTCH1 receptor inactivation (Patched 1) or oncogenic activation of the SMO receptor (Smoothened). In Gorlin-Goltz syndrome (nevoid basal cell syndrome), which is an autosomal dominant disease characterized by multiple BCCs, abnormalities in facial and skeletal development, and an increased risk of medulloblastoma and rhabdomyosarcoma, a disorder in the gene encoding the PTCH1 inhibitor receptor is found.

Diagnostics

Initial diagnosis is made on the basis of medical history and clinical picture of the skin lesion characteristic for BCC and SCC (III, 2A); 80% of skin cancers are located within the head and neck, the remaining 20% occur on the limbs and trunk.

Skin cancers are characterized by frequent multifocal development, especially in patients over 70 years of age with severe skin photodamage; as a rule, BCC grows slowly. It is not uncommon in these patients to have up to several foci of basal cell carcinoma, numerous foci of actinic keratosis, and foci of Bowen's disease or melanomas. Due to this clinical feature, it is very important to take a detailed medical history and do a physical examination, including a full-body skin assessment. As the usefulness of dermoscopy in the diagnosis of early skin cancers was proven in numerous publications, it is recommended to treat this quick and non-invasive diagnostic method as a permanent element of the physical examination. It is especially important to perform a dermoscopic examination in atypical cases, requiring the exclusion of lesions of a different etiology (differential diagnosis), when assessing lesions of small size or differentiating actinic keratosis from pre-invasive SCC (*in situ*). This examination should also be used to assess tumor burden before the planned treatment, as well as to assess treatment radicality and follow-up (Tab. 2 and 3). Detailed recommendations for dermoscopy of basal cell carcinoma and squamous cell carcinoma are presented in a separate study [15, 16]. There is no screening program for the detection of population-based skin cancers [17].

The diagnosis is based on the histopathological examination of an excisional biopsy or skin lesion sample. In addition to determining the histological type of tumor, the pathological report should also identify the cancer subtype, especially if there is a higher-risk subtype. In the case of invasive cancer, the greatest dimension and depth of infiltration (in millimeters) should be reported. Determining the status of the surgical margin and the infiltration of vessels and perineural spaces constitute other essential elements complementing the histopathological diagnosis. Usually, a microscopic picture is sufficient to determine the type of cancer. The presence of intercellular bridges and keratosis are indicative of squamous cell carcinoma, while atypical, mitotically active basaloid cells arranged in a palisade in the periphery are typical of basal cell carcinoma. In case of doubts regarding the histological type (BCC *vs.* SCC), the examination should be supplemented with the basic differentiating immunohistochemical staining panel: BerEP4 (+), EMA (–), CK5/6 (–) in basal cell carcinoma, CK5/6 (+), EMA (+) and BerEP4 (–) in squamous cell carcinoma.

The histopathological type and stage of the neoplasm, together with the assessment of the patient's condition, will be decisive in making further decisions. In the case of clinical cancer suspicion, radical excision of the skin lesion can be performed; in case

Table 2. Dermoscopic symptoms of BCC and SCC and their differentiation (based on [7])

	Dermoscopic symptoms of non-pigmented BCC	Dermoscopic symptoms of pigmented BCC	Dermoscopic symptoms of non-pigmented SCC	Dermoscopic symptoms of pigmented SCC
Early stage	— Milky red/pink structureless area — Thin branched microvessels/telangiectasias and/or small, atypical vessels irregularly distributed within the structureless white/pink areas of the lesion — Minor ulceration/erosions — Serous/blood crust — White shiny blotches and strands (visible under polarized light)	— Gray-blue, brown globules and dots — Buck-shot scatter dots — Dark brown, blue or black concentricglobules — *Spoke-wheel*-like *structures* — leaf -like structuresbrown or blue-gray — + Features of early-stage non-pigmented BCC	Actinic keratosis **On the face:** — strawberry pattern = white circles on a pink background = pink/red pseudo-network — erythema — white or yellow scales on the surface — thin wavy, twisted vessels around the hair follicles openings — white circles surrounding the yellow plug located at the hair follicles openings/ targetoid hair follicles — white rosettes at the hair follicles openings (visible in polarized light) **Outside the face:** — white/yellow scale on the surface — erythema — keratin and dotted vessels — rosette sign — thin irregular telangiectasias **Bowenoid actinic keratosis:** Glomerular vessels regularly covering the entire surface of the lesion **Bowen's disease (SCC *in situ*):** — white/yellow scale on the surface of the lesion — glomerular vessels in clusters; these vessels may appear as tiny red dots or globules — minor ulceration/erosion/crust	**Pigmented Actinic keratosis** **On the face:** — annular–granular structures, — asymmetric follicular openings — rhomboidal structures — a pseudonetwork formed by yellowish horn plugs in the hair follicles openings, surrounded by a gray halo/ /targetoid hair follicles **Pigmented Bowen's disease (SCC *in situ*):** — brown or gray dots on the edges of the lesion arranged in radial lines — pink or skin-colored structureless eccentric areas — glomerular vessels/red dots randomly distributed/in clusters/on the periphery of the lesion — desquamation of the lesion surface
Late stage	— Thick, sharp arborising blood vessels visible on the periphery of the lesion, pointing towards its center (nodular type only) — Ulceration — Crust — White shiny blotches and strands, rainbow symptom (visible under polarized light)	— Globules and large blue-gray nests of ovoid/oval structures — + Features of late-stage non-pigmented BCC	Invasive SCC — Centrally located yellow plug/keratin mass/within ulcer — Ulcer surrounded by concentric hairpin vessels/irregular linear vessels surrounded by a white halo — Targetoid hair follicles/white circles on a background of white/pink structureless areas — rusts red-orange/brown and even black/sore — In some areas of lesion, it is possible to observe structures typical of the early stage SCC	Invasive pigmented SCC — Diffuse, homogeneous blue pigmentation — Irregularly distributed blue--gray granular structures — If ulcerated, dark brown or black crust — Poorly visible vessels
Differentiation	— Metastasis of melanoma/other cancers — Spitz nevus — Dermal nevi of pink/flesh color	— Nevi — Melanoma — Melanoma metastases — Seborrheic keratosis	— Spitz nevus — Non-pigmented BCC — Melanoma — Keratoacanthoma	— Melanoma/LMM (on the face) — Pigmented BCC — Lichenoid keratosis/regressive seborrheic keratosis

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

Table 3. Classification of actinic keratosis currently considered to be IEN or SCC *in situ* (based on [18–20])

The extent and number of actinic keratosis (AK) foci	Histopathological picture	Clinical picture
Single AK lesions ≥ 1 and ≤ 5 palpable or visually visible lesions in a given area or region of the body	**Type I AK = early SCC *in situ*** Presence of atypical keratinocytes in the basal layer of the epidermis and the lower third of the epidermis	**Grade I — mild** Foci more palpable than visible to the naked eye
Numerous AK lesions ≥ 6 palpable or visually visible lesions in a given area or region of the body	**Type II AK early SCC *in situ*** Presence of atypical keratinocytes in the lower 2/3 of the epidermis	**Grade II — moderate** Lesions are both visible and palpable
Cancerization field ≥ 6 AK lesions in a given area or region of the body and extensive, extending areas of skin chronically damaged by the sun with symptoms of hyperkeratosis	**III type AK Bowenoid AK/SCC *in situ*** Presence of atypical keratinocytes covering the lower 2/3 to full thickness of the epidermis	**Grade III — severe** The lesions are covered with thick hyperkeratotic scales and are evident
Immunosuppressed patients with symptoms of AK Any number and size of AK lesions, immunosuppression	**Invasive SCC** The nests of keratinocytes penetrate the dermis Cancer cells are large, have abundant eosinophilic cytoplasm, and clearly enlarged nuclei Various degrees of keratosis are present, and cancerous pearls may be visible Depending on the degree of SCC differentiation, the intensity of cell pleomorphism, mitotic activity, and features typical of squamous epithelium are different. The inflammation and the reaction of the stroma are differently expressed depending on the histological type	**Suspected invasive SCC** When symptoms occur: — major criteria: ulceration, infiltration, bleeding, size > 1 cm, rapid enlargement of the lesion, erythema — minor criteria: pain, itching, pigmentation, hyperkeratosis, palpation

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

of clinical doubts, a biopsy of the lesion is necessary, and a decision is made after receiving the results of histopathological examination (lesion sampling or excisional biopsy — the latter is also of therapeutic importance).

