OFFICIAL JOURNAL OF THE POLISH SOCIETY OF CLINICAL ONCOLOGY

Oncology IN CLINICAL PRACTICE

2022, Vol. 18, Number 2

ISSN 2450–1654
e-ISSN 2450–6478

VIA MEDICA

Oncology in Clinical Practice 2022, Vol. 18, Number 2, 69–138

ONCOLOGY
IN CLINICAL PRACTICE

Official Journal of the Polish Society of Clinical Oncology

https://journals.viamedica.pl/oncology_in_clinical_practice

Oncology in Clinical Practice (ISSN 2450–1654, e-ISSN 2450–6478) is published six times a year by

VM Media sp. z o.o. VM Group sp.k.
ul. Świętokrzyska 73, 80–180 Gdańsk, Poland
Phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
e-mail: redakcja@viamedica.pl,
http://www.viamedica.pl

21-0532.002.001

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Indexed in Index Copernicus (ICV 2020 = 97.15), Ulrich's Periodicals Directory and CAS.

According to the statement of the Polish Ministry of Education and Science publication in the journal has been awarded with 100 points.

Editorial policies and author guidelines are published on journal website: http://journals.viamedica.pl/oncology_in_clinical_practice

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

Case Report Contest Policies

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

1. The aim of the contest is to encourage submission of quality case reports related to oncological practice and to promote them in the scientific deliberations.
2. All respective manuscripts submitted to OCP between June 1st, 2021 and May 31st, 2022 and accepted for publication will qualify.
3. Manuscripts should be prepared in line with Authors' guidelines and should be submitted only through the manuscript system available at Journal's website: https://journals.viamedica.pl/oncology_in_clinical_practice
4. All submitted manuscripts will be evaluated during the peer review process and authors will be informed about their qualification for publication in OCP. Accepted papers will be evaluated by the Contest Committee based upon fulfillment of the Contest criteria as well as practical significance, originality, applicability and addressing of current/critical concerns.
5. The first author of the winning paper will be eligible for a prize of gross 1000,00 Euro gross (one thousand euro).
6. Results will be announced during the XXV National Congress of The Polish Society of Clinical Oncology and subsequently at the Journal website.
7. Winner will be notified via email.
8. Contest Committee may exclude a paper from participation in case of potential conflict of interest or ask submitting author for adequate clarifications.
9. The Sponsor at any stage and in any respect, will not participate in the evaluation of entries and selection of a winning paper.
10. The award amount shall be paid based on the copyright transfer agreement to the paper.
11. These Regulations are the sole and exclusive document defining the principles and conditions for the Contest. In all matters not regulated, decisions are made by The Organizer.

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Patronage NOVARTIS

Expert recommendation on diagnostic--therapeutic management in skin carcinomas

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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

Received: 27.09.2021 Accepted: 29.09.2021 Early publication date: 26.04.2022

Translation: dr n. med. Dariusz Stencel
Oncology in Clinical Practice, DOI: 10.5603/OCP.2021.0032, Copyright © 2022 Via Medica, ISSN 2450–1654, e-ISSN 2450–6478

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

→

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

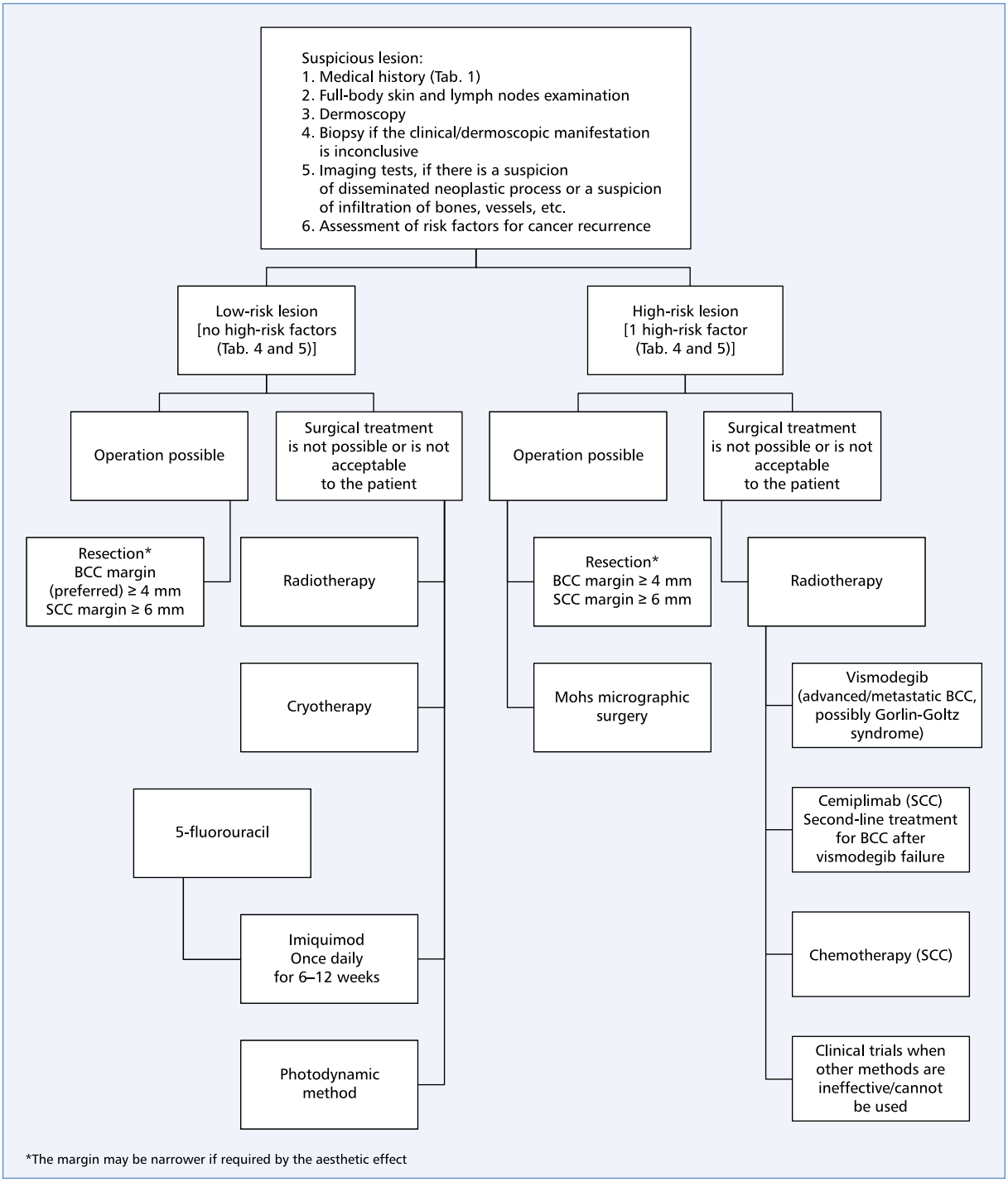

Figure 1. Recommended diagnostic and therapeutic procedures in patients with basal cell and squamous cell carcinoma of the skin; BCC — basal cell carcinoma; SCC — squamous cell carcinoma

— 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

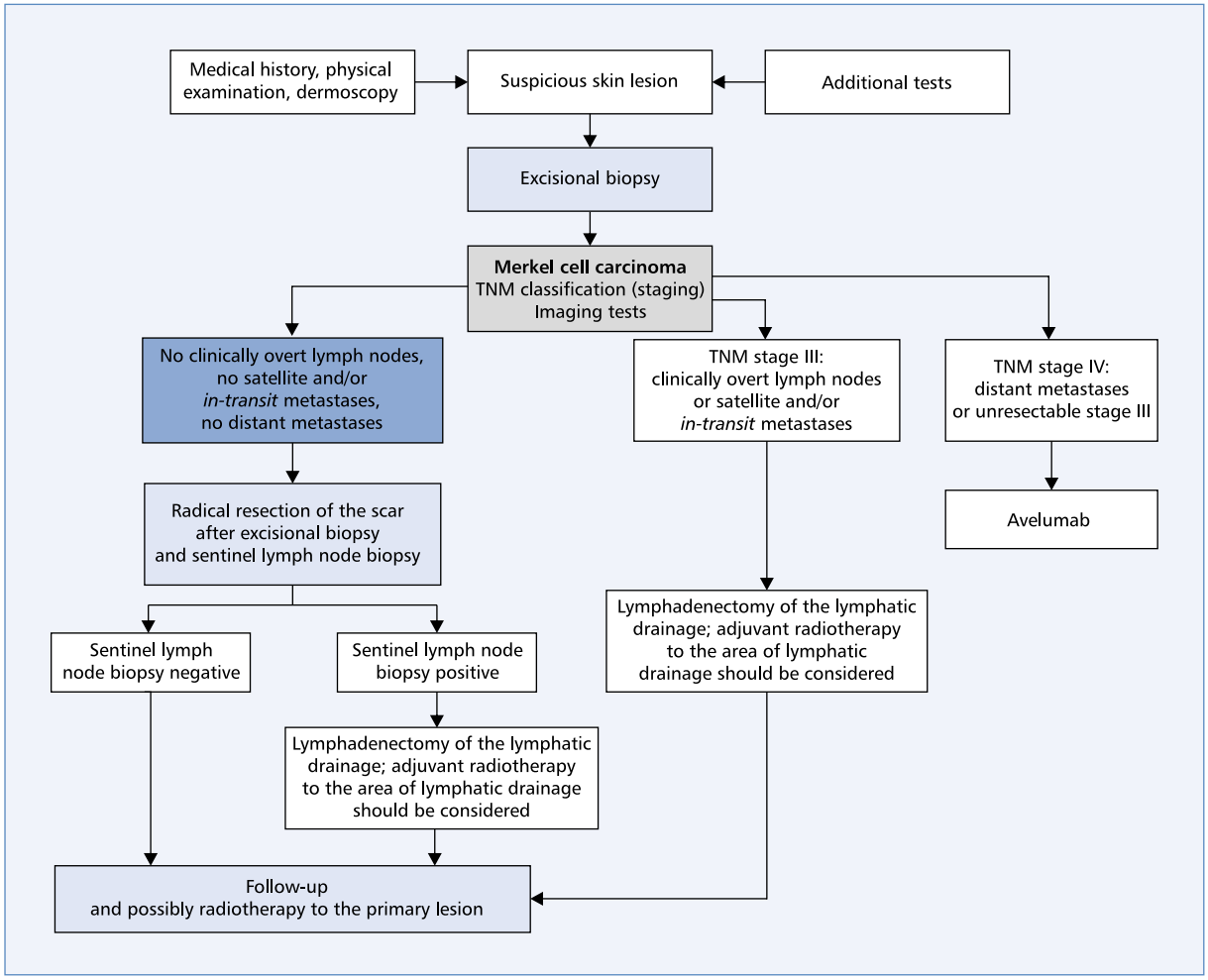

Figure 2. Diagnostic and therapeutic management in patients with Merkel cell carcinoma

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.

References

1. NCCN Clinical Practice Guidelines in Oncology. Basal Cell Skin Cancer 2.2022. www.nccn.org.
2. Trakatelli M, Morton C, Nagore E, et al. BCC subcommittee of the Guidelines Committee of the European Dermatology Forum. Update of the European guidelines for basal cell carcinoma management. Eur J Dermatol. 2014; 24(3): 312–329, doi: 10.1684/ejd.2014.2271, indexed in Pubmed: 24723647.
3. Bonerandi JJ, Beauvillain C, Caquant L, et al. French Dermatology Recommendations Association (aRED). Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma and precursor lesions. J Eur Acad Dermatol Venereol. 2011; 25 Suppl 5: 1–51, doi: 10.1111/j.1468-3083.2011.04296.x, indexed in Pubmed: 22070399.
4. Bath FJ, Bong J, Perkins W, et al. Interventions for basal cell carcinoma of the skin. Cochrane Database Syst Rev. 2003(2): CD003412, doi: 10.1002/14651858.CD003412, indexed in Pubmed: 12804465.
5. Bath-Hextall FJ, Matin RN, Wilkinson D, et al. Interventions for cutaneous Bowen's disease. Cochrane Database Syst Rev. 2013(6): CD007281, doi: 10.1002/14651858.CD007281.pub2, indexed in Pubmed: 23794286.
6. NCCN Clinical Practice Guidelines in Oncology. Squamous Cell Skin Cancer 2.2020. www.nccn.org (27.02.2021).
7. Marghoob AM, Malvehy J, Braun RP. Atlas of dermoscopy. Second edition. Informa healthcare 2012.
8. Argenziano G, Zalaudek I, Giacomel J. Preface. Dermoscopy. Dermatol Clin. 2013; 31(4): xiii–xiv, doi: 10.1016/j.det.2013.07.002, indexed in Pubmed: 24075555.
9. Berking C, Hauschild A, Kölbl O, et al. Basal cell carcinoma-treatments for the commonest skin cancer. Dtsch Arztebl Int. 2014; 111(22): 389–395, doi: 10.3238/arztebl.2014.0389, indexed in Pubmed: 24980564.
10. Rutkowski P, Owczarek W, Nejc D, et al. Skin carcinomas. Oncol Clin Pract. 2020; 16(4): 143–162, doi: 10.5603/ocp.2020.0018.
11. Bologni JL, Jorizzo JL, Schaffer JV. Dermatology. Elsevier Saunders 2012.
12. Nawrocka A, Owczarek W. Zasady diagnostyki u pacjentów z nowotworem skóry. Chirurgia Po Dyplomie 2014.
13. Rutkowski P, Owczarek W. Dermatochirurgia. Via Medica, Gdańsk 2018.
14. Wojciechowska Urszula, Didkowska Joanna. Zachorowania i zgony na nowotwory złośliwe w Polsce. Krajowy Rejestr Nowotworów, Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie – Państwowy Instytut Badawczy. http://onkologia.org.pl/raporty/ (22.03.2020; 15.02.2021).
15. Lesiak A, Czuwara J, Kamińska-Winciorek G, et al. Basal cell carcinoma. Diagnostic and therapeutic recommendations of Polish Dermatological Society. Dermatology Review. 2019; 106(2): 107–126, doi: 10.5114/dr.2019.85572.
16. Lesiak A, Czuwara J, Kamińska-Winciorek G, et al. Squamous cell carcinoma and Merkel-cell carcinoma. Diagnostic and therapeutic recommendations of the Polish Dermatological Society. Dermatology Review. 2019; 106(2): 127–149, doi: 10.5114/dr.2019.85573.
17. Choudhury K, Volkmer B, Greinert R, et al. Effectiveness of skin cancer screening programmes. Br J Dermatol. 2012; 167 Suppl 2: 94–98, doi: 10.1111/j.1365-2133.2012.11091.x, indexed in Pubmed: 22881593.
18. Werner RN, Stockfleth E, Connolly SM, et al. International League of Dermatological Societies, European Dermatology Forum. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. J Eur Acad Dermatol Venereol. 2015; 29(11): 2069–2079, doi: 10.1111/jdv.13180, indexed in Pubmed: 26370093.
19. Fernandez Figueras MT. From actinic keratosis to squamous cell carcinoma: pathophysiology revisited. J Eur Acad Dermatol Venereol. 2017; 31 Suppl 2: 5–7, doi: 10.1111/jdv.14151, indexed in Pubmed: 28263020.
20. Garrett GL, Yuan JT, Shin TM, et al. Transplant Skin Cancer Network (TSCN). Validity of skin cancer malignancy reporting to the Organ Procurement Transplant Network: A cohort study. J Am Acad Dermatol. 2018; 78(2): 264–269, doi: 10.1016/j.jaad.2017.09.003, indexed in Pubmed: 29031659.
21. Peris K, Fargnoli MC, Garbe C, et al. European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer. 2019; 118: 10–34, doi: 10.1016/j.ejca.2019.06.003, indexed in Pubmed: 31288208.
22. Patel G, Armstrong AW, Eisen DB. Efficacy of photodynamic therapy vs other interventions in randomized clinical trials for the treatment of actinic keratoses: a systematic review and meta-analysis. JAMA Dermatol. 2014; 150(12): 1281–1288, doi: 10.1001/jamadermatol.2014.1253, indexed in Pubmed: 25162181.
23. Owczarek W, Rutkowski P, Słowińska M, et al. Zalecenia dotyczące leczenia raka podstawnokomórkowego i raka kolczystokomórkowego przygotowane przez Sekcję Onkologiczną Polskiego Towarzystwa Dermatologicznego i Sekcję Akademia Czerniaka Polskiego Towarzystwa Chirurgii Onkologicznej. Onkol Prakt Klin Edu. 2015; 1(2): 96–106.
24. Gupta AK, Paquet M, Villanueva E, et al. Interventions for actinic keratoses. Cochrane Database Syst Rev. 2012; 12: CD004415, doi: 10.1002/14651858.CD004415.pub2, indexed in Pubmed: 23235610.
25. McGillis ST, Fein H. Topical treatment strategies for non-melanoma skin cancer and precursor lesions. Semin Cutan Med Surg. 2004; 23(3): 174–183, doi: 10.1016/j.sder.2004.06.005, indexed in Pubmed: 15584683.
26. Hansen EK, Roach M. Handbook of evidence-based radiation oncology 2nd ed. Springer, New York 2010.
27. Hernández-Machin B, Borrego L, Gil-García M, et al. Office-based radiation therapy for cutaneous carcinoma: evaluation of 710 treatments. Int J Dermatol. 2007; 46(5): 453–459, doi: 10.1111/j.1365-4632.2006.03108.x, indexed in Pubmed: 17472670.
28. Rowe DE, Carroll RJ, Day CL. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol. 1989; 15(3): 315–328, doi: 10.1111/j.1524-4725.1989.tb03166.x, indexed in Pubmed: 2646336.
29. Rowe DE, Carroll RJ, Day CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol. 1989; 15(4): 424–431, doi: 10.1111/j.1524-4725.1989.tb03249.x, indexed in Pubmed: 2925988.
30. Rowe D, Carroll R, Day C. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. J Am Acad Dermatol. 1992; 26(6): 976–990, doi: 10.1016/0190-9622(92)70144-5.
31. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. Br J Cancer. 1997; 76(1): 100–106, doi: 10.1038/bjc.1997.343, indexed in Pubmed: 9218740.
32. Garbutcheon-Singh KB, Veness MJ. The role of radiotherapy in the management of non-melanoma skin cancer. Australas J Dermatol. 2019; 60(4): 265–272, doi: 10.1111/ajd.13025, indexed in Pubmed: 30931531.
33. Fort M, Guet S, Colson-Durand L, et al. Role of radiation therapy in non-melanoma cancers, lymphomas and sarcomas of the skin: Systematic review and best practice in 2016. Crit Rev Oncol Hematol. 2016; 99: 200–213, doi: 10.1016/j.critrevonc.2016.01.001, indexed in Pubmed: 26839172.
34. Karagas MR, McDonald JA, Greenberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For The Skin Cancer Prevention Study Group. J Natl Cancer Inst. 1996; 88(24): 1848–1853, doi: 10.1093/jnci/88.24.1848, indexed in Pubmed: 8961975.
35. Lichter MD, Karagas MR, Mott LA, et al. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. Arch Dermatol. 2000; 136(8): 1007–1011, doi: 10.1001/archderm.136.8.1007, indexed in Pubmed: 10926736.
36. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2005; 23(16): 3733–3741, doi: 10.1200/JCO.2005.06.237, indexed in Pubmed: 15923570.
37. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med. 2012; 366(23): 2171–2179, doi: 10.1056/NEJMoa1113713, indexed in Pubmed: 22670903.
38. Sekulic A, Migden MR, Basset-Seguin N, et al. ERIVANCE BCC Investigators. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. BMC Cancer. 2017; 17(1): 332, doi: 10.1186/s12885-017-3286-5, indexed in Pubmed: 28511673.
39. Basset-Séguin N, Hauschild A, Kunstfeld R, et al. Vismodegib in patients with advanced basal cell carcinoma: Primary analysis of STEVIE, an international, open-label trial. Eur J Cancer. 2017; 86: 334–348, doi: 10.1016/j.ejca.2017.08.022, indexed in Pubmed: 29073584.
40. Słowińska M, Dudzisz-Śledź M, Sobczuk P, et al. Analysis of efficacy and safety of vismodegib therapy in patients with advanced basal cell carcinoma - real world multicenter cohort study. J Eur Acad Dermatol Venereol. 2022 [Epub ahead of print], doi: 10.1111/jdv.18070, indexed in Pubmed: 35279879.
41. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med. 2012; 366(23): 2180–2188, doi: 10.1056/NEJMoa1113538, indexed in Pubmed: 22670904.