Suspicion of an invasive lesion (manifested by deep infiltration, involvement of tissues and structures located below/in the vicinity of the tumor, i.e. muscles, bones, nerves, lymph nodes, eyeball) is an indication to extend the diagnosis to include imaging tests (computed tomography, magnetic resonance imaging) [1–6, 9–11]. If enlarged regional lymph nodes are found on physical examination or imaging tests, a fine-needle biopsy or the whole lymph node resection for histopathological examination should be performed [1–6, 9–11].

Assessment of prognostic factors and staging

The next step is to assess the occurrence of prognostic factors related to a specific neoplastic lesion, which determine its classification to the high or low-risk group (Tab. 4 and 5) and staging according to the 2009 and 2017 revisions of the American Joint Committee on Cancer (AJCC), (Tab. 6) [1–6, 9–11].

Treatment

The primary goal of treatment in patients with skin cancers is the complete removal of the neoplastic tissues (III, 1). Therefore, in the first place, it is necessary to choose methods with the greatest radicality and, at the same time, the lowest risk of local failure. The choice of therapy should be determined based on [21]:

— clinical assessment, number, and size of skin lesions;
— histological type;
— the grade of cancer invasiveness, the risk of local and distant recurrence;
— preservation of organ/body part function and final aesthetic effect of the treated area;
— the effectiveness of therapy assessed as relapse rates for 4–6 months and 3–5 years (verified by physical examination, dermoscopy, and histopathology);
— treatment tolerance (pain, treatment duration, side effects, risk of complications);
— the availability of a given therapeutic method;
— the efficacy of the patient's immune system;
— individual patients' preferences.

Figure 1 shows an algorithm for the recommended diagnostic and therapeutic procedures in patients with suspected skin cancer.

Table 4. Risk assessment for squamous cell carcinoma (SCC)[1–6, 9–11]

Risk factors for local and distant SCC recurrence		
	Low-risk lesion	**High-risk lesion**
Location and size	L area < 20 mm	L area > 20 mm and ≤ 40 mm
	M area < 10 mm	M any area
		H area
Lesion borders	Well, sharply demarcated	Borders not sharp
Primary/recurrent tumor	Primary	Recurrent
Immunosuppression	No	Yes
Prior radiotherapy or chronic tumor inflammation	No	Yes
Rapid tumor growth	No	Yes
Neurological symptoms	No	Yes
Grade of histological differentiation	Well/moderately differentiated G1, G2	Poorly differentiated G3
Thickness of tumor invasion	< 2 mm Clark level I–III	≥ 2 mm Clark level IV–V
Infiltration of nerves and vessels	No	Yes
Histopathological type	Metatypical Verrucosus Fusiformis Mixtus	Acantholitic Desmoplastic Adenoidalis, adenoidosquamous Mucosoadenoidalis Fusiformis (after radiotherapy)

Area L — torso and limbs, excluding the front surface of the lower leg, hands, feet, ankles, and nails; area M — cheeks, forehead, scalp, neck, front surface of the lower leg; area H — head and neck, excluding area M, genitals, hands, and feet

Table 5. Risk assessment for basal cell carcinoma (BCC) [1, 22]

Risk factors for BCC recurrence		
	Low-risk lesion	**High-risk lesion**
Location and size	L area < 20 mm	L area ≥ 20 mm
	M area < 10 mm	M any area
		H any area
Lesion borders	Well, sharply demarcated	Borders not sharp
Primary/recurrent tumor	Primary	Recurrent
Immunosuppression	No	Yes
Prior radiotherapy	No	Yes
Histopathological type	Nodular Superficial Pigmented Infundibulocystic Fibroepitelial	Basosquamous carcinoma Sclerosing/morphoeic Infiltrative With sarcomatoid differentiation Micronodular
Perineural infiltration	No	Yes

L area — torso and limbs, excluding the front surface of the lower leg, hands, feet, ankles, and nails; M area — cheeks, forehead, scalp, neck, front surface of the lower leg; H area — head and neck, excluding M area, genitals, hands and feet

Surgical procedure is often the fastest and most effective curative method; however, when choosing this strategy, one should take into account, *inter alia*, the advanced age of the patient and numerous comorbidities, as well as psychological and aesthetic aspects. Therefore, in some cases, it is permissible to use alternative removal methods instead of surgical excision (especially in cancers with a low risk of recurrence) (III, 2B). The following methods of treatment are distinguished:

Table 6A. Classification TNM of the stages of skin cancer (2018)

Feature T (primary tumor)

Tx	Not possible to evaluate
T0	No features of the primary tumor
Tis	Carcinoma *in situ*
T1	Tumor with the greatest dimension ≤ 2 cm
T2	Tumor with the greatest dimension > 2 cm and i ≤ 4 cm
T3	Tumor of the greatest dimension ≥ 4 cm with superficial bone erosion, perineural infiltration and deep infiltration
T4	
T4a	Tumor with macroscopic cortical bone or marrow invasion
T4b	Tumor with axial skeleton invasion including skull base and/or intervertebral foramina involvement, penetrating into epidural space

#Deep invasion is defined as subcutaneous fat invasion or > 6 mm (measured in millimeters from the granular layer of the nearest adjacent normal epidermis to the deepest point of the tumor); perineural invasion in stage T3 is defined as clinical or pathological nerves involvement except for crossing the skull base

Feature N (regional lymph nodes)

Nx	Not possible to evaluate
N0	No lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node; lymph node size ≤ 3 cm in the greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimention or in multiple ipsilateral lymph nodes none more than 6 cm in greatest dimention
N3	Metastasis in a lymph node more than 6 cm in greatest dimention

Feature M (distant metastases)

M0	No metastases
M1	Present metastases

Cancer 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 IVA	T1	N2, N3	M0
	T2	N2, N3	M0
	T3	N2, N3	M0
	or		
	T4	Any N	M0
Stage IVB	Any T	Any N	M1

TNM classification of head and neck skin cancers (2018 version)

Feature T (primary tumor)

Tx	Not possible to evaluate
T0	No features of the primary tumor
Tis	Carcinoma *in situ*
T1	Tumor with the greatest dimension < 2 cm
T2	Tumor with the greatest dimension ≥ 2 cm and < 4 cm
T3	Tumor of the greatest dimension ≥ 4 cm with superficial bone erosion, perineural infiltration and deep infiltration
T4	
T4a	Tumor with macroscopic cortical bone or marrow invasion
T4b	Tumor with axial skeleton invasion including skull base and/or intervertebral foramina involvement, penetrating into epidural space

#Deep invasion is defined as subcutaneous fat invasion or > 6 mm (measured in millimeters from the granular layer of the nearest adjacent normal epidermis to the deepest point of the tumor); perineural invasion in stage T3 is defined as clinical or pathological nerves involvement except for crossing the skull base

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Table 6A cont. Classification TNM of the stages of skin cancer (2018)

Feature N (regional lymph nodes)	
Nx	Not possible to evaluate
N0	No lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimention, without extranodal extension
N2	
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimention and without extranodal extension
N2b	Multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimention, without extranodal extension
N2c	Bilateral or contralateral metastases, ≤ 6 cm in greatest dimention, without extranodal extension
N3	
N3a	Lymph node metastasis > 6 cm in the greatest dimension and without extranodal extension
N3b	Metastasis in single or multiple lymph nodes with extranodal extension (infiltration of adjacent skin or subcutaneous tissue with adjacent muscle or nerve involvement)
Additionally, a U or L designation may be used for metastases above or below the lower edge of the cricoid, respectively	