42. Erdem GU, Sendur MA, Ozdemir NY, et al. A comprehensive review of the role of the hedgehog pathway and vismodegib in the management of basal cell carcinoma. Curr Med Res Opin. 2015; 31(4): 743–756, doi: 10.1185/03007995.2015.1018988, indexed in Pubmed: 25690490.
43. Peris K, Licitra L, Ascierto PA, et al. Identifying locally advanced basal cell carcinoma eligible for treatment with vismodegib: an expert panel consensus. Future Oncol. 2015; 11(4): 703–712, doi: 10.2217/fon.14.281, indexed in Pubmed: 25686123.
44. Proctor AE, Thompson LA, O'Bryant CL. Vismodegib: an inhibitor of the Hedgehog signaling pathway in the treatment of basal cell carcinoma. Ann Pharmacother. 2014; 48(1): 99–106, doi: 10.1177/1060028013506696, indexed in Pubmed: 24259609.
45. Dreno B, Basset-Seguin N, Caro I, et al. Clinical benefit assessment of vismodegib therapy in patients with advanced basal cell carcinoma. Oncologist. 2014; 19(8): 790–796, doi: 10.1634/theoncologist.2014-0003, indexed in Pubmed: 25001266.
46. Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. J Eur Acad Dermatol Venereol. 2018; 32(3): 372–381, doi: 10.1111/jdv.14542, indexed in Pubmed: 28846163.
47. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med. 2018; 379(4): 341–351, doi: 10.1056/NEJMoa1805131, indexed in Pubmed: 29863979.
48. Migden M, Khushalani N, Chang A, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol. 2020; 21(2): 294–305, doi: 10.1016/s1470-2045(19)30728-4.
49. Migden MR, Khushalani NI, Chang AL, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol. 2020; 21(2): 294–305, doi: 10.1016/S1470-2045(19)30728-4, indexed in Pubmed: 31952975.
50. Rischin D, Khushalani N, Schmults C, et al. Phase II study of cemiplimab in patients (pts) with advanced cutaneous squamous cell carcinoma (CSCC): Longer follow-up. J Clin Oncol. 2020; 38(15_suppl): 10018–10018, doi: 10.1200/jco.2020.38.15_suppl.10018.
51. Stratigos A, Sekulic A, Peris K, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol. 2021; 22(6): 848–857, doi: 10.1016/s1470-2045(21)00126-1.
52. Lipson EJ, Lilo MT, Ogurtsova A, et al. Basal cell carcinoma: PD-L1/PD-1 checkpoint expression and tumor regression after PD-1 blockade. J Immunother Cancer. 2017; 5: 23, doi: 10.1186/s40425-017-0228-3, indexed in Pubmed: 28344809.
53. Ikeda S, Goodman AM, Cohen PR, et al. Metastatic basal cell carcinoma with amplification of PD-L1: exceptional response to anti-PD1 therapy. NPJ Genom Med. 2016; 1, doi: 10.1038/npjgenmed.2016.37, indexed in Pubmed: 27942391.
54. Stevenson ML, Wang CQF, Abikhair M, et al. Expression of Programmed Cell Death Ligand in Cutaneous Squamous Cell Carcinoma and Treatment of Locally Advanced Disease With Pembrolizumab. JAMA Dermatol. 2017; 153(4): 299–303, doi: 10.1001/jamadermatol.2016.5118, indexed in Pubmed: 28259107.
55. Ran X, Yang K. Inhibitors of the PD-1/PD-L1 axis for the treatment of head and neck cancer: current status and future perspectives. Drug Des Devel Ther. 2017; 11: 2007–2014, doi: 10.2147/DDDT.S140687, indexed in Pubmed: 28721019.
56. Nagasaka M, Zaki M, Kim H, et al. PD1/PD-L1 inhibition as a potential radiosensitizer in head and neck squamous cell carcinoma: a case report. J Immunother Cancer. 2016; 4: 83, doi: 10.1186/s40425-016-0187-0, indexed in Pubmed: 27895920.
57. Tran DC, Colevas AD, Chang AL. Follow-up on Programmed Cell Death 1 Inhibitor for Cutaneous Squamous Cell Carcinoma. JAMA Dermatol. 2017; 153(1): 92–94, doi: 10.1001/jamadermatol.2016.3884, indexed in Pubmed: 27784038.
58. Ran X, Yang K. Inhibitors of the PD-1/PD-L1 axis for the treatment of head and neck cancer: current status and future perspectives. Drug Des Devel Ther. 2017; 11: 2007–2014, doi: 10.2147/DDDT.S140687, indexed in Pubmed: 28721019.
59. Hauschild A, Eichstaedt J, Möbus L, et al. Regression of melanoma metastases and multiple non-melanoma skin cancers in xeroderma pigmentosum by the PD1-antibody pembrolizumab. Eur J Cancer. 2017; 77: 84–87, doi: 10.1016/j.ejca.2017.02.026, indexed in Pubmed: 28365530.
60. Arits A, Mosterd K, Essers B, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. Lancet Oncol. 2013; 14(7): 647–654, doi: 10.1016/s1470-2045(13)70143-8.
61. Morton CA, Szeimies RM, Basset-Seguin N, et al. European Dermatology Forum guidelines on topical photodynamic therapy 2019 Part 1: treatment delivery and established indications - actinic keratoses, Bowen's disease and basal cell carcinomas. J Eur Acad Dermatol Venereol. 2019; 33(12): 2225–2238, doi: 10.1111/jdv.16017, indexed in Pubmed: 31779042.
62. Cohen DK, Lee PK. Photodynamic Therapy for Non-Melanoma Skin Cancers. Cancers (Basel). 2016; 8(10), doi: 10.3390/cancers8100090, indexed in Pubmed: 27782043.
63. Christensen E, Mørk C, Skogvoll E. High and sustained efficacy after two sessions of topical 5-aminolaevulinic acid photodynamic therapy for basal cell carcinoma: a prospective, clinical and histological 10-year follow-up study. Br J Dermatol. 2012; 166(6): 1342–1348, doi: 10.1111/j.1365-2133.2012.10878.x, indexed in Pubmed: 22309486.
64. Zou Y, Zhao Y, Yu J, et al. Photodynamic therapy versus surgical excision to basal cell carcinoma: meta-analysis. J Cosmet Dermatol. 2016; 15(4): 374–382, doi: 10.1111/jocd.12236, indexed in Pubmed: 27363535.
65. Vinciullo C, Elliott T, Francis D, et al. Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. Br J Dermatol. 2005; 152(4): 765–772, doi: 10.1111/j.1365-2133.2005.06484.x, indexed in Pubmed: 15840111.
66. Basset-Seguin N, Bissonnette R, Girard C, et al. Consensus recommendations for the treatment of basal cell carcinomas in Gorlin syndrome with topical methylaminolaevulinate-photodynamic therapy. J Eur Acad Dermatol Venereol. 2014; 28(5): 626–632, doi: 10.1111/jdv.12150, indexed in Pubmed: 23581795.
67. Cabete J, Rafael M, Cravo M, et al. Long-term recurrence of nonmelanoma skin cancer after topical methylaminolevulinate photodynamic therapy in a dermato-oncology department. An Bras Dermatol. 2015; 90(6): 846–850, doi: 10.1590/abd1806-4841.20154080, indexed in Pubmed: 26734866.
68. Morton CA, Horn M, Leman J, et al. A randomized, placebo-controlled, European study comparing MAL-PDT with cryotherapy and 5-fluorouracil in subjects with Bowen's disease. Arch Dermatol. 2006; 142: 729–735.
69. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. Br J Dermatol. 2007; 156(5): 793–801, doi: 10.1111/j.1365-2133.2007.07833.x, indexed in Pubmed: 17419691.
70. Truchuelo M, Fernández-Guarino M, Fleta B, et al. Effectiveness of photodynamic therapy in Bowen's disease: an observational and descriptive study in 51 lesions. J Eur Acad Dermatol Venereol. 2012; 26(7): 868–874, doi: 10.1111/j.1468-3083.2011.04175.x, indexed in Pubmed: 21740466.
71. Cavicchini S, Serini SM, Fiorani R, et al. Long-term follow-up of metil aminolevulinate (MAL)-PDT in difficult-to-treat cutaneous Bowen's disease. Int J Dermatol. 2011; 50(8): 1002–1005, doi: 10.1111/j.1365-4632.2011.04962.x, indexed in Pubmed: 21781078.
72. López N, Meyer-Gonzalez T, Herrera-Acosta E, et al. Photodynamic therapy in the treatment of extensive Bowen's disease. J Dermatolog Treat. 2012; 23(6): 428–430, doi: 10.3109/09546634.2011.590789, indexed in Pubmed: 21787214.
73. Toker C. Trabecular carcinoma of the skin. Arch Dermatol. 1972; 105(1): 107–110, indexed in Pubmed: 5009611.
74. Wolf-Peeters CDe, Marien K, Mebis J, et al. A cutaneous apudoma or merkel cell tumor? A morphologically recognizable tumor with a biological and histological malignant aspect in contrast with its clinical behavior. Cancer. 1980; 46(8): 1810–1816, doi: 10.1002/1097-0142(19801015)46:8<1810::aid-cncr2820460819>3.0.co;2-7.
75. Agelli M, Clegg L. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol. 2003; 49(5): 832–841, doi: 10.1016/s0190-9622(03)02108-x.
76. Reichgelt BA, Visser O. Epidemiology and survival of Merkel cell carcinoma in the Netherlands. A population-based study of 808 cases in 1993-2007. Eur J Cancer. 2011; 47(4): 579–585, doi: 10.1016/j.ejca.2010.11.002, indexed in Pubmed: 21144740.
77. Albores-Saavedra J, Batich K, Chable-Montero F, et al. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol. 2010; 37(1): 20–27, doi: 10.1111/j.1600-0560.2009.01370.x, indexed in Pubmed: 19638070.
78. Sadeghinia A, Ghanadan A, Ehsani A, et al. Can dermoscopy open a new way to diagnosing Merkel cell carcinoma? Int J Dermatol. 2019; 58(3): e68–e71, doi: 10.1111/ijd.14386, indexed in Pubmed: 30675720.
79. Michalak-Stoma A, Małkińska K, Krasowska D. Usefulness of Dermoscopy to Provide Accurate Assessment of Skin Cancers. Clin Cosmet Investig Dermatol. 2021; 14: 733–746, doi: 10.2147/CCID.S305924, indexed in Pubmed: 34234499.

80. Dalle S, Parmentier L, Moscarella E, et al. Dermoscopy of Merkel cell carcinoma. Dermatology. 2012; 224(2): 140–144, doi: 10.1159/000337411, indexed in Pubmed: 22487601.
81. Miller RW, Rabkin CS. Merkel cell carcinoma and melanoma: etiological similarities and differences. Cancer Epidemiol Biomarkers Prev. 1999; 8(2): 153–158, indexed in Pubmed: 10067813.
82. Lunder EJ, Stern RS. Merkel-cell carcinomas in patients treated with methoxsalen and ultraviolet A radiation. N Engl J Med. 1998; 339(17): 1247–1248, doi: 10.1056/NEJM199810223391715, indexed in Pubmed: 9786759.
83. Engels E, Frisch M, Goedert J, et al. Merkel cell carcinoma and HIV infection. Lancet. 2002; 359(9305): 497–498, doi: 10.1016/s0140-6736(02)07668-7.
84. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation. 1999; 68(11): 1717–1721, doi: 10.1097/00007890-199912150-00015, indexed in Pubmed: 10609948.
85. Koljonen V, Kukko H, Tukiainen E, et al. Incidence of Merkel cell carcinoma in renal transplant recipients. Nephrol Dial Transplant. 2009; 24(10): 3231–3235, doi: 10.1093/ndt/gfp334, indexed in Pubmed: 19586970.
86. Feng H, Shuda M, Chang Y, et al. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008; 319(5866): 1096–1100, doi: 10.1126/science.1152586, indexed in Pubmed: 18202256.
87. Kassem A, Schöpflin A, Diaz C, et al. Frequent detection of Merkel cell polyomavirus in human Merkel cell carcinomas and identification of a unique deletion in the VP1 gene. Cancer Res. 2008; 68(13): 5009–5013, doi: 10.1158/0008-5472.CAN-08-0949, indexed in Pubmed: 18593898.
88. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol. 2008; 58(3): 375–381, doi: 10.1016/j.jaad.2007.11.020, indexed in Pubmed: 18280333.
89. Allen PJ, Zhang ZF, Coit DG. Surgical management of Merkel cell carcinoma. Ann Surg. 1999; 229(1): 97–105, doi: 10.1097/00000658-199901000-00013, indexed in Pubmed: 9923806.
90. Merkel Cell Carcinoma. NCCN Guidelines. Version 1. 2020.
91. Bichakjian CK, Nghiem P, Johnson T, Wright CL, Sober AJ. Merkel Cell Carcinoma. AJCC Cancer Staging Manual, Eight Edition. Springer 2017.
92. Harms KL, Healy MA, Nghiem P, et al. Analysis of Prognostic Factors from 9387 Merkel Cell Carcinoma Cases Forms the Basis for the New 8th Edition AJCC Staging System. Ann Surg Oncol. 2016; 23(11): 3564–3571, doi: 10.1245/s10434-016-5266-4, indexed in Pubmed: 27198511.
93. Oram CW, Bartus CL, Purcell SM. Merkel cell carcinoma: a review. Cutis. 2016; 97(4): 290–295, indexed in Pubmed: 27163912.
94. Lebbe C, Becker JC, Grob JJ, et al. European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. Eur J Cancer. 2015; 51(16): 2396–2403, doi: 10.1016/j.ejca.2015.06.131, indexed in Pubmed: 26257075.
95. Gupta SG, Wang LC, Peñas PF, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. Arch Dermatol. 2006; 142(6): 685–690, doi: 10.1001/archderm.142.6.685, indexed in Pubmed: 16785370.
96. Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol. 2005; 23(10): 2300–2309, doi: 10.1200/JCO.2005.02.329, indexed in Pubmed: 15800320.
97. Strom T, Carr M, Zager JS, et al. Radiation Therapy is Associated with Improved Outcomes in Merkel Cell Carcinoma. Ann Surg Oncol. 2016; 23(11): 3572–3578, doi: 10.1245/s10434-016-5293-1, indexed in Pubmed: 27251134.
98. Garneski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: current data support radiation but not chemotherapy. J Am Acad Dermatol. 2007; 57(1): 166–169, doi: 10.1016/j.jaad.2007.03.011, indexed in Pubmed: 17482714.
99. Poulsen M, Rischin D, Walpole E, et al. Trans-Tasman Radiation Oncology Group. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study--TROG 96:07. J Clin Oncol. 2003; 21(23): 4371–4376, doi: 10.1200/JCO.2003.03.154, indexed in Pubmed: 14645427.
100. Poulsen MG, Rischin D, Porter I, et al. Does chemotherapy improve survival in high-risk stage I and II Merkel cell carcinoma of the skin? Int J Radiat Oncol Biol Phys. 2006; 64(1): 114–119, doi: 10.1016/j.ijrobp.2005.04.042, indexed in Pubmed: 16125873.
101. Topalian S, Bhatia S, Kudchadkar R, et al. Nivolumab (Nivo) as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358. J Clin Oncol. 2018; 36(15_suppl): 9505–9505, doi: 10.1200/jco.2018.36.15_suppl.9505.
102. Schadendorf D, Lebbé C, Zur Hausen A, et al. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer. 2017; 71: 53–69, doi: 10.1016/j.ejca.2016.10.022, indexed in Pubmed: 27984768.
103. Kaufman H, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016; 17(10): 1374–1385, doi: 10.1016/s1470-2045(16)30364-3.
104. Nghiem P, Bhatia S, Brohl A, et al. Two-year efficacy and safety update from JAVELIN Merkel 200 part A: A registrational study of avelumab in metastatic Merkel cell carcinoma progressed on chemotherapy. J Clin Oncol. 2018; 36(15_suppl): 9507–9507, doi: 10.1200/jco.2018.36.15_suppl.9507.
105. Kaufman HL, Russell JS, Hamid O, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after ≥1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. J Immunother Cancer. 2018; 6(1): 7, doi: 10.1186/s40425-017-0310-x, indexed in Pubmed: 29347993.
106. D'Angelo SP, Bhatia S, Brohl AS, et al. Avelumab in patients with previously treated metastatic Merkel cell carcinoma: long-term data and biomarker analyses from the single-arm phase 2 JAVELIN Merkel 200 trial. J Immunother Cancer. 2020; 8(1), doi: 10.1136/jitc-2020-000674, indexed in Pubmed: 32414862.
107. Bullement A, D'Angelo S, Amin A, et al. Predicting overall survival in patients (pts) with treatment-naive metastatic Merkel cell carcinoma (mMCC) treated with avelumab. J Clin Oncol. 2018; 36(15_suppl): e21620–e21620, doi: 10.1200/jco.2018.36.15_suppl.e21620.
108. D'Angelo SP, et al. First-line avelumab treatment in patients with metastatic Merkel cell carcinoma: primary analysis after ≥15 months of follow-up from JAVELIN Merkel 200, a registrational phase 2 trial. SITC. 2019: P362.
109. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med. 2016; 374(26): 2542–2552, doi: 10.1056/NEJMoa1603702, indexed in Pubmed: 27093365.
110. Nghiem P, Bhatia S, Lipson EJ, et al. Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. J Clin Oncol. 2019; 37(9): 693–702, doi: 10.1200/JCO.18.01896, indexed in Pubmed: 30726175.
111. Medina-Franco H, Urist MM, Fiveash J, et al. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol. 2001; 8(3): 204–208, doi: 10.1007/s10434-001-0204-4, indexed in Pubmed: 11314935.
112. Nelson B, Hamlet K, Gillard M, et al. Sebaceous carcinoma. Journal of the American Academy of Dermatology. 1995; 33(1): 1–15, doi: 10.1016/0190-9622(95)90001-2.
113. Nijhawan N, Ross MI, Diba R, et al. Experience with sentinel lymph node biopsy for eyelid and conjunctival malignancies at a cancer center. Ophthalmic Plast Reconstr Surg. 2004; 20(4): 291–295, doi: 10.1097/01.iop.0000131733.36054.36, indexed in Pubmed: 15266143.
114. Shields JA, Demirci H, Marr BP, et al. Sebaceous carcinoma of the ocular region: a review. Surv Ophthalmol. 2005; 50(2): 103–122, doi: 10.1016/j.survophthal.2004.12.008, indexed in Pubmed: 15749305.
115. Song A, Carter KD, Syed NA, et al. Sebaceous cell carcinoma of the ocular adnexa: clinical presentations, histopathology, and outcomes. Ophthalmic Plast Reconstr Surg. 2008; 24(3): 194–200, doi: 10.1097/IOP0b013e31816d925f, indexed in Pubmed: 18520834.
116. Paties C, Taccagni G, Papotti M, et al. Apocrine carcinoma of the skin. A clinicopathologic, Immunocytochemical, and ultrastructural study. Cancer. 1993; 71(2): 375–381, doi: 10.1002/1097-0142(19930115)71:2<375::aid-cncr2820710218>3.0.co;2-4.
117. Mehta NJ, Torno R, Sorra T. Extramammary Paget's disease. South Med J. 2000; 93(7): 713–715, indexed in Pubmed: 10923963.
118. Pucevich B, Catinchi-Jaime S, Ho J, et al. Invasive primary ductal apocrine adenocarcinoma of axilla: A case report with immunohistochemical profiling and a review of literature. Dermatol Online J. 2008; 14(6), doi: 10.5070/d33zc2p6qn.
119. Chiller K, Passaro D, Scheuller M, et al. Microcystic adnexal carcinoma: forty-eight cases, their treatment, and their outcome. Arch Dermatol. 2000; 136(11): 1355–1359, doi: 10.1001/archderm.136.11.1355, indexed in Pubmed: 11074698.
120. Płachta I, Kleibert M, Czarnecka AM, et al. Current Diagnosis and Treatment Options for Cutaneous Adnexal Neoplasms with Apocrine and Eccrine Differentiation. Int J Mol Sci. 2021; 22(10), doi: 10.3390/ijms22105077, indexed in Pubmed: 4064849.
121. Mehregan A. Eccrine Adenocarcinoma. Archives of Dermatology. 1983; 119(2): 104, doi: 10.1001/archderm.1983.01650260012008.
122. Yeung KY, Stinson J. Mucinous (adenocystic) carcinoma of sweat glands with widespread metastasis:Case report with ultrastructural study. Cancer. 1977; 39(6): 2556–2562, doi: 10.1002/1097-0142(197706)39:6<2556::aid-cncr2820390637>3.0.co;2-d.
123. Płachta I, Kleibert M, Czarnecka AM, et al. Current Diagnosis and Treatment Options for Cutaneous Adnexal Neoplasms with Follicular Differentiation. Int J Mol Sci. 2021; 22(9), doi: 10.3390/ijms22094759, indexed in Pubmed: 33946233.

VIA MEDICA

ORIGINAL ARTICLE

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Comparative analysis of main clinical features in melanoma patients with and without sentinel lymph node biopsy

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2021.0039

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. Sentinel lymph node biopsy is fundamental in the treatment and prognosis of cutaneous malignant melanoma. This study aims to identify differences in baseline clinical characteristics and survival of patients with melanoma with and without a sentinel lymph node biopsy (SLNB) performed.

Material and methods. In 2018, a retrospective study of 151 patients with malignant melanoma (MM) was conducted. The patients were hospitalized at the Second Clinic of University Hospital — Pleven, from 2012 to 2017. The patients were divided into two groups: Group A included 58 (38.4%) patients with SLNB performed; Group B included 93 (61.6%) patients who did not undergo SLNB. A double-detection method was used while performing SLNB.

Results. The incidence of achromatic malignant melanoma is significantly higher in patients without SLNB (12 or 12.9%) than in patients with SLNB (2 or 3.4%) — $\chi 2 = 3.796$, df = 1, p = 0.051. Of all 151 patients in the study, 46 died, representing 30.5% of patients with melanoma. The mortality rate was higher in the patients without SLNB (32.3% *vs.* 27.6% in Group A). However, the differences in the two groups are not statistically significant.

Conclusions. Patients with achromatic melanoma have significantly fewer sentinel lymph node (SLN) biopsies performed because of a late diagnosis. Most of our patients are diagnosed at a later stage when lymphatic metastases are already present, which leads to a significant increase in lymph node dissections performed. There is no significant difference in mortality and survival in the SLNB and non-SLNB groups.

Key words: Sentinel lymph node biopsy, Malignant melanoma of skin, Melanoma

Oncol Clin Pract 2022; 18, 2: 92–97

Introduction

The term *melanoma* was first employed by René Laennec, who, in his manuscript in 1812, describes a case of disseminated disease [1]. Cutaneous malignant melanoma develops after the malignant transformation of its pigment-forming melanocytes [2]. Australia and New Zealand are world leaders in terms of morbidity and mortality rates of 54/100,000 and 5.6/100,000, respectively, for 2015 [3]. In Bulgaria, the morbidity rate for the same year is 6.5/100,000, and the mortality rate is 2.1/100,000. The main risk factors for its development

Received: 19.07.2021 Accepted: 05.09.2021 Early publication date: 16.12.2021

are exposure to ultraviolet radiation [4], skin phototype [5], the presence of pigmented nevi [6], severe sunburn [7], and geographical location [8].

A sentinel lymph node biopsy is fundamental in the treatment and prognosis of cutaneous malignant melanoma. The sentinel lymph node is defined as the first stop for metastases accumulation from a malignant tumor process. Depending on the detection method used, the first sentinel lymph node detected is described as a *hot* node (radiocolloid labeled) or blue stained (Patent Blue V marked) [9]. Its histological examination provides an accurate prognosis of the involvement of other nodes in the lymphatic chain. During an SLN biopsy, the sentinel lymph node(s) is surgically removed. Patients with a sentinel lymph node histologically positive for metastases undergo compulsory complete lymph node dissection of the entire basin.

A sentinel lymph node biopsy in the management of cutaneous malignant melanoma was first performed by Donald Morthon and team in 1992 in order to avoid the frequent postoperative complications occurring with the previously used elective lymph node dissection [10, 11].

This study aims to identify differences in baseline clinical characteristics and survival rates of two groups of patients with cutaneous malignant melanoma — with and without a sentinel lymph node biopsy (SLNB) performed.

Material and methods

In 2018, a retrospective study of 151 patients with malignant melanoma (MM) was conducted. The patients were hospitalized at the Second Clinic of University Hospital — Pleven, from 2012 to 2017. Patients with a diagnosis other than MM were excluded from the study.

The patients were divided into two groups: Group A included 58 (38.4%) patients with SLNB performed; Group B included 93 (61.6%) patients who did not undergo SLNB (Tab. 1). A double-detection method was used while performing SLNB with the application of Technetium Tc-99m Sulfur Colloid radiopharmaceutical and Patent Blue V staining dye.

The documentary method is used to extract primary sociological information. Data are collected on: age, sex, Breslow thickness, the level of tumor invasion (Clark level), a histologic variant, the lymph node dissection performed, the stage of disease [pathologoanatomical tumor staging system (pTNM) classification], and survival (expressed in months).

The statistical software used for data processing is SPSS v.24.0. Descriptive statistics were applied. Pearson's chi-squared test ($\chi 2$) was used to identify differences in the groups, and Spearman's Rank correlation coefficient was used to measure correlation dependencies. Results at a p-value significance level (p) less than or equal to 0.05 were considered statistically significant. Survival estimates for both groups of patients with MM were computed by log rank test and Kaplan-Meier survival curve.

Results

Demographic characteristics

Table 1 shows the distribution of patients in the two groups — total, by age, and sex.

The mean age of patients with MM is 65.0 years, with the youngest aged 17 and the oldest 91. The median age in Group B was 67.0 years and was higher than in Group A — 63.5 years.

The distribution of patients by sex indicates 78 (51.7%) males (44.8% in Group A, and 55.9% in Group B, respectively).

Clinical characteristics

Histological variant of the tumor

The incidence of achromatic malignant melanoma (Fig. 1) is significantly higher in the patients without SLNB (12 or 12.9%) than in patients with SLNB (2 or 3.4%) — $\chi 2 = 3.796$, df = 1, p = 0.051. There is a weak correlation (r = 0.159, p = 0.050, N = 151).

Melanoma thickness (Breslow classification)

The mean melanoma thickness was 2.50 mm (Mdn, 0–11 Min, Max) in the patients in Group B, and was higher than in the patients in Group A (1.8 Mdn, 1–5 Min, Max).

Using Breslow classification, we report that the proportion of patients with melanoma thickness greater than 4.1 mm in Group B (32.2%) was approx. three times higher compared to Group A (13.8%). Differences are significant ($\chi 2 = 29.563$, df = 5, p = 0.001). For the rest of the cases, there was a higher proportion of patients with MM and performed SLNB, with tumor invasion in the range of 0.76 — 1.0 mm, 1.1 — 2.0 mm, and 2.1 — 4.0 mm (Tab. 2). There was no correlation between the two variables (p = 0.547).

Performed lymph node dissection

Lymph node dissection was performed in 48 (31.8%) patients with MM, respectively in 18 (31.0%) patients in Group A and 30 (32.3%) patients in Group B (Tab. 2). The causes for lymph node dissection were different in the two comparative groups. The cause in non-SLNB patients was the discovery of a clinically positive lymph node, whereas, in SLNB patients, the cause was a posi-

Table 1. Distribution of patients with malignant melanoma according to sentinel lymph node biopsy performance — total, by sex and age (Valid N, %)

Variable	Group A Number (%)	Group B Number (%)	Total Number (%)
Gender			
Male	26 (44.8%)	52 (55.9%)	78 (51.7%)
Female	32 (55.2%)	41 (44.1%)	73 (48.3%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
Age			
Mean age (Mdn, Min–Max)	63.5 (17–81)	67.0 (32–91)	65.0 (17–91)
Total	**58 (38.4%)**	**93 (61.6%)**	**151 (100.0%)**

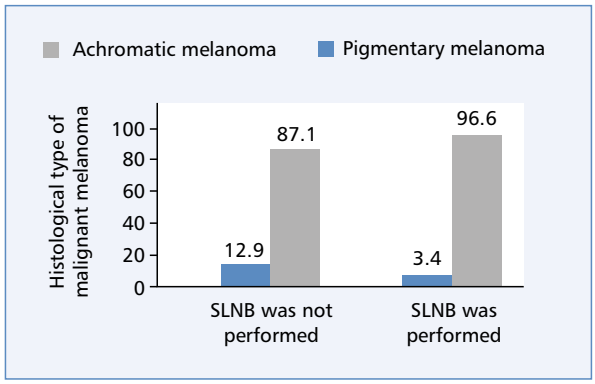

Figure 1. Distribution of patients with malignant melanoma according to the performance of sentinel lymph node biopsy (SLNB) and histologic variant of tumor (%)

tive sentinel lymph node identified by histological analysis. There were no statistically significant differences between the groups studied.

Tumor staging (pTNM classification system)

The pTNM classification in our study shows the latest data from the National Cancer Registry of Bulgaria for 2018. We found that every fourth patient with MM was in stage IV, respectively 20.7% of Group A and 28.0% of Group B (Tab. 2). Significantly higher was the proportion of Group-B patients classified in stage 0 (8.6% *vs.* 1.7% in Group A) and stage IA (18.1% *vs.* 6.9% in Group A). With disease progression (stage IB–IIC), the proportion of patients with SLNB increases ($\chi 2 = 27.287$, df = 7, p = 0.001). There is no correlation between the studied variables (p = 0.567).