Feature M (distant metastases)	
M0	No metastases
M1	Present metastases

Cancer 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 IVA	T1	N2, N3	M0
	T2	N2, N3	M0
	T3	N2, N3	M0
	or T4	Any N	M0
Stage IVB	Any T	Any N	M1

Table 6B. Classification AJCC of the stages of skin cancer (2009)

Feature T (primary tumor)*	
Tx	Not possible to evaluate
T0	No features of the primary tumor
Tis	Carcinoma *in situ*
T1	Tumor with the greatest dimension ≤ 2 cm with < 2 high-risk factors[#]
T2	Tumor with the greatest dimension > 2 cm or neoplasm of any dimension with ≥ 2 high-risk factors[#]
T3	Neoplasm with infiltration of maxilla, mandible, orbit, or temporal bone
T4	Tumor with infiltration of the skeleton or perineural infiltrates on skull base

*Not applicable to the clinical form of eyelid squamous cell carcinoma; [#] High-risk factors of the primary lesion (feature T)

→

Table 6B cont. Classification AJCC of the stages of skin cancer (2009)

High-risk factors	
The depth of primary lesion infiltration	> 2 mm Clark level ≥ IV Perineural space infiltrates
Lesion localization	Earlobe Vermillion Lip not covered with hair
Differentiation	Poorly differentiated or undifferentiated

Feature N (regional lymph nodes)	
Nx	Not possible to evaluate
N0	No lymph node metastasis
N1	Metastasis to a single lymph node located within the primary lesion drainage; lymph node size ≤ 3 cm in the greatest dimension
N2	Metastasis to a single lymph node located within the primary lesion drainage; lymph node size > 3 cm but < 6 cm; or to multiple ipsilateral lymph nodes, however, no lymph node is larger than 6 cm; or bilateral metastases, or contralateral metastases, but lymph nodes < 6 cm
N2a	Metastasis to a single lymph node located within the primary lesion drainage; lymph node size > 3 cm but < 6 cm
N2b	Ipsilateral metastases to multiple lymph nodes, but no lymph node larger than 6 cm
N2c	Bilateral or contralateral metastases, but lymph nodes not larger than 6 cm
N3	Lymph node metastasis > 6 cm in greatest dimension

Feature M (distant metastases)	
M0	No metastases
M1	Present metastases

Cancer 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

Histological malignancy grading (G)	
Gx	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

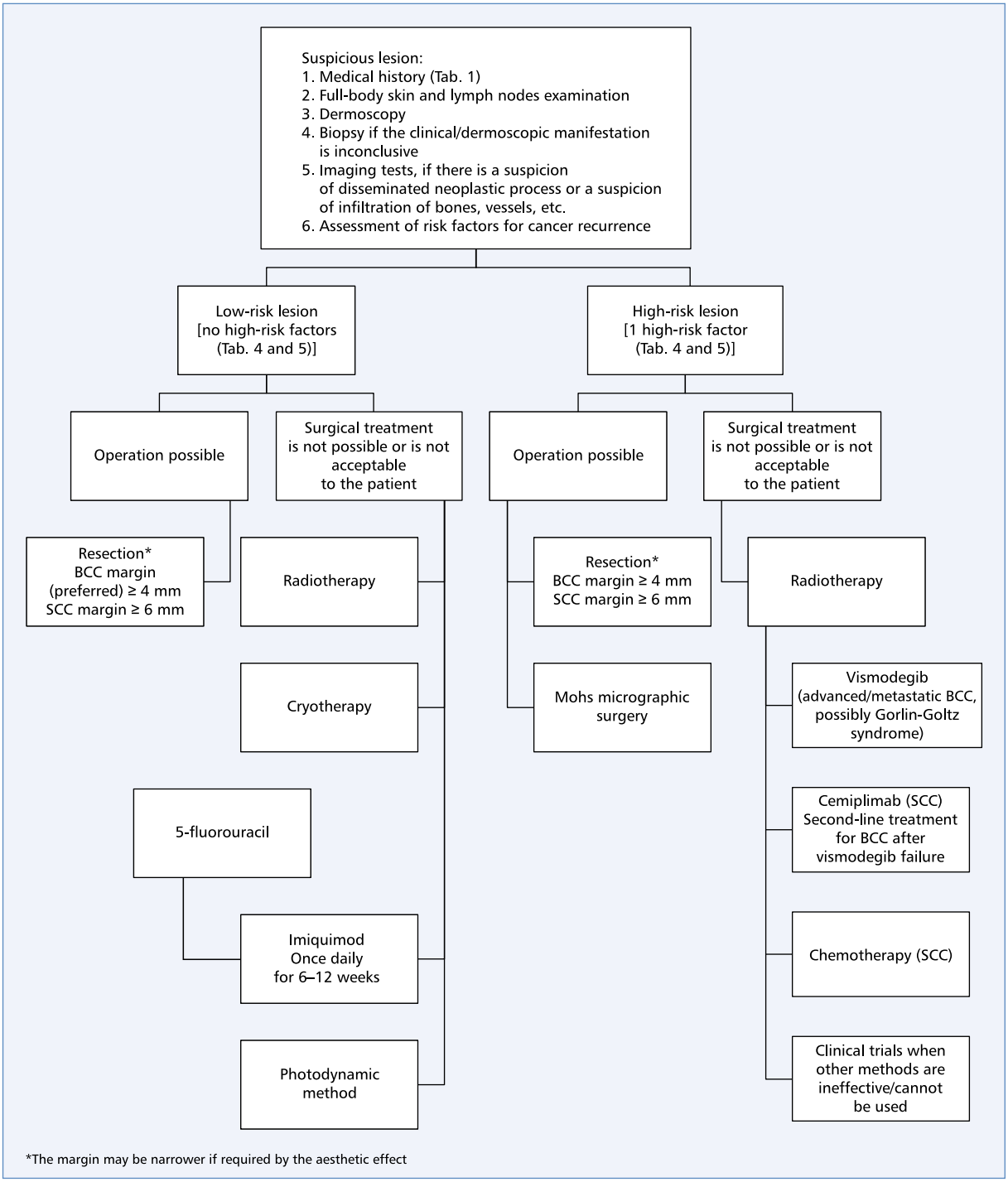

Figure 1. Recommended diagnostic and therapeutic procedures in patients with basal cell and squamous cell carcinoma of the skin; BCC — basal cell carcinoma; SCC — squamous cell carcinoma

— superficial: 5-fluorouracil, imiquimod (an immune response modulator applied topically for 6–8 weeks, treatment may be extended to 12–16 weeks to achieve long-term remission. Treatment should be performed by a physician experienced in using imiquimod), diclofenac sodic (only in actinic keratosis), photodynamic therapy;

— local:
  - without the possibility of assessing treatment margins: laser therapy, cryotherapy, electrocoagulation, radiotherapy,
  - with the assessment of treatment margins: radical surgical excision (possibly Mohs micrographic surgery).

It should be emphasized that there is still a lack of good-quality, comparative studies on various methods of skin cancer treatment. Most of the publications concern lesions in localization associated with a low risk of recurrence/invasiveness. In the case of skin cancer (except for inoperable lesions), surgical treatment remains the "gold standard" (III, 1) [1–13, 23].

Skin cancer treatment — basic treatment

Excision with histological evaluation of the surgical margins

It is the most commonly used skin cancer treatment (for both high and low risk of recurrence).

It is recommended to preserve an operating margin of at least 4 mm for BCC and 6 mm for SCC (II, 2A). For high-risk cancer, intraoperative volume control (Mohs micrographic surgery) is recommended. If this is not possible, we recommend wider cutting margins of 10 mm. Where such extensive margins of neoplastic skin affect the cosmetic effect, radical excision with a smaller margin (R0 margin) may be considered, as such a margin is required for Mohs micrographic surgery. This method consists of layered tumor excision with an intraoperative evaluation of frozen sections from the edges and bottom of the tumor bed. Individual sections are marked in detail to expand only those surgical margins in which neoplastic cells were found. This procedure allows for radical excision of the tumor with the greatest possible saving of healthy tissues [1–6, 9, 11, 13, 24, 25].