Table 2. Distribution of the patients in Group A and Group B by Breslow`s thickness of malignant melanoma (MM), pathologoanatomical tumor staging system classification and lymph node dissection (Number, %)

Variable	Group A Number (%)	Group B Number (%)	Total Number (%)
Breslow`s thickness of MM			
In situ	0 (0.0%)	10 (10.8%)	10 (6.6%)
Thickness less than 0.75 cm	4 (6.9%)	15 (16.1%)	19 (12.6%)
Thickness 0.76–1.0 cm	5 (8.6%)	5 (5.4%)	10 (6.6%)
Thickness 1.1–2.0 cm	29 (39.7%)	9 (9.7%)	32 (21.2%)
Thickness 2.1–4.0 cm	18 (31.0%)	24 (25.8%)	42 (27.8%)
Thickness greater than 4.0 cm	8 (13.8%)	30 (32.2%)	38 (35.2%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
pTNM Classification			
Stage 0	1 (1.7%)	8 (8.6%)	9 (6.0%)
Stage IA	4 (6.9%)	17 (18.1%)	21 (13.9%)
Stage IB	17 (29.3%)	9 (9.7%)	26 (17.2%)
Stage IIA	8 (13.8%)	5 (5.4%)	13 (8.6%)
Stage IIB	7 (12.1%)	6 (6.5%)	13 (8.6%)
Stage IIC	9 (15.3%)	10 (10.8%)	19 (12.6%)
Stage III	0 (0.0%)	12 (12.9%)	12 (7.9%)
Stage IV	12 (20.7%)	26 (28.0%)	38 (25.2%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
Lymph node dissection			
Yes, done	18 (31.0%)	30 (32.3%)	48 (31.8%)
No, not done	40 (69.0%)	63 (67.7%)	103 (68.2%)
Total	58 (100.0%)	93 (100.0%)	151 (100.0%)
Total	**58 (38.4%)**	**93 (61.6%)**	**151 (100.0%)**

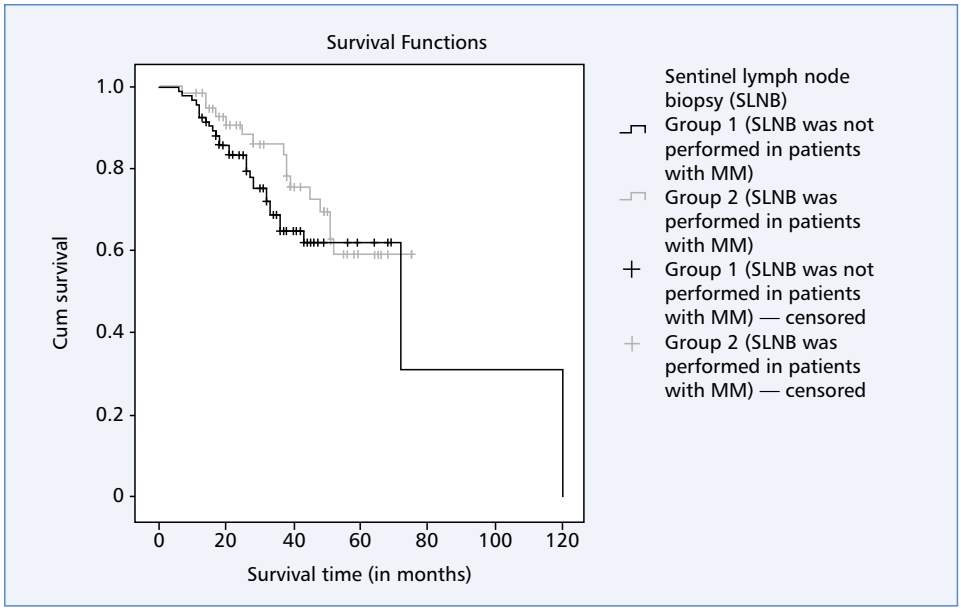

Figure 2. Kaplan-Meier Survival Curve for Patients with malignant melanoma (MM) in Group A and Group B; SLNB — sentinel lymph node biopsy

Mortality and survival

Of all 151 patients in the study, 46 died, representing 30.5 per 100 patients with malignant melanoma. The mortality rate was higher in the patients without SLNB (32.3% *vs.* 27.6% in Group A). However, the differences in the two groups are not statistically significant ($p = 0.544$).

Median survival (expressed in months) in patients with malignant melanoma (MM) is 72 months, SE = 20.704 at S (t) = 0.5. The median survival ($\bar{x}$) in patients with MM and SLNB performed is 59.1 months (SE = 3.2, CI = 52.7–65.4) and is lower than in patients with the same diagnosis but without SLNB ($\bar{x}$ = 68.8 months, SE = 11.5 months, CI = 46.2–91.5). However, the log rank test does not confirm these differences to be significant (log rank = 1.372, df = 1, $p = 0.241$).

The likelihood of a patient with MM without SLNB to survive 7 months is 97.8%, and in patients with melanoma and performed SLNB – 98.3%. The 14-month probability was 91.2% for Group B and 94.7% for Group A. The survival curve for the patients in Group B has a steep downward trend which shows a worse prognosis in the first months after diagnosis compared to Group A (Fig. 2).

Discussion

For a sentinel lymph node biopsy to be performed, the sentinel node must be stained with a lymphotropic agent, which makes it easier to detect. It is a molecule weighing more than 5000 D, which is injected intradermally and reaches predilectionally the lymphatic system. Patent blue V and radioactive Technetium 99Th Sulfur Colloid are used as tracers [12, 13].

The main advantages of sentinel lymph node biopsy in cutaneous malignant melanoma, according to the most recent trials (MSLT 1 and 2) are:

— the result is a powerful prognostic factor;
— complete lymph node dissection after detection of the positive sentinel lymph node in some patients with thin malignant melanomas, all medium-thick malignant melanomas, and thick malignant melanomas, improves their survival in good health;
— complete lymph node dissection after detection of the positive sentinel lymph node in some patients with thin malignant melanomas, and in all medium-thick malignant melanomas, improves their survival in good health and overall survival;
— the result is the basis for the implementation of effective postoperative therapy;
— it is a very sparing operative procedure [14, 15].

There is a direct correlation between the thickness of cutaneous malignant melanoma and the percentage of sentinel lymph nodes affected by the metastatic process, which is shown in Table 3.

A comprehensive analysis of data regarding patients' distribution by sex shows a slight prevalence of males 78 (51.7%). The differences are minimal and nonsignificant, however, still presenting a higher risk of developing malignant melanoma in men. This trend is reflected in other similar, large-scale surveys conducted in Australia and New Zealand [16, 17].

Table 3. Percentage of positive entinel lymph node biopsies by thickness of malignant melanoma

Breslow Thickness (mm)	Positive sentinel lymph nodes
≤ 1	≤ 5%
1–4	15–20%
> 4	> 40%

The sex distribution of our patients in the two groups shows the prevalence of women in the SLN biopsy group — 32 (55.2%), whereas men were predominant in the non-SLN group — 52 (55.9%). The results of a multicenter study with 612 patients by Gershenwald et al. [18] contradict ours and demonstrate a predominance of men (57.5%) in the SLN biopsy group. The data are not straightforward, and the differences are not significant. This suggests that no significant causal link can be drawn.

The median age of 65.0 years in our patients with cutaneous malignant melanoma is higher than that reported by Ali et al. [19] — 57.0 years, in a worldwide study of the epidemiology of malignant melanoma. The majority of our patients were older, which should not reassure us because our youngest patient was only 17 years old. This is a particular concern meaning that the disease is affecting much younger people.

The differences between the median age of our patients in the two study groups are not significant, which correlates with the results of a multicenter study by Gutzmer et al. [20] involving 673 patients.

Achromatic skin melanoma is defined as a malignant lesion, lacking the pigment melanin or where said pigment is present in only a minimal amount. The significantly higher percentage of patients with achromatic melanoma was in the non-SLN biopsy group (12.9% to 3.4%) because this histologic variant of cutaneous melanoma is diagnosed at a later clinical stage because of its atypical clinical manifestation, which in most cases does not allow for an SLN biopsy [21].

We can report a lower mean Breslow tumor thickness of 1.8 mm (Mdn, 1–5 Min, Max) in the SLN biopsy group, compared to an average thickness of 2.5 mm (Mdn, 0–11 Min, Max) in the group without SLN biopsy. Additionally, we observed a significantly lower percentage of patients with a melanoma thickness greater than 4.1 mm — 13.2% in the same group, compared to 32.2% for the other one. This indicates that we have met precisely one of the main indications for performing SLNB, namely, for the Breslow thickness of malignant melanoma to be between 0.75 and 4.1 mm [22–25].

Statistical data analysis of the performed lymph node dissection in the two groups shows that their frequency was very close and was getting on for 31–32%. This is 10% higher than 20.8% reported by Morton et al. [26] in the results of the largest MSLT I study to date and indicates that the majority of our patients were in an advanced stage of the disease when melanomas had already spread to lymphatic metastases. This is a very negative trend shown in our study, in all likelihood related to the late diagnosis of the disease.

Comparing our data on the MM stage for the SLNB group to those in the non-SLNB group, we observed that the percentage of patients in the first two and the last two stages of the disease was significantly higher in the non-SLNB group. This shows once again that we have strictly adhered to the rule that SLN biopsy is not recommended for patients with tumor thickness < 0.75 mm and stage 0 and IA, respectively, as the risk of lymphatic metastases, is below 5%. The same refers to the cases with tumor thickness > 4.1 mm because the risk of lymphatic metastases is greater than 40% and the benefit of SLN biopsy is unclear [22–25].

Statistical analysis of mortality in the groups with and without SLN biopsy shows slightly lower rates for the first one (27.6% to 32.3%); the differences are not significant. We did not find any significant differences between survival rates in the two groups. This matches the conclusion of Sladen et al., made upon summarizing data from the largest MSLT I study so far, that there is no significant difference in survival and mortality of patients from the two groups [27].

Conclusions

Patients with achromatic melanoma have significantly fewer SLN biopsies performed because of a late diagnosis. Most of our patients were diagnosed at a later stage when lymphatic metastases are already present, which led to a significant increase in the number of lymph node dissections performed. There is no significant difference in mortality and survival in the SLNB and non-SLNB groups.

Funding

The authors do not have any grants, contracts, and other forms of financial support.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization — S.S.
Methodology — S.S. and A.K.

Software — A.Y., M.V., and Y.S.
Validation — S.S., A.Y., and A.K.
Formal Analysis — S.S., M.V., and Y.S.
Investigation — S.S. and A.K.
Resources — S.S. and A.Y.
Data Curation - S.S., M.V., and Y.S.
Writing — Original Draft Preparation - S.S.
Writing — Review & Editing - S.S., A.K., and A.Y.
Visualization — S.S., M.V., and Y.S.
Supervision — S.S. and Y.S.
Project Administration — S.S.

Compliance with ethics requirements

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study

The study was approved by the Ethics Committee of the Medical University of Pleven, Bulgaria through document number 454-КЕНИД / 21.06.2017.

References

1. Chin L, Merlino G, DePinho RA. Malignant melanoma: modern black plague and genetic black box. Genes Dev. 1998; 12(22): 3467–3481, doi: 10.1101/gad.12.22.3467, indexed in Pubmed: 9832500.
2. Jhappan C, Noonan FP, Merlino G. Ultraviolet radiation and cutaneous malignant melanoma. Oncogene. 2003; 22(20): 3099–3112, doi: 10.1038/sj.onc.1206450, indexed in Pubmed: 12789287.
3. Karimkhani C, Green AC, Nijsten T, et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. Br J Dermatol. 2017; 177(1): 134–140, doi: 10.1111/bjd.15510, indexed in Pubmed: 28369739.
4. Kozmin S, Slezak G, Reynaud-Angelin A, et al. UVA radiation is highly mutagenic in cells that are unable to repair 7,8-dihydro-8-oxoguanine in Saccharomyces cerevisiae. Proc Natl Acad Sci U S A. 2005; 102(38): 13538–13543, doi: 10.1073/pnas.0504497102, indexed in Pubmed: 16157879.
5. Bishop JAN. Lentigos, Melanocytic Naevi and Melanoma. Rook's Textbook of Dermatology. 2010: 1–57, doi: 10.1002/9781444317633.ch54.
6. Loria D, Matos E. Risk factors for cutaneous melanoma: a case--control study in Argentina. Int J Dermatol. 2001; 40(2): 108–114, doi: 10.1046/j.1365-4362.2001.01132.x, indexed in Pubmed: 11328391.
7. Hausauer AK, Swetter SM, Cockburn MG, et al. Increases in melanoma among adolescent girls and young women in California: trends by socioeconomic status and UV radiation exposure. Arch Dermatol. 2011; 147(7): 783–789, doi: 10.1001/archdermatol.2011.44, indexed in Pubmed: 21422322.
8. de Vries E, Bray FI, Coebergh JW, et al. Changing epidemiology of malignant cutaneous melanoma in Europe 1953-1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. Int J Cancer. 2003; 107(1): 119–126, doi: 10.1002/ijc.11360, indexed in Pubmed: 12925966.
9. Levenback C. Intraoperative Lymphatic Mapping and Sentinel Node Identification: Gynecologic Applications. Recent Results in Cancer Research. 2000: 150–158, doi: 10.1007/978-3-642-57151-0_13.
10. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27(36): 6199–6206, doi: 10.1200/JCO.2009.23.4799, indexed in Pubmed: 19917835.
11. Leong SPL, Mihm MC, Murphy GF, et al. Sentinel lymph node biopsy as the standard of care for cutaneous melanoma. Clin Adv Hematol Oncol. 2007; 5(6): 483–490, indexed in Pubmed: 17679922.
12. Baitchev G. Biopsy of the sentinel lymph nodes in malignant melanoma. My surgery.bg 28.09.2011.
13. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992; 127(4): 392–399, doi: 10.1001/archsurg.1992.01420040034005, indexed in Pubmed: 1558490.
14. Morton DL. Overview and update of the phase III Multicenter Selective Lymphadenectomy Trials (MSLT-I and MSLT-II) in melanoma. Clin Exp Metastasis. 2012; 29(7): 699–706, doi: 10.1007/s10585-012-9503-3, indexed in Pubmed: 22729520.
15. Spillane A, Read R, Thompson J. Sentinel node biopsy should be the standard of care for patients with intermediate and thick melanomas. Aust Fam Physician. 2015; 44(8): 604–606, indexed in Pubmed: 26510152.
16. Australian Institute of Health and Welfare 2017. Australian Cancer Incidence and Mortality (ACIM) books: Melanoma of the skin. Canberra: AIHW. www.aihw.gov.au/acim-books.
17. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. 2008. www.nhmrc.gov.au/guidelines/publications/cp111 (6.06.2013).
18. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. J Clin Oncol. 1999; 17(3): 976–983, doi: 10.1200/JCO.1999.17.3.976, indexed in Pubmed: 10071292.
19. Gutzmer R, Al Ghazal M, Geerlings H, et al. Sentinel node biopsy in melanoma delays recurrence but does not change melanoma-related survival: a retrospective analysis of 673 patients. Br J Dermatol. 2005; 153(6): 1137–1141, doi: 10.1111/j.1365-2133.2005.06941.x, indexed in Pubmed: 16307648.
20. Ali Z, Yousaf N, Larkin J. Melanoma epidemiology, biology and prognosis. EJC Suppl. 2013; 11(2): 81–91, doi: 10.1016/j.ejcsup.2013.07.012, indexed in Pubmed: 26217116.
21. Thomas NE, Kricker A, Waxweiler WT, et al. Genes, Environment, and Melanoma (GEM) Study Group. Comparison of clinicopathologic features and survival of histopathologically amelanotic and pigmented melanomas: a population-based study. JAMA Dermatol. 2014; 150(12): 1306–1314, doi: 10.1001/jamadermatol.2014.1348, indexed in Pubmed: 25162299.
22. Ferrone CR, Panageas KS, Busam K, et al. Multivariate prognostic model for patients with thick cutaneous melanoma: importance of sentinel lymph node status. Ann Surg Oncol. 2002; 9(7): 637–645, doi: 10.1007/BF02574479, indexed in Pubmed: 12167577.
23. Gajdos C, Griffith KA, Wong SL, et al. Is there a benefit to sentinel lymph node biopsy in patients with T4 melanoma? Cancer. 2009; 115(24): 5752–5760, doi: 10.1002/cncr.24660, indexed in Pubmed: 19827151.
24. Gershenwald JE, Mansfield PF, Lee JE, et al. Role for lymphatic mapping and sentinel lymph node biopsy in patients with thick (> or = 4 mm) primary melanoma. Ann Surg Oncol. 2000; 7(2): 160–165, doi: 10.1007/s10434-000-0160-4, indexed in Pubmed: 10761797.
25. Gutzmer R, Satzger I, Thoms KM, et al. Sentinel lymph node status is the most important prognostic factor for thick (> or = 4 mm) melanomas. J Dtsch Dermatol Ges. 2008; 6(3): 198–203, doi: 10.1111/j.1610--0387.2007.06569.x, indexed in Pubmed: 18093216.
26. Sladden M, Zagarella S, Popescu C, et al. No survival benefit for patients with melanoma undergoing sentinel lymph node biopsy: critical appraisal of the Multicenter Selective Lymphadenectomy Trial-I final report. Br J Dermatol. 2015; 172(3): 566–571, doi: 10.1111/bjd.13675, indexed in Pubmed: 25776246.
27. Morton DL, Thompson JF, Cochran AJ, et al. MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014; 370(7): 599–609, doi: 10.1056/NEJMoa1310460, indexed in Pubmed: 24521106.

VIA MEDICA

ORIGINAL ARTICLE

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Grief reactions of family members after the death of cancer patients: a phenomenological study

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0014

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. The death of a family member due to cancer is one of the most stressful events of life. The purpose of the present study was to investigate lived experiences of family members grieving after the death of their relatives from cancer in Iran.

Material and methods. A phenomenological study was performed. The seven-stage process of data analysis was employed. The study was conducted in two hospitals that have oncology wards in Tehran, Iran. We interviewed 14 bereaved family members. Participants went through semi-structured, in-depth, and face-to-face interviews.

Results. Study participants' lived experiences were classified into 2 main themes including 'grief management' and 'evaluating death'. 'Grief management' had two subthemes: 'cultural adaptation to death' and 'emotional reactions'. 'Evaluating death' also had two subthemes: 'good death' and 'bad death'. One constitutive pattern `families' effort to accept the cancer patient's death' was identified.

Conclusions. According to our findings, family members of cancer patients require more supportive programs such as supportive care. Our study indicated the need for culture-based care for the bereaved family members of cancer patients.

Key words: cancer, death, family, phenomenological study, supportive care

Oncol Clin Pract 2022; 18, 2: 98–103

Introduction

In 2020, 1,806,590 new cancer cases and 606,520 cancer deaths are projected to occur in the United States [1]. In Iran, cancer is the third common cause of death, after heart disease and road accidents [2]. The death of a family member due to cancer is one of the most stressful events of life [3]. In other words, the death of a family member is identified as an emotional crisis in life [4]. Many family members of cancer patients experience a major emotional imbalance after the death of a loved one [5]. When a patient is dying due to cancer, family members often put their lives on hold to give comprehensive care [6]. Bereaved family members of cancer patients have a lower health-related quality of life than the other people [7]. Therefore, the concept of bereavement in cancer is affected by a group of elements, including health concerns, social considerations, and family interactions [8].

A wide range of studies about bereaved family members has been published. According to the findings of a study in Denmark, relatives of terminally ill patients reported functional impairment at 6 months after bereavement [9]. Results of another study in Belgium demonstrated that the first moments of bereavement included feelings of disbelief, regret, and relief. Also, loneliness is considered a dominant feeling throughout the bereavement period [10]. The results of a study

Received: 22.11.2021 Accepted: 03.01.2022 Early publication date: 24.03.2022

in Ireland indicated that factors that have a positive influence on bereavement among family carers of patients who died of cancer included patients having no preference for place of death and carers remaining in employment pre- or post-bereavement [11]. According to the findings of a British study, bereaved individuals reported a predominance of negative and upsetting memories and more negative intrusive imagery [12]. It seems that a complex of factors influences family members' experiences.

Reviewing the literature, we found that there is a lack of qualitative studies regarding the lived experiences of bereaved family members of cancer patients in the Iranian context. Respect for bereaved family members seems to be very important in Iranian culture. However, there are limited studies of bereaved families in this regard. Thus, it is important to comprehend the lived experiences of this group, as well as identify the bereaved family members' feelings and beliefs. Since the death of cancer patients can culturally affect family members, it is necessary to continue developing studies that evaluate and deepen our knowledge from the families' lived experiences. The present study aimed to explore the lived experiences of family members about grief reactions to cancer patient's death in Iran. Results of this study can promote awareness and respect for the opinions of families toward the death of cancer patients in clinical settings in end-of-life care.

Material and methods

The phenomenological methodology of the study was used to develop an understanding of the lived experiences of the individuals who have experienced the death of a patient. This is a good methodology for the study because the phenomenological approach can provide an answer to a research question that seeks to comprehend how people experience a common phenomenon [13]. This study was performed using a hermeneutic phenomenological approach. It assists us in evaluating the meaning of 'being in the world' [14]. Thus, contributing to the lived experiences of family members is a way of 'being in the world'. Furthermore, the hermeneutic approach in the present study would permit family members to concentrate on their lived experiences through an explanation of their individual experiences of cancer patients' death.

The study was conducted in two hospitals that have oncology wards in Tehran, Iran. Referring to the hospitals' and patients' documents, 14 bereaved close family members of cancer patients were identified. We employed a purposeful maximum variation sampling. The inclusion criteria specified that individuals must (a) be at least 12 months past the death of a cancer patient, (b) be young adult age or older and (c) receive no psychotropic drugs. Thanks to head nurses' coordination with the medical records unit, the families' phone numbers were obtained and the families were contacted. The participants were called by the second author. Accompanied by a letter including some information about the aim of the study, the interviews were done by the authors over 3 months (Oct-Dec 2019). The main criterion for inclusion was the experience of a cancer patient's death.

Of the 14 participants, there were 9 females and 5 males. The family members were aged from 19 to 60 years old. Eight of the participants were married; the rest were single. Four participants had a university education, seven of them had completed secondary education and three participants had lower than secondary education. Regarding the type of their relatives' cancers, 6 patients had breast cancer, 5 hematologic cancer, 2 colorectal cancer, and 1 patient had prostate cancer. The deceased relatives were mothers, husbands, brothers, or sisters of the participants.

We performed face-to-face, semi-structured interviews, lasting 55–65 minutes. The interviews were flexible enough to be conducted in a comfortable place based on participants' requests. Most participants preferred to be interviewed at home. Because of it, most of the interviews were conducted in private at their home. Since 2 participants were interviewed twice, a full number of 16 interviews were conducted. Each interview was transcribed word for word. The interviews were continued until no new data appeared. Data saturation was obtained after all the interviews. Our interviews were carried out using the opening question 'What is the meaning of grief for a bereaved family member of a cancer patient?' After they responded to the main question, additional questions were asked to gain more data, such as: 'Could you clarify this further?', 'What is the meaning of that idea?', and 'Could you please provide me an example to assist us in comprehending your point of view?'

The data gathering was performed after obtaining signed informed consent outline from the family members. Following all interviews, the researcher conversed with the family members about neutral topics to decrease any emotional distress that may have occurred that was related to the talk about death.

Data gathering and analysis occurred in parallel. Teamwork was used in our study to analyze the data. In this regard, we performed the seven-phase method of data analysis [15].

Stage 1: The authors read each interview transcript to gain an overall understanding of it.

Stage 2 and 3: Probable common meaning units were then recognized, using extracts for clarification. The authors frequently listened to the tape recordings to abstract the accurate meaning of the data.

Stage 4: The research group assessed their explanations for similarities and differences, getting more clarification and agreement by reconsidering the main transcript.

Stage 5: All transcripts were then reviewed to confirm emergent themes. Next, the emerging themes were categorized by the research team.

Stage 6: A constitutive pattern was identified that showed the connection between themes and subthemes.

Stage 7: The authors created a final report, including quotes that were permitted for confirmation by the reader.

The rigor of this study is assessed by 4 criteria: credibility, dependability, confirmability, and transferability [16]. To achieve credibility, authors' ideas were used in the interviews and data analysis. Interview transcripts, reduced meaning units, and themes were discussed by some family members. To determine data dependability, views of an outside viewer, who was a researcher familiar with the phenomenological approach and not a member of the research team, were used. There was an agreement on the findings. To obtain confirmability, all the procedures were documented, and a report was presented on the research progress. To obtain transferability, data gathered from 2 family members outside of the study who were in situations similar to those of the participants were discussed and confirmed.

This article is part of a research project with the number: IR.ZAUMS.REC.1399.350 approved by Zahedan University of Medical Sciences. The human subject protection committee at the ZAUMS approved this study. The study was conducted according to the criteria set by the declaration of Helsinki.

Results

Study participants' lived experiences were grouped into 2 main themes including 'grief management' and 'evaluating death'. 'Grief management' had two subthemes: 'cultural adaptation to death' and 'emotional reactions'. 'Evaluating death' also had two subthemes: 'good death' and 'bad death'. These themes reflected the meaning of cancer patient's death to our participants. The constitutive pattern of the study was families' effort to accept the cancer patient's death.

The study themes and the participants' views are explained below.

Grief management

This theme consisted of 2 subthemes: 'cultural adaptation to death' and 'emotional reactions'.

Cultural adaptation to death

The presence of the bereaved people in funeral and mourning ceremonies helped them to cope with grief. 'When my mother died, my attendance in different mourning ceremonies held on the third, 7th and 40th day after her death really helped me in dealing with it' [Participant (P) 6].

In addition, supporting a grieving person played an important role in adaptation. One of our participants expressed: 'When my husband died due to colon cancer, his family did not leave me alone. In fact, their support helped me to accept the reality of his death' (P3).

Some participants claimed that belief in death as an inevitable fact resulted in accepting the death of the patient. 'Death is a phase of our life process. When my son died, I told myself it was his destiny' (P10).

Moreover, reconciling oneself with the loss could be facilitated by visiting the grave. 'Date offerings, washing the gravestone of my father and leaving flowers on it are the things I do on Thursdays' (P14).

Emotional reactions

Generally, after loss, it can be hard to accept what happened and some participants had trouble believing that the loss really happened or even denied the truth. Below are some examples: 'In the hospital, when I heard that my father had died, I could not accept it and shouted angrily this can't be happening to me' (P9).

Furthermore, some families reacted to the death of a family member by bargaining with God. 'My daughter was really kind. When she died I complained to God, why my daughter should die while there are many bad and sinful people all over the world. She was really meek and her death was unfair' (P1).

A group of participants experienced shock and disbelief after loss. One participant said: 'chemotherapy was not effective for my brother. After his shocking death, I experienced sleep and appetite disturbances and lack of concentration' (P5).

Evaluating death

The main theme 'evaluating death' included two subthemes: 'good death' and 'bad death'.

Good death

It seems that some factors such as providing ongoing support to grieving families and the patient receiving narcotics resulted in the death being evaluated as an easy going out of the world. 'My sister experienced a good death. All family members took care of her and met her needs. We wanted to help her enjoy the last days of life' (P11).

'My father experienced severe pain. Receiving narcotics was effective in him having a good death' (P8).

Also, the participants mentioned the death at home as a good experience because of the opportunity of providing care to the patient in the last hours of his/her life: 'My husband died at our home. Despite many bad

memories, I have good memories of his presence at our own house in the last moments' (P2).

Bad death

According to our participants, one factor which played an important role in evaluating death as a bad experience was dying in the prime of life which resulted in depression of family members: 'My young brother died from Leukemia, his death was really difficult and resulted in depression of my parents' (P12).

Grieving people mentioned death as a bitter experience because it prevented the deceased from fulfilling his/her wishes: 'My mom wished to celebrate the wedding party of her children and have grandchildren… it is a sad fact' (P4).

In addition, some participants experienced death as a catastrophic event. One of them stated that: 'When I was a child, my mother died in an accident and my sister played the role of a mother for us… her death due to breast cancer was really tragic … I feel alone' (P7).

The constitutive pattern: families' effort to accept the cancer patient's death

In the social context of Iran, families manage grief based on cultural adaptation to death and emotional reactions, but on the other hand, they experience it as an inevitable stage in life.

Discussion

The experiences of the participants showed that they have grief reactions regarding the death of cancer patients. The perspective on death among individuals with diverse socio-cultural contexts has key differences. Since death is an important part of life, understanding this phenomenon is essential. On the whole, cultural adaptation to death was a strategy to deal with grief in the families of cancer patients. They believed that being offered support was a key factor that led to acceptance. Results of a study carried out in Taiwan indicated that providing support to caregivers of cancer patients results in a shorter grieving process [17]. Iranian people often meet the family of the deceased in the period following the death.

Appropriate care after the cancer patient's death is needed to facilitate family members' acceptance of the loss of their relative. Also, some participants accepted death as a part of life that stems from destiny. Results of research in Lithuania demonstrated that people who had accepted death as a part of life showed fewer grief symptoms [18]. In the Islamic culture of Iran, Islam deliberates remembrance of death as a part of life journey. Thus, people are created for a life duration, and death is a part of the contract with God. Considering several rituals in the 3rd, 7th, and 40th days after death in Iran, the presence of the bereaved in funeral and mourning rituals for the deceased had a positive effect on the cultural adaptation to death. In Iranian culture, the mourning period officially lasts for 40 days. Also, visiting the place where the body is buried, on Thursdays, could facilitate acceptance of the reality of the loss. Thus, health professionals should be aware of the diversity of cultural values surrounding death and assess the values of cancer patients' families. In Iranian culture, bereavement is an element of death, so expressing sadness is suitable in prescribed ways [19].

On the other hand, some participants refused to accept the death of their relatives and experienced severe distress and anger. Results of the study in Taiwan showed that bereaved families of cancer patients had experienced severe distress [20]. In this regard, a multicenter survey of bereaved families in Japan showed that family distress was experienced when the physician stated that nothing could be done for the patient [21]. In this study, death has been a serious challenge for family members. In this situation, people started bargaining with God as a way to manage grief. In addition, death was a shocking event for them which resulted in sleep and appetite disturbances, lack of concentration, and confusion. This is consistent with the results of a systematic review that said people experienced sleep disturbances and anxiety in confrontation with death [22]. As several families experienced a psychological crisis when their relatives died, the psychological context of bereavement for family members is uniquely challenging and must be considered when providing care. Generally, our findings demonstrated that participants have experienced death as an inevitable stage in life. Bereaved families believed that taking care of patients, meeting their needs, and helping them to enjoy the last days of life resulted in a good death. According to American study, care for terminal phase of cancer patients was categorized into some themes such as support of daily life [23]. Moreover, based on the experiences of bereaved families, narcotics resulted in the good death of patients. Results of a study on cancer patients in Belgium showed that sedation was a key factor in a good death [24]. In addition, the results of another study demonstrated that reducing the pain of cancer patients helped them to enjoy their final phase of life [25].

Another factor that caused the good death of the patients was the death at home. To provide care to the patients at home and the opportunity to say goodbye to family was valuable for the patients and helped them to have a good death. Results of a study carried out in Norway showed that bereaved family members of cancer patients preferred to provide care to the patient and experience his/her death at home [26]. On the other hand, some of our participants had a negative evalua-

tion of death because it resulted in the depression of bereaved families, prevented patients from fulfilling their dreams, and deprived the survivors of the support of the deceased. A study in Germany showed that family caregivers of cancer patients had experienced depression at the final phase of life and after the death of their patients [27].

In general, the results of this study showed that there are cultural customs related to mourning ceremonies and grief reactions in Iran. Given that the results of the present study highlighted the role of culture in the lived experiences of bereaved family members about cancer patient's death, further studies are recommended with an ethnographic approach to explain how the culture of family members influences this phenomenon. It is also recommended that studies with an action research approach should be conducted to address the problems caused by this phenomenon.

This study had some limitations as well. The small participant size and the nature of the phenomenological research restricted the ability to generalize the results. However, as with all qualitative research, the findings were not intended to be generalized.