Lymphadenectomy is indicated in the presence of skin cancer metastases in clinically overt lymph nodes (II, 1), confirmed by cytology or histopathology.

Radiotherapy

In the case of skin cancers (NMSC, e.g. BCC and SCC), radiotherapy may be an alternative treatment if there are contraindications to surgery or the patient does not consent to surgical treatment (III, 2A). In addition, radiotherapy may be the procedure of choice in unresectable neoplasms, and it can also be used to obtain a better cosmetic effect and maintain the functions of a given area (mainly in patients over 60 years of age). Irradiation should be considered in the case of lesions greater than 5 mm, situated in the area of the mouth, eyelids, tip/wings of the nose, and greater than 2 cm in the area of the ears, forehead, and scalp [26], especially if a serious cosmetic defect is expected. Radiotherapy is an effective treatment, the 5-year success rate in retrospective studies was 94.4% for BCC and 92.7% for SCC, and the 15-year success rate was 84.8% and 78.6%, respectively [27]. The local recurrence rate in meta-analyzes is approximately 10% for both SCC and BCC [25–27]. The results of comparative studies show the advantage of surgical treatment — the 4-year local recurrence rate is 0.7% in the group treated with surgery and 7.5% after irradiation for BCC [28–31]. In radical radiotherapy of skin neoplasms, both conventional fractionated (60–70 Gy over 6–7 weeks or 45–55 Gy over 3–4 weeks) and hypofractionated regimens (40–44 Gy over 2 weeks or 30 Gy in 5 fractions over 2–3 weeks) are used [32]. Complementary radiotherapy is used in cases of locoregionally advanced skin cancers (in particular, when perineural infiltration is found), after lymphadenectomy due to SCC metastases to regional lymph nodes, and when the operation was incomplete, and there is no possibility of surgical radicalization. This method is also recommended when skin cancer resection was performed nonradically using the Mohs micrographic method. Additional risk factors for local recurrence are tumor location in the head and neck region, size (> 2 cm), low differentiation grade, recurrence, and immunosuppression [33]. In adjuvant radiotherapy, doses of 50–66 Gy over 5–7 weeks are used, while higher doses are used in the case of positive margins and unoperated lymph node metastases [1, 6, 32]. Radiotherapy is also a valuable method of palliative treatment. Brachytherapy is a valuable treatment method in selected patients with superficial tumors (up to 2 cm) and after nonradical procedures.

Complications with a tendency to worsen over time are the disadvantage of radiotherapy. They include acute skin reaction in the form of erythema, wet and dry exfoliation, and in some cases also skin necrosis, late reaction with telangiectasia, pigmentation changes (permanent skin discoloration), and fibrosis. The cosmetic effect may thus deteriorate over time. A significant complication is the possibility of secondary neoplasm induction, mainly NMSC, especially in the case of irradiation at a young age [34–36].

Contraindications to the use of radiotherapy are (III, 2B):

— the patient's age below 60 years of age (relative contraindication);
— connective tissue diseases (relative contraindication);
— systemic lupus erythematosus, systemic scleroderma;
— genetic syndromes associated with the occurrence of skin neoplasms — Gorlin-Goltz syndrome (nevoid basal cell carcinoma syndrome), xeroderma pigmentosum;
— scleroderma-like basal cell carcinoma (SBCC);
— the occurrence of lesions in the following locations: hands (especially back), soles of the feet, limbs (especially below the elbows and knees);
— relapse after radiotherapy.

Chemotherapy

There are no data for patients with disseminated SCC that would clearly confirm the efficacy of chemotherapy with cisplatin in monotherapy or in combination with 5-fluorouracil, interferon, cis-retinoic acid. There

are reports on the potential efficacy of EGFR inhibitors (cetuximab, gefitinib), which, however, require further clinical trials [1–5].

Hedgehog pathway inhibitors

In patients with a genetic predisposition to develop multiple BCCs (Gorlin-Goltz syndrome), with disseminated BCC, as well as patients with regionally advanced BCC who have exhausted surgical and radiotherapy treatment options, vismodegib (a small molecule inhibitor of the Hedgehog pathway) administration should be considered (II, 1). This drug (at a dose of 150 mg/day) prolonged the time to disease progression, with an objective response rate ranging from 30 to 60%. The ERIVANCE BCC study evaluated the effectiveness of vismodegib at a dose of 150 mg/day in patients with metastatic (mBCC) or locally advanced (laBCC; unresectable or ineligible for radiotherapy) basal cell skin carcinoma [37]. The primary endpoint was the objective response rate (ORR). Based on an independent evaluation, ORR was 33.3% in the mBCC group and 47.6% in the laBCC group (including 22.2% of complete responses); the median investigator-assessed duration of response (DoR) was 14.8 and 26.2 months, respectively; the median of investigator-assessed progression-free survival (PFS) was 9.3 months in the mBCC group and 12.9 months in the laBCC group. In the majority of patients in both groups, a reduction in the size of neoplastic lesions was found [38]. The long-term results of this study confirmed the durability of response and efficacy of vismodegib in both groups of patients, with an investigator-assessed ORR of 48.5% in the mBCC group and 60.3% in the laBCC group. Median overall survival (OS) was 33.4 months in the mBCC group, whilst it was not achieved in the laBCC group. The effectiveness of vismodegib therapy was also assessed in a large group of patients (> 500) in the STEVIE study, which showed comparable results [39]. Similar results were also obtained in the analysis of Polish patients treated under the appropriate National Health Fund drug program [40]. The efficacy of vismodegib in Gorlin-Goltz syndrome was assessed in another multicenter, randomized, placebo-controlled phase II study (n = 41) [41]. In this study, the incidence of new BCCs in patients treated with vismodegib was significantly lower compared to placebo (2 and 29 new cases per year, respectively), and a reduction in the size of existing BCCs was additionally found in the vismodegib group; no BCC progression was observed in any of the patients treated with vismodegib.

Vismodegib is used orally at a dose of 150 mg once a day until disease progression or unacceptable toxicity, in Poland, as part of a drug program. The most common side effects of vismodegib therapy (in more than 30% of patients) include muscle cramps, alopecia, dysgeusia, weight loss, fatigue, and nausea [1–4, 37, 42–45]. It is recommended to use effective contraception methods during therapy and 24 months after its completion.

Another inhibitor of the Hedgehog pathway, approved for laBCC therapy, is sonidegib, the efficacy of which was assessed in the BOLT phase II study [46].

Immunotherapy in the treatment of advanced SCC

The phase I/II study confirmed the activity of anti-PD-1 immunotherapy with cemiplimab in the treatment of patients with advanced (unresectable or metastatic) SCC. The response rate was 50% in the group of 26 patients in the phase I study and 47% in 59 patients in the phase II study. The responses were long-lasting and exceeded 6 months in 57% of patients. Adverse events occurred in 15% of patients, and only 7% of patients discontinued treatment for this reason [47, 48]. An updated analysis of the results of treatment in patients with laCSCC included in the second group in the phase II study was published in 2020; the analysis included 78 patients. The median duration of follow-up was 9.3 months. An objective response to treatment was found in 34 patients (44%; 95% CI: 32–55), with 10 and 24 patients achieving CR and PR, respectively. Neither median PFS nor median OS was reached [49]. This drug was registered in 2019 for the treatment of adult patients with metastatic or locally advanced squamous cell carcinoma of the skin who do not qualify for radical surgical treatment or radical radiotherapy (II, 1). In Poland, it is available in the frame of Drug Programme. The safety of cemiplimab has been assessed in 591 patients with advanced solid tumors, including 219 patients with advanced squamous cell skin carcinoma, who received cemiplimab monotherapy in two clinical trials (R2810-ONC-1423 and R2810-ONC-1540) [47, 48]. In 2020, the updated results of cemiplimab treatment in the full analysis set of patients with advanced CSCC participating in a phase II trial (n = 193, including 128 systemic therapy-naïve patients) were published [50]. In the group of systemically untreated patients, the investigator-assessed overall response rate (ORR) was 57.8% (95% CI: 48.8–66.5). In the group of 65 patients who had received anticancer treatment before study enrollment ORR was 47.7% (95% CI: 35.1–60.5). The median duration of response (1.8–34.2 months) was not reached. The estimated response rate after 24 months was 76%, with median OS not reached. The survival rate after 24 months was 73.3%.

Immunotherapy in the treatment of advanced BCC after failure of therapy with Hedgehog pathway inhibitors

The results of a phase 2 clinical trial in 84 patients with advanced BCC after the failure of treatment with hedgehog pathway inhibitors who were treated with cemiplimab confirmed the activity of this drug in the form of, among others, objective responses in excess of

30% [51]. On this basis, cemiplimab has been approved for the treatment of patients with locally advanced or metastatic BCC who have a progressed disease or who are intolerant to a Hedgehog pathway inhibitor (III, 2A).

Cemiplimab in the second line treatment of BCC can be used as part of individual reimbursement consents based on the emergency Access to Drug Technology procedure.

Clinical trials

In patients with regionally advanced or generalized BCC or SCC, who have exhausted treatment options, participation in clinical trials should be considered [1–5]. For several years, there have been publications on the effectiveness of immunotherapy (PD-1 inhibitors) in advanced BCC or SCC [52–59].

Moreover, Hauschild et al. reported a case of a patient with xeroderma pigmentosum type E, in the course of which four melanomas, numerous invasive and non-invasive SCC lesions, and extensive cancerization areas were newly diagnosed, in whom treatment with pembrolizumab was initiated due to melanoma metastases. The authors not only observed a response to the treatment of metastatic disease but also a very fast regression of extensive actinic keratoses and invasive SCC lesions [59].

Treatment of advanced skin cancers with the use of irradiation and/or systemic therapy should take place in highly specialized cancer centers.

External treatment of skin cancer

In BCC and SCC with a low risk of recurrence, superficial treatments may be considered. Due to the lower effectiveness of these methods, their use should be limited to patients with contraindications to the use of basic methods (mainly surgery). Superficial treatment may also be considered in patients with superficial basal cell carcinoma with a low risk of recurrence if the expected aesthetic outcomes are better (III, 2B).

5-fluorouracil (0.5%)

The drug is used in the treatment of actinic keratosis, superficial and AC/SCC *in situ*, as well as BCC. The agent is used twice a day for a period of 4, 6, or 11 weeks in the case of the superficial form of BCC (90% of patients achieve complete response).

Imiquimod (5%)

The drug is used in the treatment of actinic keratosis, SCC *in situ*/Bowen's disease, and non-invasive forms of superficial BCC. Currently, the cream is used longer, as studies have shown that extending treatment duration from 6 to 12 weeks and more frequent application (1–2 times/day) reduce the risk of treatment failure (II, 2A). The use of the drug in occlusion in superficial and nodular forms of BCC up to 2 cm in diameter is associated with comparable efficacy. For example, 84% of patients with superficial BCC survived 5 years without disease symptoms. In immunocompetent patients, cream can be used alone, and in immunosuppressed patients, treatment with imiquimod should be combined with cryosurgery, Mohs microsurgery, or the photodynamic method [1–6, 11–13, 24, 25, 60].

Photodynamic method

The use of the PDT method in the treatment of NMSC is associated with registration restrictions concerning both elements of the therapeutic protocol, e.g. the photosensitizing substance (which may differ in the USA and Europe) and the light source (specific length of light/specific device) [61]. It should be emphasized that PDT is a second-line treatment for BCC with a low risk of recurrence and is reserved for superficial variants of BCC (II, 2A) and Bowen's disease (II, 2A). Therefore, when withdrawing from surgery, an adequate histological examination result should be available.

The efficacy of the photodynamic method in the treatment of basal cell carcinoma (superficial type and/or smaller than 2 cm) has been assessed in numerous clinical studies that have shown higher efficacy and a lower relapse rate (14% *vs.* 30.7%) with the use of MAL/PDT (Metvix; the drug is currently unavailable in Poland) compared to ALA/PDT [61, 62]. A study by Christiansen et al. with the longest post-treatment follow-up to date (10 years) showed a 75% complete response rate for selected BCC subtypes treated with ALA/PDT; 60% and 87% of complete response rates after single irradiation and two irradiations, respectively [63]. 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%) over a 5-year follow-up in one study [64]. Vinciullo et al. assessed the effectiveness of MAL/PDT in "difficult to treat" BCCs defined as cancers that are large-sized or located in the H zone with the highest recurrence rate or cancers that occur in patients at high risk of postoperative complications [65]. The study showed a treatment failure rate of 18% after 12 months and 24% after 24 months. In 2013, a consensus for the treatment of BCC in patients with Gorlin-Goltz syndrome was published [66]. In 2013, a consensus on the photodynamic method of treatment of BCC foci in patients with Gorlin-Goltz syndrome was published. Based on the analysis of 9 reviews summarizing the results obtained in 83 patients, the photodynamic method was considered safe and effective in the treatment of superficially spreading BCC and nodular BCC with a depth of infiltration below 2 mm. The consensus authors recommended that the frequency of follow-up visits should depend on the number of BCC foci, the frequency of relapses, and the

location of lesions. The possibility of simultaneous treatment of many lesions was emphasized as a significant advantage of photodynamic therapy.

MAL/PDT can also be used in the treatment of Bowen's disease but based on a different therapeutic protocol [61]. It should be emphasized that up to now, there are no studies conducted on a large number of patients, whose results could be compared. One should expect response rates of around 80% after approx. one year of follow-up, and up to 50% relapse rates after around 40 months of follow-up [67]. However, the results of SCC *in situ* treatment with the use of the PDT method are characterized by higher response rates after one-year follow-up than cryotherapy and 5-fluorouracil, e.g. 85–72% *vs.* 48–69% [68, 69]; the oncological purity index of 68–89% after 17–50 months can be achieved after an average of 3 irradiations of a given lesion [70–72]. Given the higher metastatic potential of SCC than BCC and the above data, qualification for PDT treatment should be careful, and the patient should be closely monitored with a dermoscope.

Cryosurgery

This is a technique that leads to necrosis of tumor cells by lowering the tissue temperature up to –50 or –60°C. It is used in the treatment of superficial skin cancers with a low risk of recurrence and size up to 2 cm, as well as actinic keratosis foci. Its use in nodular lesions is not recommended. Due to the diversity of cryotherapy techniques used, it is impossible to compare the effectiveness of this method presented in various studies (IV, 2B) [1–6].

Comment

Due to the lack of reliable scientific evidence based on results of randomized clinical trials demonstrating the effectiveness of treating skin cancers with the use of curettage and electrode destruction, the use of this method is not recommended.

For the same reasons, it is not recommended to use other methods of destroying neoplastic tissue, i.e. laser therapy, dermabrasion, and chemical peel (with trichloroacetic acid), due to the inability to control treatment completeness [15–16].

Few randomized studies evaluating the effectiveness of treatment with intralesional interferon injections in BCC showed a high percentage (approx. 30%) of early failures and frequent side effects, although they indicated some effectiveness in the treatment of superficial and nodular BCCs of small size [1–6]. Vismodegib is currently the therapeutic standard indicated for use in adults with symptomatic basal cell carcinoma with metastases or locally advanced basal cell carcinoma, who are not eligible for radical surgery or radiotherapy. This drug is available in Poland in the frame of Drug Programme (II, 1).

Follow-up after completed oncological treatment

The need for close monitoring of skin cancer patients results, among others, from the following reasons:

— 30–50% of patients who have had skin cancer will develop another focus of a similar tumor within 5 years;
— 70–80% of SCC recurrences appear within the first 2 years of follow-up;
— patients with skin cancer have a 10-fold higher risk of developing skin cancer compared to the general population;
— patients with skin cancer have a higher risk of skin melanoma;
— chronically immunosuppressed patients are at high risk of developing invasive SCC.