Conclusions

This study highlighted reactions to grief of bereaved families of cancer patients and their need for psychological support during the bereavement period. Understanding the bereaved family's lived experiences can lead to the development of psychological approaches to relieve their grief reactions. The findings of our study indicated the need for culture-based care and supportive services for the bereaved family members in Iran. Oncology nurses should assess the effect of death and the cultural background of the families. They should focus more attention on this vulnerable group. According to the findings, oncology nurses can design a care model for these families, which includes cultural elements for caring for bereaved families.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70(1): 7–30, doi: 10.3322/caac.21590, indexed in Pubmed: 31912902.
2. Kalan Farmanfarma K, Mahdavifar N, Hassanipour S, et al. Epidemiologic Study of Gastric Cancer in Iran: A Systematic Review. Clin Exp Gastroenterol. 2020; 13: 511–542, doi: 10.2147/CEG.S256627, indexed in Pubmed: 33177859.
3. Sharp KM, Lindwall JJ, Willard VW, et al. Cancer as a stressful life event: Perceptions of children with cancer and their peers. Cancer. 2017; 123(17): 3385–3393, doi: 10.1002/cncr.30741, indexed in Pubmed: 28472536.
4. O'Sullivan A, Alvariza A, Öhlen J, et al. Bereaved Family Members' Satisfaction with Care during the Last Three Months of Life for People with Advanced Illness. Healthcare (Basel). 2018; 6(4), doi: 10.3390/healthcare6040130, indexed in Pubmed: 30404147.
5. Van Hout E, Peters S, Jansen L, et al. An exploration of spousal caregivers' well-being after the death of their partners who were older cancer patients - A phenomenological approach. Eur J Oncol Nurs. 2020; 47: 101779, doi: 10.1016/j.ejon.2020.101779, indexed in Pubmed: 32559712.
6. Galloway T, Horlick S, Cherba M, et al. Perspectives of Nunavut patients and families on their cancer and end of life care experiences. Int J Circumpolar Health. 2020; 79(1): 1766319, doi: 10.1080/22423982.2020.1766319, indexed in Pubmed: 32449489.
7. Wen FH, Chou WC, Chen JS, et al. Associations of preloss and postloss factors with severe depressive symptoms and quality of life over the first 2 years of bereavement for family caregivers of terminally ill cancer patients. Psychooncology. 2019; 28(11): 2157–2165, doi: 10.1002/pon.5201, indexed in Pubmed: 31418502.
8. Pottle J, Hiscock J, Neal RD, et al. Dying at home of cancer: whose needs are being met? The experience of family carers and healthcare professionals (a multiperspective qualitative study). BMJ Support Palliat Care. 2020; 10(1): e6, doi: 10.1136/bmjspcare-2016-001145, indexed in Pubmed: 28093387.
9. Nielsen MK, Christensen KS, Neergaard MA, et al. Exploring Functional Impairment in Light of Prolonged Grief Disorder: A Prospective, Population-Based Cohort Study. Front Psychiatry. 2020; 11: 537674, doi: 10.3389/fpsyt.2020.537674, indexed in Pubmed: 33362592.
10. Van Hout E, Peters S, Jansen L, et al. An exploration of spousal caregivers' well-being after the death of their partners who were older cancer patients - A phenomenological approach. Eur J Oncol Nurs. 2020; 47: 101779, doi: 10.1016/j.ejon.2020.101779, indexed in Pubmed: 32559712.
11. Roulston A, Campbell A, Cairnduff V, et al. Bereavement outcomes: A quantitative survey identifying risk factors in informal carers bereaved through cancer. Palliat Med. 2017; 31(2): 162–170, doi: 10.1177/0269216316649127, indexed in Pubmed: 27170617.
12. Smith KV, Rankin H, Ehlers A. A qualitative analysis of loss-related memories after cancer loss: a comparison of bereaved people with and without prolonged grief disorder. Eur J Psychotraumatol. 2020; 11(1): 1789325, doi: 10.1080/20008198.2020.1789325, indexed in Pubmed: 33062204.
13. Creswell JW. Qualitative inquiry and research design: Choosing among five designs. Thousand Oaks, CA: Sage 1998.
14. Heidegger M. Being and Time. Translated by Macquarie & Robinson, 1st ed. Basil Blackwell, Oxford 1962.
15. Diekelmann N, Allen D, Tanner C. The NLN Criteria for Appraisal for Baccalaureate Programs: A Critical Hermeneutic Analysis. National League for Nursing, New York 1989.
16. Lincoln YS, Guba EG. Naturalistic Inquiry. Sage Publications Inc, London 1985.
17. Tsai WI, Prigerson HG, Li CY, et al. Longitudinal changes and predictors of prolonged grief for bereaved family caregivers over the first 2 years after the terminally ill cancer patient's death. Palliat Med. 2016; 30(5): 495–503, doi: 10.1177/0269216315603261, indexed in Pubmed: 26311571.
18. Gegieckaite G, Kazlauskas E. Fear of Death and Death Acceptance Among Bereaved Adults: Associations With Prolonged Grief. Omega (Westport). 2022; 84(3): 884–898, doi: 10.1177/0030222820921045, indexed in Pubmed: 32326832.
19. Edalati A. Hooshmand Abarkouhye N. Death in Iranian Culture (A Case Study of Abarkouh, Yazd). Int Rev Soc Sci Humanit. 2012; 2: 200–202.
20. Wen FH, Chou WC, Shen WC, et al. Distinctiveness of prolonged-grief--disorder- and depressive-symptom trajectories in the first 2 years of bereavement for family caregivers of terminally ill cancer patients. Psychooncology. 2020; 29(10): 1524–1532, doi: 10.1002/pon.5441, indexed in Pubmed: 32539210.
21. Yamagishi A, Morita T, Kawagoe S, et al. [Talking about home hospices with terminally ill cancer patients -- a multicenter survey of bereaved families]. Gan To Kagaku Ryoho. 2015; 42(3): 327–333, indexed in Pubmed: 25812502.
22. Lancel M, Stroebe M, Eisma MC. Sleep disturbances in bereavement: A systematic review. Sleep Med Rev. 2020; 53: 101331, doi: 10.1016/j.smrv.2020.101331, indexed in Pubmed: 32505968.

23. Lavalley SA. Caregiver informational support in different patient care settings at end of life. Home Health Care Serv Q. 2018; 37(2): 97–112, doi: 10.1080/01621424.2018.1438951, indexed in Pubmed: 29424667.
24. Robijn L, Chambaere K, Raus K, et al. Reasons for continuous sedation until death in cancer patients: a qualitative interview study. Eur J Cancer Care (Engl). 2017; 26(1), doi: 10.1111/ecc.12405, indexed in Pubmed: 26515814.
25. Yamanaka M. A Concept Analysis of Self-Management of Cancer Pain. Asia Pac J Oncol Nurs. 2018; 5(3): 254–261, doi: 10.4103/apjon.apjon_17_18, indexed in Pubmed: 29963587.
26. Fjose M, Eilertsen G, Kirkevold M, et al. "Non-palliative care" - a qualitative study of older cancer patients' and their family members' experiences with the health care system. BMC Health Serv Res. 2018; 18(1): 745, doi: 10.1186/s12913-018-3548-1, indexed in Pubmed: 30268149.
27. Oechsle K, Ullrich A, Marx G, et al. Prevalence and Predictors of Distress, Anxiety, Depression, and Quality of Life in Bereaved Family Caregivers of Patients With Advanced Cancer. Am J Hosp Palliat Care. 2020; 37(3): 201–213, doi: 10.1177/1049909119872755, indexed in Pubmed: 31596115.

VIA MEDICA

REVIEW ARTICLE

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Immune checkpoint inhibitors in the first-line treatment of metastatic small-cell lung cancer

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0011

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Small-cell lung cancer is the most aggressive form of lung cancer. Most patients are diagnosed at a late disease stage when the prognosis is poor. The treatment algorithm for small-cell lung cancer remained unchanged for years, with chemotherapy as the first-line option. However, progress has been made with the recent development of immune checkpoint inhibitors, two of which — atezolizumab and durvalumab — have been approved in combination with chemotherapy as first-line treatment for advanced small-cell lung cancer. This review presents detailed data concerning the efficacy and safety of atezolizumab and durvalumab from both registration trials and real-world studies, as well as the results of clinical trials of other immune checkpoints inhibitors. Finally, the issue of identifying biomarkers to predict the efficacy of immunochemotherapy is discussed.

Key words: small-cell lung cancer, chemotherapy, immunotherapy, predictive markers, systemic therapy

Oncol Clin Pract 2022; 18, 2: 104–114

Introduction

Small-cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma that is diagnosed in about 15% of patients with primary lung neoplasms. It is estimated that SCLC causes 250 000 new cases and at least 200 000 deaths globally each year. In Europe, the prevalence of SCLC is about 1–5 per 10 000 people [1–3]. In Poland, 21 226 new cases of lung cancer were reported in 2018 and more than 3 000 were estimated to be SCLC [4].

When lung cancer is diagnosed, a pathological evaluation according to the current World Health Organization (WHO) classification criteria is required to determine the histological type of the tumor and relevant staging parameters [1–5]. Cells of SCLC under a microscope appear round, oval, or spindle-shaped, and have poorly defined cell borders, scant cytoplasm, high nuclear-to-cytoplasmic ratio, granular nuclear chromatin, and absent or inconspicuous nucleoli. Numerous mitoses are characteristic features of SCLC cells. In rare cases, combined SCLC can occur, which consists of typical small cells and other cells of adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, or sarcomatoid (spindle- or giant-cell) carcinoma areas, and non-small-cell lung cancer (NSCLC) [6]. Additionally, when a pathomorphological diagnosis is equivocal, immunohistochemical staining should be applied. The most sensitive marker is CD56, but it has low specificity. Thyroid transcription factor 1 (TTF1) is also a helpful marker, and Ki-67 is used to distinguish high-grade SCLC from carcinoid tumors [5, 7, 8].

Small-cell lung cancer grows rapidly, and distant metastases develop early, leading most cases to be diagnosed at an advanced stage. Staging of SCLC should be made according to the Union for International Cancer Control (UICC) Tumor, Nodes, Metastases (TNM) classification (8th edition) [9]. However, due to the

Received: 27.02.2022 Accepted: 27.02.2022 Early publication date: 17.03.2022

high dynamics of disease progression, the usefulness of TNM classification in treatment planning may be limited. Therefore, to unify the different stages in relation to therapeutic options the terms limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC) are often used in clinical trials and in practice [1, 10]. Only about 30% of patients with SCLC are diagnosed with LS-SCLC, which means that it is confined to one hemithorax and regional lymph nodes. Hence, most patients have ES-SCLC at diagnosis, which corresponds to stage IV according to the TNM classification in most publications [1, 10, 11].

Treatment options for patients with SCLC are determined by stage, general condition (WHO performance status), and comorbidities. Although treatment for LS-SCLC is of curative intent and treatment for ES-SCLC is palliative, chemotherapy forms the backbone of treatment, either alone or combined with irradiation [3]. Surgery (followed by chemotherapy and radiotherapy) is performed in only the very few patients who are diagnosed at a very early disease stage. However, more typically, patients with early-stage or locally advanced disease are also treated with radiochemotherapy [1, 10].

Recently, there has been a breakthrough in the treatment of ES-SCLC with the introduction of a new class of drugs, and this will be described in this article.

Treatment of metastatic SCLC

For many years the first-line treatment for metastatic SCLC was chemotherapy with cisplatin or carboplatin and etoposide. In patients under 75 years, with good performance status (PS) after treatment, and with documented stabilization or regression of lesions, prophylactic cranial irradiation (PCI) should be considered. For patients not undergoing PCI, magnetic resonance imaging (MRI) of the brain is recommended, and serial MRIs are then advised as part of follow-up [1].

When first-line treatment is ineffective or if relapse occurs within three months, treatment with topotecan may be considered in patients with acceptable general condition and without persistent side effects of previous chemotherapy. When the response to first-line chemotherapy lasts more than three months, repetition of the first-line regimen (reinduction) may be favorable [1, 10, 12].

Although the response rate to chemotherapy is high and could reach more than 70%, most patients relapse; as a consequence, the overall prognosis in patients with SCLC is poor. The 5-year relative survival rate has improved over time but is still very low (about 6%) [3, 10, 13]. For patients with ES-SCLC, median survival is less than 12 months and long-term disease-free survival is rare [14]. These facts highlighted the urgency of developing novel treatments; however, standard therapy remained unchanged for years, as trials failed to offer any improvement.

Immune checkpoint inhibitors

It is known that SCLC, like other cancers, expresses some neoantigens on the cell surface, which are recognized by T cells. This should be followed by a multi-step antitumor immune system response and protective immunity (Fig. 1); however, this mechanism often fails. This may be due to the tumor's ability to attenuate or avoid T-cell-mediated anticancer activity at each step of the immune response. One strategy involves interaction between the programmed cell death 1 (PD-1; also known as CD279) and programmed cell death ligand 1 (PD-L1; also called CD274). Immune checkpoint protein PD-1 is an apoptosis-associated molecule expressed mainly on the surface of activated T lymphocytes. In turn, PD-L1 is the ligand for PD-1 and is expressed on the surface of antigen-presenting cells or macrophages. The binding of PD-L1 with PD-1 plays a role in the maintenance of peripheral tolerance, and the prevention of autoimmunity via several mechanisms (e.g. by affecting the production of cytokines and inhibiting activation of immune cells) [15–18].

This fact shifted researchers' interest in immune checkpoint inhibitors (ICIs) as inhibition of the PD-1/PD-L1 axis was assumed to prevent suppression of T cells and to enhance antitumor activity. Several studies of monoclonal antibodies targeting PD-L1 or PD-1 in different tumors indicated that such therapy may be effective [19, 20]. The efficacy of ICIs was investigated in various cancers and beneficial outcomes led to the registration of this class of drugs for many indications (e.g. melanoma, Hodgkin lymphoma, renal-cell cancer, and NSCLC) as monotherapy or in combination with chemotherapy [21–24]. This prompted investigators to evaluate the synergistic effects of ICIs combined with chemotherapy in patients with ES-SCLC. Finally, after many years of unsuccessful attempts, progress in the treatment of ES-SCLC has been made. In 2019 and 2020, atezolizumab and durvalumab in combination with carboplatin and etoposide were approved by the US Food and Drug Administration (FDA) for the first-line treatment of patients with ES-SCLC [25]. In the same years, the European Medicines Agency (EMA) recommended the use of these drugs in European Union countries [26, 27].

Immunochemotherapy with atezolizumab and durvalumab in ES-SCLC

Atezolizumab

Atezolizumab is a fully-humanized kappa IgG1 monoclonal antibody that can bind to PD-L1 and inhibit its interaction with PD-1, preventing the downregulation of T-cell function and allowing T cells to mediate tumor cell death [28]. Atezolizumab can also bind B7-1, which

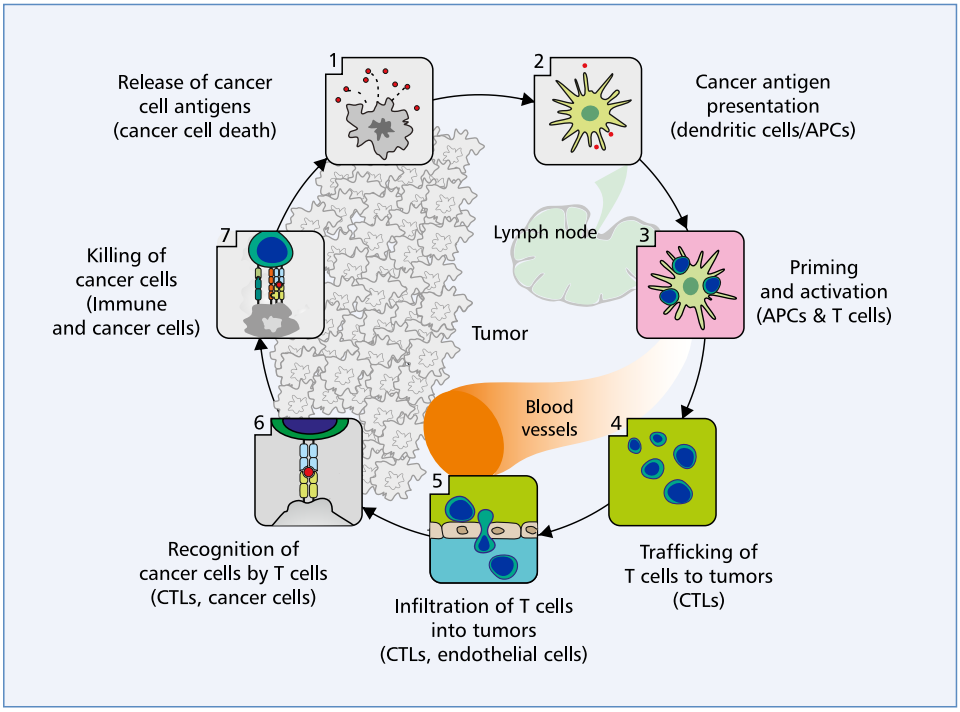

Figure 1. Cancer-immunity cycle [18]; APCs — antigen-presenting cells; CTLs — cytotoxic T lymphocytes

is found on activated antigen-presenting cells and can inhibit T-cell proliferation via binding to PD-L1 [29].

Approval of atezolizumab was based on data from the multinational, phase-3, IMpower133 trial [30], which evaluated the efficacy and safety of atezolizumab in 403 adult chemotherapy-naive patients with ES-SCLC. The induction phase involved four cycles administered every 21 days, and the maintenance phase lasted until disease progression, as assessed with Response Evaluation Criteria in Solid Tumor Version 1.1. (RECIST v1.1), or unacceptable toxicity. Patients were randomized to two arms: atezolizumab (1200 mg intravenously on day 1 of cycles 1–4 and cycle 5 onward) or placebo, both with carboplatin (AUC = 5 intravenously on day 1 of cycles 1–4) and etoposide (100 mg/m^2 intravenously on days 1–3 of cycles 1–4).

The primary outcomes were progression-free survival (PFS) assessed with RECIST v1.1, measured from baseline until disease progression or death, whichever occurred first (up to approximately 23 months), and overall survival (OS), measured from baseline until death from any cause (up to approximately 23 months). The median age of all patients was 64 years, and most were male (65%) and current or previous smokers (97%). Approximately 9% of patients in each treatment arm had brain metastases at baseline. The first evaluation was performed after a median follow-up of 13.9 months, a median of 4.7 months of atezolizumab (4.1 months for placebo) treatment, and a median of seven atezolizumab doses (six doses for placebo). The median number of chemotherapy doses was the same in both groups [31].

The addition of atezolizumab to chemotherapy significantly prolonged PFS and OS (Tab. 1). The 12-month OS rate was also higher in the atezolizumab group than in the placebo group (51.7 *vs.* 38.2%). In the atezolizumab group, 51.7% of patients died *vs.* 66.3% in the control group, and 85.1% had disease progression or died *vs.* 93.6% of patients in the control group. Adverse events (AEs) related to the regimen occurred in 94.9% of patients in the atezolizumab group *vs.* 92.3% in the placebo group. Rates of grade 3 or 4 treatment-related AEs (TRAEs) were similar between the groups (56%), with myelosuppression being the most common. Immune-related AEs (irAEs) occurred slightly more often in the atezolizumab group (39.9 *vs.* 24.5%), with rash and hypothyroidism being the most common [31].