Any suspicion of skin cancer recurrence should be confirmed by histopathological examination. Dermoscopic examination often allows for precise determination of the biopsy site and diagnosis of recurrence at an earlier stage.

If enlarged regional lymph nodes are found, a fine-needle biopsy should be performed (less often the entire lymph node is collected for histopathological examination) and imaging tests [computed tomography (CT), magnetic resonance imaging (MRI)] to stage disease.

Principles of follow-up after treatment (V, 2B):

— BCC or SCC:
  • year-round photoprotection SPF 30–50+,
  • self-monitoring once a month,
  • dermatological and dermoscopic full-body skin examination: every 4–6 months for 5 years, then every 6–12 months lifelong;
— Regionally advanced/metastatic BCC or SCC:
  • year-round photoprotection SPF 30–50+,
  • self-monitoring once a month,
  • dermatological and dermoscopic full-body skin examination: every 1–3 months for the first year, every 2–4 months in the second year, every 4–6 months in the third year, then every 6–12 months lifelong,
  • multi-specialist care (including dermatological, oncological, radiotherapeutic, neurological, ophthalmological).

Supervision of patients after organ transplantation during chronic immunosuppression:

— year-round photoprotection SPF 30–50+;
— self-monitoring once a month;
— dermatological and dermoscopic full-body skin examination every 6–12 months lifelong;
— in case of skin cancer, follow-up visits are recommended every 3–6 months lifelong.

Supervision of patients with a genetically determined predisposition to develop skin cancer:

— year-round photoprotection SPF 30–50+;
— self-monitoring once a month;
— dermatological and dermoscopic full-body skin examination every 3–6 months lifelong;
— in patients with xeroderma pigmentosum, consideration of the reversal of the circadian rhythm and absolute avoidance of exposure to UV, IR, X radiation during work.

Prevention of skin cancer

Primary prevention:
— close dermatological supervision of patients with a genetic predisposition to developing skin cancer induced by UV radiation;
— public education on the proper use of photoprotection and the possibility of early detection of skin cancer.

Secondary prevention:
— patient education on the proper use of photoprotection;
— patient education about symptoms of skin cancer and the need for self-examination;
— regular dermatological monitoringcombined with a dermoscopic examination according to an established schedule;
— in chronically immunosuppressed patients with actinic keratoses and/or NMSCs, consider treatment modification by reducing the doses of calcineurin inhibitors and/or antimetabolic drugs in favor of mTOR inhibitors.

Merkel cell carcinoma (neuroendocrine skin cancer)

Merkel cell carcinoma (MCC) is a rare, highly malignant skin cancer, probably originating from neuroendocrine cells (Merkel cells) [73, 74].

The incidence of MCC is low, estimated at 0.25–0.32/100,000 inhabitants annually, higher in men than in women (ratio 1.5:1). Cancer is much more common in Caucasians than in other ethnic groups. The risk of developing the disease increases with age. The incidence of MCC in patients under 50 is very low and grows noticeably between the ages of 50 and 65. In men, this tumor occurs on average 5 years earlier than in women. The most common location is the skin of the head and neck (44–48% of cases), followed by the skin of the upper limbs (approx. 19% of cases) and lower limbs (16–20% of cases) [75, 76].

Most cases of MCC are located on the skin and other locations are rare (e.g. mucous membranes or dissemination of MCC of unknown primary site) [77].

Dermoscopy in neuroendocrine carcinoma does not show the presence of characteristic structures, usually showing milky-red unstructured areas, white shiny bands, coexisting with vascular structures: irregular linear vessels, tree vessels, dotted or glomerular vessels, red lumps / blurred red globules [78–80]

Etiology

The etiology is unknown, but there are well-identified factors that predispose to MCC development, with the most important as follow:
— exposure to ultraviolet radiation (UV) (natural or artificial, e.g. after treatment of psoriasis with phototherapy and psoralen [PUVA, psoralen ultraviolet A]) [81, 82];
— immunodeficiency diseases such as:
  • HIV/AIDS infection (11-fold increased risk of disease development) [83],
  • immunosuppression after organ transplantation (5-fold increased risk of disease development) [84, 85],
  • chronic lymphocytic leukemia;
— some viral infections, of which the greatest importance is attributed to polyomavirus infection [variant characteristic for MCC: Merkel carcinoma polyomavirus (MCPyV, Merkel cell polyomavirus)] [86, 87].

Diagnostics

Merkel cell carcinoma most often appears as a fairly rapidly growing tumor or hard skin infiltrate, often red to purple in color. Ulceration is rare. Sometimes the tumor spreads rapidly through the local lymphatic vessels, leading to the formation of satellite foci. The tumor is usually not accompanied by other symptoms and in most cases is painless [88]. Due to the uncharacteristic clinical picture, the suspicion of MCC is rarely established before the histopathological result is obtained from excisional biopsy or sampling.

In the Anglo-Saxon literature, a mnemonic acronym was proposed to facilitate the diagnosis of MCC — AEIOU (A — asymptomatic; E — expanding rapidly; I — immune-suppressed; O — older than 50 years; U — UV-exposed skin). Only about 7% of patients with MCC meet all these criteria, but in about 90% at least 3 of them can be observed [71].

The clinical manifestation and a short history that may suggest the malignant nature of the lesion should be an indication for excisional biopsy, performed following generally applicable rules. Histopathological examination with the use of immunohistochemical staining is necessary to establish the diagnosis and carry out the differential diagnosis with primary and metastatic neoplasms with morphology similar to MCC. In the patho-

morphological examination, Merkel cell carcinoma is composed of small and medium-sized (less often large) cells, with a sparse cytoplasm, granular nuclear chromatin (neuroendocrine type — "salt with pepper" image). A strongly expressed crush artifact is often observed. In addition, numerous mitotic figures and apoptotic bodies are visible. Immunohistochemistry helps differentiate it from other small round cell neoplasms. A typical MCC immunoprofile is CKAE1/AE3 (+), CK20 (+) ("dot-like" reaction), SATB2(+), CD56 (+), synaptophysin (+/–), chromogranin (+/–), NSE (+), INSM1(+/–), LCA (–), TTF1 (–), CDX2 (–), and p40 (–). The histopathological diagnostics should also take into account the need to use uniform reporting protocols for sentinel lymph nodes. For their evaluation, it is necessary to use additional immunohistochemical staining (CKAE1/AE3, SATB2) in order to visualize micrometastases foci.

If Merkel cell carcinoma histology is found, physical examination and imaging tests are recommended to assess the disease stage. Depending on individual indications, radiological examinations (X-ray, CT, MRI) combined with possible pathological or cytological diagnostics (fine-needle aspiration biopsy) of suspicious lesions are used.

In some cases, when the histopathological diagnosis is doubtful and in the case of an extracutaneous primary tumor (spread to the skin of neuroendocrine neoplasms other than MCC, e.g. small-cell lung cancer), there may be indications to extend the diagnosis with positron emission tomography (PET) in combination with CT.

Clinical staging and prognosis

The American Joint Committee on Cancer (AJCC) system, version 8, based on typical TNM criteria (tumor, node, metastases) is currently used (Tab. 7 and 8) [77, 89–92]. However, it seems that the factors with the greatest prognostic value include the size of the primary tumor, the presence of metastases at diagnosis, and the extent of lymph node metastases.

Currently, the 10-year overall survival rate of patients with MCC is estimated at 65% in women and 50.5% in men (on average, about 57% for all patients). Depending on the size of the primary tumor, the 10-year survival rate is 61% for lesions with a diameter of 2 cm or less, while for those larger than 2 cm it is only 39% [77].