Detailed analysis of safety data and patient-reported outcomes in the IMpower133 trial two years later revealed that the addition of atezolizumab to chemotherapy does not reduce the safety of treatment or patients' quality of life [32].

The most recent updated analysis of the IMpower133 study outcomes was performed at a median follow-up of 22.9 months [33] and showed that OS, PFS, and the rate of AEs were similar to those obtained in the interim analysis (Tab. 1). The updated data continued to demonstrate the clinical benefit of adding atezolizumab to chemotherapy [33].

Table 1. Comparison of data from registration studies of atezolizumab and durvalumab in patients with ES-SCLC

		IMpower133 NCT02763579		CASPIAN NCT03043872	
Reference		Horn et al., 2018 [31]	Liu et al., 2021 [33]	Paz-Ares et al., 2019 [38]	Goldman et al., 2021 [39]
Study type		Phase 1/3, randomized, double-blind, placebo-controlled		Phase 3, randomized, open-label	
Patients	Number	403		537/805	805
	PS score	0/1		0/1	
	Treated asymptomatic brain metastases	+ (9%)		+ (10%)	
Treatment	Arms	Atezolizumab + CP/ET *vs.* placebo + CP/ET		(I) Durvalumab + tremelimumab + P/ET *vs.* (II) durvalumab + P/ET *vs.* (III) P/ET	
				(II) and (III) assessed	(I) and (II) and (III) assessed
	Number of ICI doses [median (range)]	7 (1–30)	7 (1–39)	7 (6–11)	(I) 6 (4–10) (II) 7 (6–11)
	Months of ICI treatment [median (range)]	4.7 (0–21)	4.7 (0–29)	7.0 (5–11)	(I) 8.0 (4–10) (II) 7.0 (5–11)
	Chemotherapy cycles	Every 3 weeks		Every 3 weeks	
	Number of chemotherapy cycles	Four in both groups		Four in the ICI group, Six in the P/ET group	
	PCI	Permitted in both groups (11%)		Permitted in the P/ET group only (8%)	
Median follow-up (months)		13.9	22.9	14.2	25.1
Results	Median OS (months)	12.3 *vs.* 10.3	12.3 *vs.* 10.3	13.0 *vs.* 10.3	10.4 *vs.* 12.9 *vs.* 10.5
	12-month median OS (%)	51.7 *vs.* 38.2	51.9 *vs.* 39.0	54 *vs.* 40	43.8 *vs.* 52.8 *vs.* 39.3
	24-month median OS (%)	nd	22.0 *vs.* 16.8	nd	23.4 *vs.* 22.2 *vs.* 14.4
	Median PFS (months)	5.2 *vs.* 4.3 (*)	5.2 *vs.* 4.3	5.1 *vs.* 5.4	4.9 *vs.* 5.1 *vs.* 5.4
	ORR (%)	60.2 *vs.* 64.4	60.2 *vs.* 64.4	68 *vs.* 58	58 *vs.* 68 *vs.* 58
	Median DoR (months)	4.2 *vs.* 3.9	4.2 *vs.* 3.9	5.1 *vs.* 5.1	5.2 *vs.* 5.1 *vs.* 5.1
	Remaining responsive at 12 months (%)	14.9 *vs.* 5.4 (at data cutoff)	nd	23 *vs.* 6	24.9 *vs.* 23.2 *vs.* 7.3
	Remaining responsive at 24 months (%)	nd	nd	nd	17.2 *vs.* 13.5 *vs.* 3.9
	Any TRAEs (%)	94.9 *vs.* 92.3	94.9 *vs.* 92.3	89 *vs.* 90	90 *vs.* 89 *vs.* 90
	Grade 3 or 4 TRAEs (%)	56.6 *vs.* 56.1	57.1 *vs.* 56.1	46 *vs.* 52	55 *vs.* 46 *vs.* 52
	irAEs (%)	40 *vs.* 25	40 *vs.* 24	20 *vs.* 3	36 *vs.* 20 *vs.* 3

CP/ET — carboplatin plus etoposide; ICI — immune checkpoint inhibitor; irAEs — immune-related adverse events; DoR — median duration of treatment; nd — no data; ORR — overall response rate; OS — overall survival; PCI — prophylactic cranial irradiation; P/ET — platin (carboplatin or cisplatin) plus etoposide; PFS — progression-free survival; PS — performance status; TRAEs — treatment-related adverse events

An exploratory analysis focused on long-term survivors (i.e. patients who survived ≥18 months after randomization) in the IMpower133 study found that the percentage of long-term survivors was higher in the atezolizumab group than in the control group (34% *vs.* 20%). Although the authors concluded that patients with ES-SCLC can benefit from chemotherapy combined with atezolizumab regardless of patient and disease characteristics, some differences exist between subgroups. Patients with worse PS, higher lactate dehydrogenase activity, larger tumor load, and brain metastases at baseline were less likely to benefit from immunochemotherapy [34].

Based on the above results, atezolizumab was given first-in-class approval to be combined with chemotherapy as an option for untreated patients with ES-SCLC. Treatment of patients with ES-SCLC with atezolizumab was included in the current National Comprehensive Cancer Network (NCCN) guidelines [11]. Atezolizumab has been reimbursed in Poland for adult patients with ES-SCLC since July 2021 [35].

Durvalumab

The second immune checkpoint inhibitor that may be applied in ES-SCLC therapy is durvalumab, another human IgG1 kappa monoclonal antibody that targets PD-L1. The CASPIAN clinical trial recently evaluated the efficacy of durvalumab added to standard chemotherapy in patients with ES-SCLC [36]. In a subgroup of patients, dual ICIs treatment was applied using tremelimumab, an inhibitor of cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is expressed on the surface of T cells. Signaling from CTLA-4 inhibits T-cell activation, so blockade of CTLA-4 with a monoclonal antibody might be expected to enhance the antitumor response [37]. In the study, 805 adult participants with previously untreated SCLC were randomly assigned to three arms: (I) durvalumab plus tremelimumab plus platinum plus etoposide; (II) durvalumab plus platinum plus etoposide; and (III) platinum plus etoposide chemotherapy. Durvalumab was given at a dose of 1500 mg every three weeks (four cycles) followed by every four weeks in the maintenance phase. Tremelimumab was given at a dose of 75 mg every three weeks (four cycles), and an additional dose was given in week 16. Chemotherapy consisted of etoposide 80–100 mg/m^2 (administered on days 1–3 of 21-day cycles), with carboplatin (AUC = 5–6 intravenously) or cisplatin (75–80 mg/m^2 intravenously on day 1 of each cycle) and was administered for up to four cycles in the experimental arms and up to six cycles in the control arm.

The primary outcomes were OS, assessed at interim analysis, measured from baseline until death from any cause (up to approximately 23 months) for arm II and III and OS, assessed at the final analysis, measured from baseline until death from any cause (up to approximately 33 months) for arms I, II, and III.

The interim analysis performed after a median follow-up of 14.2 months presents only the results of patients from arms II and III (n = 537) [38]. Their median age was 63 years, and most were men (70%), current or former smokers (93%), with stage IV disease at diagnosis (90%); 10% of patients had brain metastases at baseline. The median duration of durvalumab treatment was 28 weeks, and patients received a median of seven doses. The median duration of chemotherapy treatment was 11.9 weeks for the immunochemotherapy group (arm II) and 18.7 weeks for the chemotherapy group (arm III). In both groups, 78% of participants received carboplatin [38]. The results of this trial showed a significant improvement in OS in patients treated with durvalumab plus platinum plus etoposide (Tab. 1). The 12-month and 18-month OS rates were also higher in the immunochemotherapy group than in the control chemotherapy group (54% *vs.* 40% 12-month OS; and 34% *vs.* 25% 18-month OS).

In the durvalumab group, 58% of patients died compared with 67% in the chemotherapy group, and 84% in the durvalumab group had disease progression or died compared with 87% in the chemotherapy group. Grade 3 or 4 TRAEs occurred with the same frequency (62%) in both groups, with neutropenia and anemia being the most common. Immune-mediated AEs were reported in 20% of patients treated with immunochemotherapy and 3% of patients treated with chemotherapy only, with most being grade 1–2 [38].

The next evaluation of CASPIAN trial results was performed after a median follow-up of 25.1 months and included all three arms of the study (805 participants) [39]. The median age of patients was 63 years, and most were male (72%), current or former smokers (94%), with stage IV disease at diagnosis (91%). The median duration of treatment with durvalumab was 23.1 weeks (median six doses) in the immunotherapy plus tremelimumab group and 28 weeks (median seven doses) in patients receiving immunotherapy. Despite a lack of OS benefit in the durvalumab and tremelimumab plus chemotherapy arm *vs.* chemotherapy alone (Tab. 1), durvalumab plus chemotherapy led to higher OS at 24 months and higher PFS at 12 and 24 months compared with chemotherapy alone. This analysis confirmed that the improvement in OS with durvalumab first demonstrated in the interim evaluation was sustained [38]. However, the survival benefit observed in patients with brain and liver metastases at baseline was negligible compared with outcomes in patients without lesions [39, 40]. The percentage of patients who died was highest in the chemotherapy group (86%) and lower in patients with immunochemotherapy (78%) or immunochemotherapy plus tremelimumab (77%). In all groups, TRAEs occurred at a similar frequency and about half were grade 3 or 4; however, immunotherapy plus tremelimumab was associated with a higher proportion of serious AEs. The most common TRAEs were neutropenia and anemia. In turn, irAEs were noted most frequently in patients treated with tremelimumab, and the most common were hypothyroid events [38]. Moreover, analysis of patient-reported outcomes revealed that the addition of durvalumab to first-line chemotherapy maintained the quality of life and delayed worsening of patient-reported symptoms, functioning, and global health status compared with chemotherapy alone [41].

Durvalumab in combination with chemotherapy was the second monoclonal antibody approved for first-line treatment of adult patients with ES-SCLC. The recommended dose of durvalumab in the induction phase is 1500 mg given before chemotherapy on the same day, every 3 weeks (21 days) for four cycles, and the maintenance phase includes 1500 mg given every 4 weeks until disease progression or unacceptable toxicity [42]. Durvalumab in combination with chemotherapy is also included in the NCCN guidelines [11]. However, in Poland, durvalumab is reimbursed only for consolidation therapy in patients with locally advanced, inoperable NSCLC after completion of concurrent chemoradiotherapy [35].

Analysis of PD-L1 expression in available tissue samples from patients included in the CASPIAN study showed expression of PD-L1 greater than 1% in 27% of samples, mainly on immunochemotherapy. No correlation between PD-L1 expression and treatment outcomes was observed, which suggests that PD-L1 is not a predictive biomarker for treatment outcomes in patients with ES-SCLC treated with durvalumab [43].

Comparison of the main results and design of the IMpower133 and CASPIAN studies

The IMpower133 and CASPIAN trials demonstrated that the addition of atezolizumab or durvalumab to chemotherapy provided benefits in the first-line treatment of patients with ES-SCLC. Moreover, a systematic review and network meta-analysis of first-line treatment options for patients with ES-SCLC revealed that the combination of durvalumab or atezolizumab with chemotherapy may be an optimal approach [44, 45]. However, data comparing the effectiveness and safety of these drugs are scant. Some insight was provided by a recent meta-analysis that demonstrated no significant difference between the drugs in improving OS and PFS. According to this analysis, durvalumab was superior to atezolizumab in terms of the overall response rate (ORR) but also had a higher risk of irAEs [46].

Conclusions concerning the efficacy of atezolizumab and durvalumab in subgroups of patients with brain or liver metastases were slightly different. The IMpower133 study found no benefit of adding atezolizumab in patients with these lesions [33]. The results of the CASPIAN trial suggested that durvalumab provides OS benefits regardless of baseline brain and liver metastases [39]. However, the observed benefit in patients with these lesions seemed to be minimal.

However, it is worth noting some differences in study designs (most are presented in Tab. 1). IMpower133 was double-blind, in contrast to the open-label design of the CASPIAN study. Furthermore, the protocol of the CASPIAN study allowed the use of either cisplatin or carboplatin, whereas only carboplatin was permitted in the IMpower133 study. The control group in the CASPIAN study also seems to be a stronger comparator than the IMpower133 control group because of the higher maximum number of chemotherapy cycles received (six *vs.* four). The number of chemotherapy cycles administered in the control group in the CASPIAN trial was also higher than that given in the durvalumab group (four cycles), whereas both the control and atezolizumab groups received the same number of cycles (four cycles) in the IMpower133 study. Another difference concerns PCI — this procedure was permitted only in the control group in the CASPIAN study but was allowed in both groups in the IMpower133 trial [31, 38].

Long-term durability of response in the IMpower133 and CASPIAN studies

The CASPIAN study results showed that the percentage of patients with a response after 12 and 24 months was more than three times higher in the durvalumab group than in the chemotherapy group [38, 39]. Moreover, this result was estimated to be sustained at a 3-year follow-up (17.6% *vs.* 5.8%) [47]. In the IMpower133 study, the percentage of patients with a response after 12 months was 14.9% for the atezolizumab group and 5.4% for the chemotherapy group. Response rates at 24 months were not provided [31].

Real-world evidence studies

Real-world evidence (RWE) studies concerning immunochemotherapy with atezolizumab or durvalumab are still limited.

The first RWE study of atezolizumab for the treatment of ES-SCLC was performed in Canada [48] and included 67 patients with ES-SCLC, 34 of whom were treated with chemotherapy plus atezolizumab and 33 of whom received chemotherapy only. Although the study aimed to include untreated patients, it was revealed during evaluation that 74% of patients in the atezolizumab group had already received at least one cycle of chemotherapy. At a median follow-up of 18 months, 18% of patients in the atezolizumab group were alive compared with 1% of patients in the chemotherapy group. Most patients in both groups developed progressive disease (91% *vs.* 97%, respectively). Median PFS and OS were better in the atezolizumab group; however, in patients with a performance status score of 2, there was no significant difference in survival between the groups. The median OS in patients without atezolizumab maintenance was half that of patients with atezolizumab maintenance. Moreover, patients who had thoracic radiation had a reduced risk of death. More patients had any AEs in the atezolizumab group. The most common AEs in both groups were hematology-related. Although the results of this study are similar to those of the Im-

power133 trial in terms of the efficacy of atezolizumab, they demonstrated a lower incidence of AEs; however, about half of AEs were severe. The studied population was rather small, and therefore outcomes should be interpreted with caution. The patient population in the RWE study was also more heterogeneous than that in the clinical trial [48].

Another RWE on ES-SCLC treatment with atezolizumab comes from Korea [49]. This study was conducted on 68 patients who were slightly older than those in the Impower133 trial, and more of them had worse PS and brain metastasis at baseline. After a median of 11.6 months of follow-up, treatment with chemotherapy plus atezolizumab led to a median OS of 12 months and median PFS of 4.6 months. The obtained ORR (75%) was higher than that in the IMpower133 study. TRAEs were noted in 89.7% of patients and half were grade 3 or 4 (mainly neutropenia, anemia, and thrombocytopenia), and irAEs were reported in 32.4% of patients [49].

Results of the third RWE study with atezolizumab were presented at the European Society for Medical Oncology (ESMO) Virtual Annual Meeting in September 2021. Although the median follow-up was half as long as in the IMpower133 study, the observed median PFS was similar [50].

At the same conference, the RWE phase-3b open-label, single-arm, multicenter trial concerning durvalumab was announced; however, the results have not yet been published [51].

Impact of brain metastases on treatment outcomes and safety

The efficacy of combining ICIs with chemotherapy in patients with ES-SCLC and brain metastases at diagnosis is controversial. The IMpower133 and CASPIAN trials included similar percentages of patients with asymptomatic or treated brain metastases at baseline, but the proportion of patients with brain involvement was small in both studies (9% *vs.* 10%). The results of the IMpower133 study showed a lack of OS benefit from the addition of atezolizumab in this subgroup [31, 33]. In the CASPIAN trial, the authors concluded that all patient subgroups benefitted; however, the observed OS and PFS benefits in patients with brain metastases were much lower than those in patients without central nervous system (CNS) lesions [39, 52]. The results may therefore be affected by the small number of patients with brain metastases included in the study (55 *vs.* 482 patients without CNS lesions) or by the worse clinical status of patients with lesions, which might reduce therapeutic benefits. Therefore, further detailed evaluation of the impact of ICIs in patients with brain metastases is necessary.

It was also observed that PCI performed in patients in the control group did not reduce the number of newly developed brain lesions. In the absence of baseline brain metastases, the safety profiles in the durvalumab and control subgroups were similar; in patients with lesions, durvalumab plus chemotherapy caused a lower number of serious AEs than chemotherapy alone [52].