Table 7. Staging of Merkel cell carcinoma (2017)

Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No primary tumor present
Tis		Carcinoma *in situ*
T1		Maximum tumor diameter ≤ 2 cm
T2		Tumor diameter in the range greater than 2 cm and up to 5 cm inclusive
T3		Maximum tumor diameter over 5 cm
T4		Tumor infiltrations of deep structures, e.g. cartilage, bone, skeletal muscles, fascia
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		
	N1a (sn)	Micrometastases (detected by sentinel lymph node biopsy)
	N1a	Micrometastases in a lymph node
	N1b	Clinically detectable macrometastases confirmed by microscopy
N2		*In-transit* metastases without lymph node metastases
N3		*In-transit* metastases with lymph node metastases
Metastases to distant organs (M)		
M0		No metastases
M1		
	M1a	Metastasis to the skin, subcutaneous tissue, lymph nodes
	M1b	Lung metastases
	M1c	Other sites of metastasis

Table 8. Clinical 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
	Any T	N1a (sn)/N1a	M0
IIIB	Any T	N1b–N3	M0
IV	Any T	Any N	M1

Treatment

Surgical treatment is the mainstay of therapy in locoregionally advanced cases; MCC treatment should be carried out in highly specialized centers (Fig. 2) [13, 90, 93, 94].

Stage I and II

In the absence of detectable metastases in regional lymph nodes, a sentinel lymph node biopsy and a wide (with a margin of at least 1–2 cm) scar excision should be performed, possibly combined with adjuvant radiotherapy (III, 2A). It results from the observation that infiltration of sentinel lymph nodes occurs in 25–35% of patients with no clinical symptoms of metastases. The risk of micrometastases increases significantly

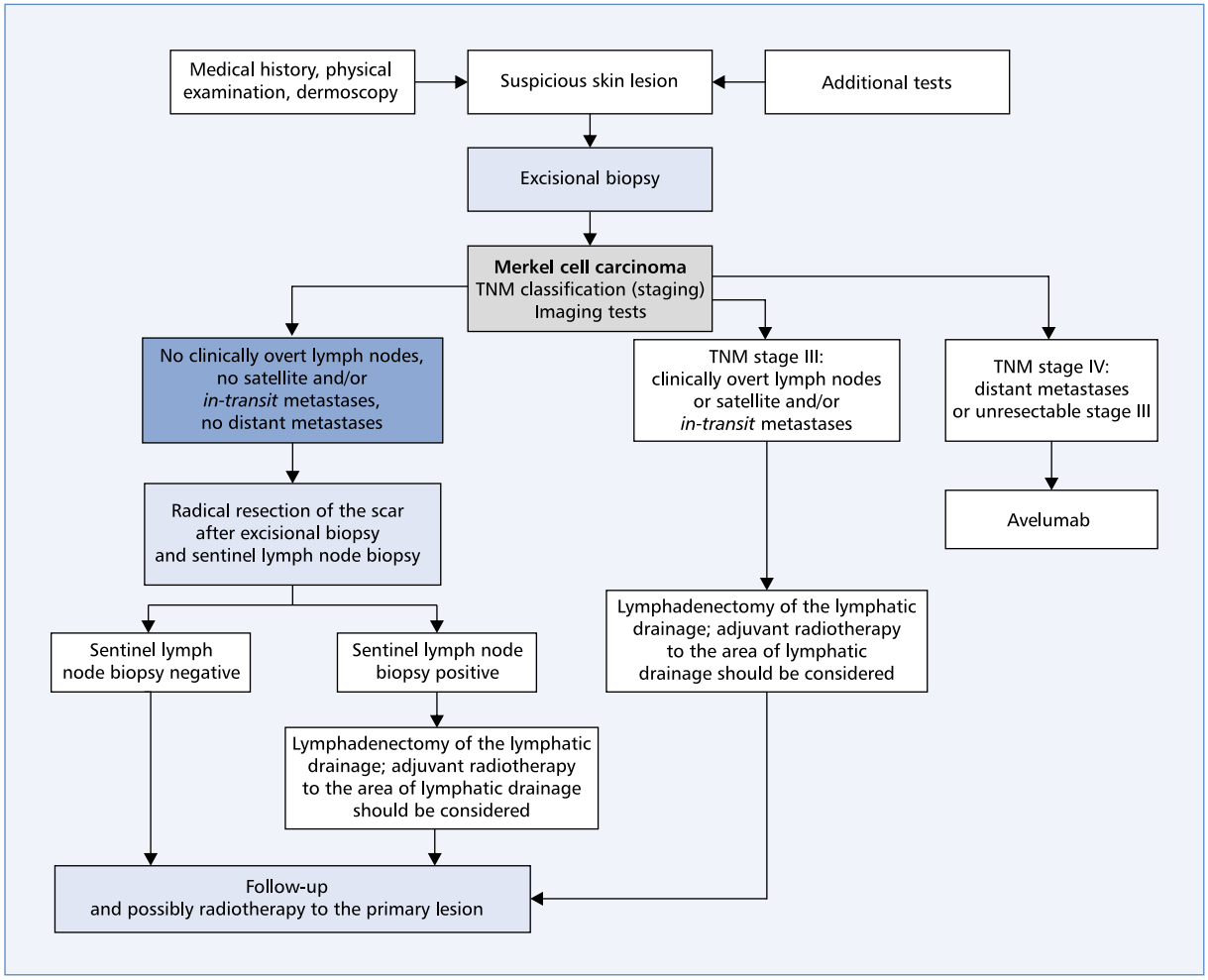

Figure 2. Diagnostic and therapeutic management in patients with Merkel cell carcinoma

in patients with a primary lesion greater than 1 cm in diameter [95, 96].

Stage III

The presence of metastases in regional lymph nodes (both micro- and macrometastases; stage III) is the indication for their excision.

Despite the lack of evidence from randomized clinical trials, the majority of retrospective studies indicate improved locoregional control and survival in patients after adjuvant radiotherapy to the bed after regional lymph node removal (50–60 Gy) (III, 2A) [97, 98].

Some authors postulate that chemotherapy should be considered in patients with massive lymph node involvement. A typical systemic treatment in this group of patients has not been established; this could be preoperative or postoperative. In some centers, lymphadenectomy in these patients is performed between cycles of chemotherapy. However, the data available in the literature do not allow for a clear determination of whether systemic treatment improves overall survival in this group of patients [98–100]. The initial results of the use of immune checkpoint inhibitors in the preoperative treatment of MCC patients are encouraging. In 2018, the results of phase I/II study with the use of nivolumab in the neoadjuvant treatment of patients with MCC stage IIa-IV (CheckMate 358) were published. The complete pathological response was achieved in 47% of patients, and a major pathological response (≤ 10% of viable neoplastic cells) in 18% of patients. In some patients, the obtained response allowed for a less extensive surgical procedure. Median PFS and median OS were not reached. In none of the patients who achieved a complete or major pathological response, the recurrence of the disease after 12 months was observed [101].

Stage IV

In patients with advanced disease, treatment is assumed to be palliative in nature. In patients with satisfactory general condition, the initiation of palliative

systemic treatment should be considered, although no objective data confirm the impact of such treatment (cytotoxic chemotherapy) on overall survival, except for immunotherapy [90, 102]. Many observations indicate the chemosensitivity of MCCs, although as a rule, responses do not exceed 8–10 months, and long-term overall survival rates range between 0 and 18%. The most commonly used therapeutic regimens include multi-drug chemotherapy with cisplatin, doxorubicin, and vincristine or etoposide, as well as 5-fluorouracil or cyclophosphamide. In justified cases, palliative surgery and/or radiotherapy may also be used.

Due to the high activity of anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors in the treatment of metastatic MCC, confirmed in phase II clinical trials, according to the current recommendations, these drugs are recommended as treatment of choice in this group of patients (II, 1). Avelumab is the only drug approved in the European Union for the treatment of adults with metastatic MCCs (II, 1).

For patients with systemic disease, the possibility of including them in a clinical trial should be considered.

In the single-arm phase II Javelin Merkel 200 study, the efficacy of avelumab in the treatment of patients with metastatic MCC was demonstrated, which was the basis for drug registration both in the first and subsequent treatment lines (initially at a dose of 10 mg/kg b.w. intravenously every 2 weeks until progression or unacceptable toxicity, currently at a fixed dose of 800 mg every 2 weeks). In patients after systemic treatment failure (part A of the Javelin Merkel 200 study; n = 28), the objective response rate was 31.8% (95% CI: 21.9–43.1%), including 8 complete responses (9%) and 20 partial responses (23%); in addition, stabilization of the disease was observed in 9 patients (10%) [103]. Responses to treatment were durable and were maintained in 23 (82%) patients at the time of analysis. The duration of response was at least 6 months in 92% of cases. The median PFS was 2.7 months (95% CI: 1.4–6.9), the progression-free survival rate after 6 months was 40%, and the PFS curve reached a plateau. The 6-month overall survival rate was 69% (95% CI: 58–78) and the median OS was 11.3 months (95% CI: 7.5–14.0). Objective responses were obtained in 20 out of 58 patients (34.5%) with positive PD-L1 expression, 3/16 patients (18.8%) PD-L1 (–), 12/46 patients (26.1%) with MCPyV (+) and 11/31 (35.5%) patients without MCPyV infection. More responses were obtained in patients who had previously received only one treatment line. Treatment with avelumab was generally well tolerated. Treatment-related adverse events occurred in 62 (70%) of 88 patients. Treatment-related adverse grade-5 events were observed in four (5%) patients: lymphopenia in 2 patients, increased creatine kinase level in 1 patient, elevated transaminases in 1 patient, and an increase in blood cholesterol in 1 patient. No grade-4 adverse events or treatment-related deaths were observed. Serious treatment-related adverse events were observed in 5 (6%) patients: enteritis, infusion-related reaction, elevated transaminases, synovitis, and interstitial nephritis (1 each). Potential immune-related side effects included hypothyroidism in 3 patients (3%), hyperthyroidism (2; 2%), pneumonia (1; 1%) and type 1 diabetes (1; 1%). Two patients (2%) permanently discontinued treatment due to adverse events. 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 from 88 patients after the median follow-up 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), the 2-year survival rate was 36% (50% of survival after 1 year and 39% after 1.5 years). The median duration of response was not achieved (2.8–31.8 months; 95% CI: 18.0 — not reached). Long-term responses to avelumab treatment determine stable PFS values after 1 year (29%), 1.5 years (29%), and 2 years of follow-up (26%) [104, 105]. Distant results confirmed a median OS of 12.6 months and a 42-month survival rate of 31% [106]. The phase II Javelin Merkel 200 study also assessed the efficacy of avelumab in the first-line treatment of metastatic MCC patients (part B of the Javelin Merkel 200 study). Estimated results published in 2018 indicate a mean overall survival of 49.9 months (6.3; 179.4), as well as 1-year and 5-year survival rates of 66% and 23%, respectively [107]. In 2019, the results of more than a 15-month follow-up of patients participating in part B of this study (first line of treatment) were published. A total of 116 patients were treated with avelumab, with a median duration of treatment of 5.5 months (0.5–35.4) and median follow-up of 21.1 months (14.9–36.6). The ORR was 39.7% (95% CI: 30.7–49.2%), 19 patients achieved CR (16.4%) and 27 patients (23.3%) had PR. The median duration of response in the full analysis set was 18.2 months [108]. Published in 2016, a phase II clinical study demonstrated the activity of the anti-PD-1 antibody, pembrolizumab, in the treatment of systemic treatment-naive patients with stage IIIB-IVC MCC [109]. In this study, 26 patients with metastatic MCC received pembrolizumab (2 mg/kg b.w. every 3 weeks) in the first-line treatment; the objective response rate was 56% (4 complete and 10 partial responses), and disease progression occurred in only 2 of 14 responders with a median follow-up of 33 weeks. As with avelumab, responses to pembrolizumab were independent of the MCPyV status. The 6-month PFS rate was 67%. Similarly, in the trial with avelumab, there was a trend towards higher response rates with fewer prior lines of treatment, which indicates, considering the results of studies with pembrolizumab, that immunotherapy in MCC should be the first-line treatment of

choice [110]. All of these studies showed responses both in MCPyV (+) and MCPyV (–) patients and confirmed that the treatment can be also used in the elderly, that is, the age range characteristic of MCC. Currently, in accordance with the Polish and international recommendations, anti-PD-1/anti-PD-L1 immunotherapy is the standard of systemic treatment of patients with unresectable/metastatic MCC, and avelumab, registered in this indication in the European Union, is available in Poland under the drug program after a positive opinion of the Agency for Health Technology Assessment and Tariff System (AOTMiT).

Treatment of local recurrences and relapses in regional lymph nodes

Local relapses are the most common form of disease recurrence. This applies to approximately 30% of patients treated surgically (postoperative radiotherapy reduces this percentage to approx. 11%) [111]. Follow-up after locoregional treatment in patients with MCC should include a complete physical examination and imaging tests for distant metastases performed every 3–6 months (V, 2B).

Local recurrences can be treated as a primary MCC with an appropriate clinical stage (I–III). If possible, tumor foci should be resected with a healthy tissue margin and with complementary radiotherapy if not used during the treatment of the primary tumor. As relapse is associated with poor prognosis; adjuvant systemic therapy should also be considered although there is no evidence to support its effectiveness.

Other rare skin cancers

Cancer that originates from sebaceous glands (sebaceous carcinoma)

Sebaceous carcinoma occurs mainly in the 7th decade of life, in the eye area, also as a component of Muir-Torre syndrome. In its early stages, the neoplasm resembles a chalazion or inflammation of the eyelid, which often results in a delayed diagnosis [112]. The primary tumor lesion is usually treated with surgery. Due to the 40% risk of lymph node infiltration, sentinel lymph node biopsy is performed in some centers, possibly followed by supplementary lymphadenectomy [113, 114]. There are no effective methods of systemic treatment, and approx. 22% of patients die as a result of neoplastic process generalization [115, 116].

Apocrine adenocarcinoma

This type of neoplasm develops in the skin around the eyes, armpits, anus, and genitals. Cancer lesion is often located in the vicinity of Paget's disease outside the breast. Lymph node metastases and a tendency to recurrence have been observed, therefore, apart from radical surgical excision with a wide margin, sentinel node biopsy is also recommended [116–118].

Eccrine carcinoma

Eccrine carcinoma has a form of nodular lesions with different growth dynamics, most often occurring in the skin of the scalp and upper limbs. Usually, it develops in individuals over 50 years of age. There are several subtypes that differ in the frequency and aggressiveness of the clinical course (MAC, microcystic adnexal carcinoma; eccrine porocarcinoma; hidradenocarcinoma; spiradenocarcinoma; eccrine mucinous carcinoma; malignant eccrine spiradenoma; malignant mixed tumor; malignant cylindroma; syringoid carcinoma) [119, 120]. MAC is the most common subtype, which requires a wide, radical excision of the primary lesion (III, 2A) or MMS procedure due to its tendency to aggressive local growth and frequent relapses [121]. Radiotherapy was used in the treatment of unresectable lesions. In the remaining subtypes of sweat-gland carcinoma, dissemination of the neoplastic disease to the lymph nodes and distant organs was observed in approximately 60% of cases. Few reports indicate low effectiveness of systemic treatment with cytostatics [122].

Cancer originating from the hair follicle

Tumors of the hair follicle, called folliculoma or trichofolliculom, include trichilemmal carcinoma, trichoblastic carcinoma, malignant proliferating trichilemmal cyst, pilomatrix carcinoma [123]. *Surgery is the mainstay* of the *treatment* of this type of cancer (III, 2A). Due to its rarity, there are no relevant data on the effectiveness of systemic therapy.

Conflict of interest

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

Monika Dudzisz -Śledź received honoraria for lectures from Pierre Fabre, Merck KGaA, Sanofi Aventis, Novartis, and BMS, for participation in Advisory Board from Merck KGaA and Novartis, and financing for participation in conferences from Novartis.

Monika Słowińska received honoraria for lectures from Novartis, Takeda, Roche, BMS, Ipsen and Medac, for participation in Advisory Board from BMS, Novartis, Takeda, Roche and financing for participation in conferences from Roche, BMS, Pierre Fabre.

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