The summary of product characteristics for atezolizumab and durvalumab does not discuss this issue and states only that subjects with treated metastases were involved in both trials and that those with active or untreated CNS metastases were excluded [42, 53]. Treatment with atezolizumab is not reimbursed for patients with CNS metastases in Poland [35]. Therefore, the effectiveness of immunochemotherapy in patients with EC-SCLC and brain metastases requires clarification in further studies.

Immunochemotherapy with pembrolizumab, nivolumab, and ipilimumab in ES-SCLC

The effectiveness of PD-L1 inhibitors (nivolumab and pembrolizumab) has also been assessed in patients with ES-SCLC. Early studies of pembrolizumab showed effectiveness in patients with previously treated ES-SCLC [54–56]. Pembrolizumab was approved as third-line therapy in patients with metastatic SCLC [25]. The efficacy of pembrolizumab as first-line therapy was recently assessed in patients with ES-SCLC within the KEYNOTE-604 study [57]. The addition of pembrolizumab to chemotherapy significantly improved PFS but did not provide the expected statistically significant benefits in OS (Tab. 2).

Significant improvements in both OS and PFS were observed when nivolumab was combined with chemotherapy for first-line treatment of previously untreated patients with ES-SCLC in a phase-2 study (Tab. 2) [58]. A phase-3 trial would therefore be reasonable for a more detailed assessment of the efficacy and safety of nivolumab in ES-SCLC. Based on the results of the CheckMate 032 trial, nivolumab was approved for third-line therapy in patients with metastatic SCLC [59]. In January 2021, nivolumab was withdrawn from the US market for the indication of SCLC with disease progression after platinum-based chemotherapy and at least one other line of therapy, following consultation with the FDA [60].

Ipilimumab is an ICI that can bind to CTLA-4 and impede immune system suppression. Ipilimumab given with carboplatin and paclitaxel improved immune-related PFS in untreated ES-SCLC in a phase-2 trial [61]. However, in a phase-3 study in a large group of patients with newly diagnosed ES-SCLC, the addition of

Table 2. Data from phase 2/3 studies of pembrolizumab, nivolumab, and ipilimumab in ES-SCLC

		KEYNOTE-604 NCT03066778	EA5161 NCT03382561	CA184-156 NCT01450761
Reference		Rudin et al., 2020 [57]	Leal et al., 2020 [58]	Reck et al., 2016 [62]
Study type		Phase 3, randomized, double-blind, placebo-controlled	Phase 2, randomized	Phase 3, randomized, double-blind
Patients	Number	453	160	1132
	PS score	0/1	0/1	0/1
	Treated brain metastases	+	+	+
Treatment	Arms	Pembrolizumab + P/ET *vs.* placebo + P/ET	Nivolumab + P/ET *vs.* P/ET	Ipilimumab + P/ET *vs.* placebo + P/ET
	Cisplatin option	+	+	+
	PCI	Permitted in both arms	Permitted in both arms	Permitted in both arms
Median follow-up (months)		21.6	nd	10.5 *vs.* 10.2
Results	Median OS (months)	10.8 *vs.* 9.7	11.3 *vs.* 9.3	11.0 *vs.* 10.9
	12-month median OS (%)	45.1 *vs.* 39.6	nd	40 *vs.* 40
	Median PFS (months)	4.5 *vs.* 4.3	5.5 *vs.* 4.7	4.6 *vs.* 4.4
	ORR (%)	70.6 *vs.* 61.8	52.3 *vs.* 47.7	62 *vs.* 62
	Median DoR (months)	4.2 *vs.* 3.7	nd	4.01 *vs.* 3.45
	Any TRAEs (%)	nd	nd	82 *vs.* 76
	Grade 3 or 4 TRAEs (%)	nd	77 *vs.* 62	48 *vs.* 44
	irAEs rate (%)	24.7 *vs.* 10.3	nd	57 *vs.* 28

irAEs — immune-related adverse events; DoR —duration of response; ORR — overall response rate; OS — overall survival; PCI — prophylactic cranial irradiation; P/ET — platin (carboplatin or cisplatin) plus etoposide; PFS — progression-free survival; PS — performance status; TRAEs — treatment-related adverse events

ipilimumab to chemotherapy showed no improvement in OS compared with chemotherapy alone (Tab. 2) [62].

The results of the above-mentioned clinical trials were verified in meta-analyses that have confirmed that combining anti-PD-1/PD-L1 inhibitors with chemotherapy as first-line treatment improves clinical efficacy in patients with SCLC compared with chemotherapy alone [63, 64]. Moreover, the efficacy of PD-1 or PD-L1 inhibitors added to chemotherapy is similar in terms of OS, PFS, and ORR. Safety profiles are also similar, although PD-L1 combined with chemotherapy demonstrated a lower risk of treatment discontinuation caused by AEs than PD-1 addition [65].

Predictive biomarkers

Despite the rational assumptions of combining ICIs with chemotherapy, many patients do not benefit from immunochemotherapy. Therefore, biomarkers are needed to predict the efficacy of ICIs in ES-SCLC.

The predictive role of PD-L1 expression in SCLC is controversial. The subgroup analysis of the IMpower133 study revealed that the efficacy of atezolizumab plus chemotherapy in patients with ES-SCLC was unrelated to PD-L1 expression [33]. Similar observations were made in the CASPIAN and KEYNOTE-604 studies, which suggests that PD-L1 expression has no predictive value in the first-line therapy of ES-SCLC [43, 57]. A combined positive score, which reflects the proportion of all PD-L1 positive cells to all viable tumor cells, seems to be a potential biomarker of response to pembrolizumab in advanced SCLC [55].

As SCLC is related to tobacco smoking, its genome exhibits a high tumor mutational burden (bTMB), defined as a high number of somatic non-synonymous mutations within a tumor genome. However, bTMB was not a valuable predictive biomarker of long-term survival after first-line immunochemotherapy; but, it might be useful in nivolumab monotherapy or nivolumab plus ipilimumab therapy in recurrent SCLC [33, 66].

Recently, it was demonstrated that SCLC can be divided into subtypes based on the expression of transcription factors. One of these subtypes, SCLC-I (the "inflamed subtype"), has low expression of ASCL1, NEUROD1, and POU2F3 but often shows high expression of genes related to immune cell infiltration, PD-L1, and other different immune checkpoint mole-

cules. This is a possible reason why the SCLC-I subtype benefits the most from the addition of PD-L1 inhibitors to chemotherapy compared with other subtypes [67]. The SCLC-I subtype, therefore, seems to be a strong candidate predictive biomarker; however, further research is needed.

Systematic inflammatory and nutritional indexes have also been evaluated as prognostic factors. The platelet-lymphocyte ratio (PLR) measured before therapy might serve as such a marker as patients with a high PLR obtained poorer OS and PFS than patients with a low PLR; however, further research is needed [68].

Data regarding the usefulness of clinical characteristics as predictors of OS benefit from the addition of ICIs to SCLC therapy are limited to subgroup analyses. Among various evaluated clinical factors (e.g. age, sex, ethnicity, PS, elevated lactate dehydrogenase activity, presence of CNS metastases, and previous PCI), none consistently predicts either response or OS duration in patients with SCLC receiving ICIs [69]. However, a recent meta-analysis demonstrated that specific clinical factors, including PS of 1, the use of cisplatin, and the absence of brain metastases, are associated with OS benefits in patients treated with ICIs added to chemotherapy [70].

Despite many attempts, definitive predictive biomarkers for responses to ES-SCLC treatment have not yet been identified. Research is impeded by the low quantity and quality of tissue samples and by the lack of molecular analysis of SCLC in clinical practice. The development of blood-based methods might, therefore, enable the analysis of a wide range of molecules and lead to the identification of predictive biomarkers [71].

Conclusions

The addition of immune checkpoint inhibitors to chemotherapy provides meaningful value in the treatment of patients with ES-SCLC. Observations from clinical practice are required to evaluate the efficacy of combined immunochemotherapy. The main challenge is to evaluate the efficacy of immunochemotherapy in patients with ES-SCLC and CNS metastases and to identify predictive biomarkers of response to immunotherapy to identify the patients who would benefit the most.

Contributions

MKW and DMK conceived the concept of the study and the drafts. MK supervised the drafts. All authors approved the final version.

Conflicts of interest

MKW received speaker's fees, conference support, consultancy, and Advisory Board: Roche-Genentech, BMS, MSD, Pfizer, Boehringer–Ingelheim, Astra Zeneca, TAKEDA, DMK received speaker's fees, conference support, consultancy, and Advisory Board: Roche-Genentech, BMS, MSD, Merck, Pfizer, Boehringer–Ingelheim, Astra Zeneca, TAKEDA, MK declares no conflict of interest.

Acknowledgments

The authors are grateful to Astra Zeneca for the grant and Proper Medical Writing sp. z o.o. for medical writing support.

References

1. Dingemans AMC, Früh M, Ardizzoni A, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(7): 839–853, doi: 10.1016/j.annonc.2021.03.207, indexed in Pubmed: 33864941.
2. Rudin C, Brambilla E, Faivre-Finn C, et al. Small-cell lung cancer. Nat Rev Dis Primer. 2021; 7(1), doi: 10.1038/s41572-020-00235-0.
3. American Cancer Society. Cancer Facts & Figures 2019. Atlanta, 2019.
4. National Cancer Registry in Poland (Krajowy Rejestr Nowotworów, KRN). http://onkologia.org.pl/raporty/ (18.11.2021).
5. Travis WD, Brambilla E, Nicholson AG, et al. WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol. 2015; 10(9): 1243–1260, doi: 10.1097/JTO.0000000000000630, indexed in Pubmed: 26291008.
6. Travis WD. World Health Organization, International Agency for Research on Cancer, et al. Hrsg. Pathology and genetics of tumours of the lung, pleura, thymus and heart. IARC Press, Oxford University Press, Lyon-Oxford 2004.
7. Pelosi G, Rindi G, Travis WD, et al. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. J Thorac Oncol. 2014; 9(3): 273–284, doi: 10.1097/JTO.0000000000000092, indexed in Pubmed: 24518085.
8. Thunnissen E, Borczuk AC, Flieder DB, et al. The Use of Immunohistochemistry Improves the Diagnosis of Small Cell Lung Cancer and Its Differential Diagnosis. An International Reproducibility Study in a Demanding Set of Cases. J Thorac Oncol. 2017; 12(2): 334–346, doi: 10.1016/j.jtho.2016.12.004, indexed in Pubmed: 27998793.
9. Brierley J, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours, 8th Edition. John Wiley & Sons, Inc, Chichester-Hoboken 2017.
10. Krawczyk P, Kowalski DM, Ramlau R, et al. Immunoterapia u chorych na drobnokomórkowego raka płuca — stanowisko ekspertów. Onkol Prakt Klin Edu. 2021; 7: 136–144.
11. Small Cell Lung Cancer - NCCN Clinical Practice Guidelines in Oncology. Version 1.2022. 09.08.2021.
12. Dómine M, Moran T, Isla D, et al. SEOM clinical guidelines for the treatment of small-cell lung cancer (SCLC) (2019). Clin Transl Oncol. 2020; 22(2): 245–255, doi: 10.1007/s12094-020-02295-w, indexed in Pubmed: 32040815.
13. Wang S, Tang J, Sun T, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. Sci Rep. 2017; 7(1): 1339, doi: 10.1038/s41598-017-01571-0, indexed in Pubmed: 28465554.
14. Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version - National Cancer Institute. 2021. https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq (18.11.2021).
15. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013; 39(1): 1–10, doi: 10.1016/j.immuni.2013.07.012, indexed in Pubmed: 23890059.

16. Harvey RD. Immunologic and clinical effects of targeting PD-1 in lung cancer. Clin Pharmacol Ther. 2014; 96(2): 214–223, doi: 10.1038/clpt.2014.74, indexed in Pubmed: 24690569.
17. Akinleye A, Rasool Z. Immune checkpoint inhibitors of PD-L1 as cancer therapeutics. J Hematol Oncol. 2019; 12(1): 92, doi: 10.1186/s13045-019-0779-5, indexed in Pubmed: 31488176.
18. Kudo M. Scientific Rationale for Combined Immunotherapy with PD-1/PD-L1 Antibodies and VEGF Inhibitors in Advanced Hepatocellular Carcinoma. Cancers (Basel). 2020; 12(5), doi: 10.3390/cancers12051089, indexed in Pubmed: 32349374.
19. Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014; 515(7528): 558–562, doi: 10.1038/nature13904, indexed in Pubmed: 25428503.
20. Fehrenbacher L, Spira A, Ballinger M, et al. POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016; 387(10030): 1837–1846, doi: 10.1016/S0140-6736(16)00587-0, indexed in Pubmed: 26970723.
21. Annex I - Summary of product characteristics. Imfinzi - EPAR - Product information. 2021.
22. Annex I - Summary of product characteristics. Tecentriq - EPAR - Product information. 2021.
23. Annex I - Summary of product characteristics. Keytruda - EPAR - Product information.
24. Annex I - Summary of product characteristics. Nivolumab BMS - EPAR - Product information.
25. U.S. Food & Drug Administration. Drug Approvals and Databases. https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases (22.11.2021).
26. European Medicines Agency Science Medicines Health. Assessment report: Tecentriq. 2019.
27. European Medical Agency Science Medicine Health. Assessment report: Imfinzi. 2020. https://www.ema.europa.eu/en/documents/variation-report/imfinzi-h-c-4771-ii-0014-g-epar-assessment-report-variation_en.pdf (22.11.2021).
28. Calles A, Aguado G, Sandoval C, et al. The role of immunotherapy in small cell lung cancer. Clin Transl Oncol. 2019; 21(8): 961–976, doi: 10.1007/s12094-018-02011-9, indexed in Pubmed: 30637710.
29. Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity. 2007; 27(1): 111–122, doi: 10.1016/j.immuni.2007.05.016, indexed in Pubmed: 17629517.
30. https://clinicaltrials.gov/ct2/show/NCT02763579 (26.11.2021).
31. Liu SV, Reck M, Mansfield AS, et al. IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018; 379(23): 2220–2229, doi: 10.1056/NEJMoa1809064, indexed in Pubmed: 30280641.
32. Mansfield AS, Każarnowicz A, Karaseva N, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. Ann Oncol. 2020; 31(2): 310–317, doi: 10.1016/j.annonc.2019.10.021, indexed in Pubmed: 31959349.
33. Liu SV, Reck M, Mansfield AS, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol. 2021; 39(6): 619–630, doi: 10.1200/JCO.20.01055, indexed in Pubmed: 33439693.
34. Liu SV, Horn L, Mok T, et al. 1781MO IMpower133: Characterisation of long-term survivors treated first-line with chemotherapy ± atezolizumab in extensive-stage small cell lung cancer. Ann Oncol. 2020; 31: S1032–S1033, doi: 10.1016/j.annonc.2020.08.1543.
35. National Drug Program B6. Treatment of non small-cell lung cancer or small-cell lung cancer. https://www.gov.pl/web/zdrowie/choroby-onkologiczne (01.12.2021).
36. https://clinicaltrials.gov/ct2/show/NCT03043872 (30.11.2021).
37. Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist. 2008; 13 Suppl 4: 2–9, doi: 10.1634/theoncologist.13-S4-2, indexed in Pubmed: 19001145.
38. Goldman JW, Dvorkin M, Chen Y, et al. CASPIAN investigators, CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019; 394(10212): 1929–1939, doi: 10.1016/S0140-6736(19)32222-6, indexed in Pubmed: 31590988.
39. Goldman JW, Dvorkin M, Chen Y, et al. CASPIAN investigators. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021; 22(1): 51–65, doi: 10.1016/S1470-2045(20)30539-8, indexed in Pubmed: 33285097.
40. Paz-Ares L. Durvalumab ± tremelimumab ± platinum-etoposide in first-line extensive-stage SCLC: Updated results from the phase 3 CASPIAN study. 2020.
41. Goldman JW, Garassino MC, Chen Y, et al. Patient-reported outcomes with first-line durvalumab plus platinum-etoposide versus platinum-etoposide in extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase III study. Lung Cancer. 2020; 149: 46–52, doi: 10.1016/j.lungcan.2020.09.003, indexed in Pubmed: 32961445.
42. European Medicines Agency. IMFINZI (durvalumab): Annex I. Summary of product characteristics. https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi (01.12.2021).
43. Paz-Ares L, Goldman JW, Garassino MC, et al. PD-L1 expression, patterns of progression and patient-reported outcomes (PROs) with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN. Ann Oncol. 2019; 30: v928–v929, doi: 10.1093/annonc/mdz394.089.
44. Zhou T, Zhang Z, Luo F, et al. Comparison of First-Line Treatments for Patients With Extensive-Stage Small Cell Lung Cancer: A Systematic Review and Network Meta-analysis. JAMA Netw Open. 2020; 3(10): e2015748, doi: 10.1001/jamanetworkopen.2020.15748, indexed in Pubmed: 33074323.
45. Arriola E, González-Cao M, Domine M, et al. Addition of Immune Checkpoint Inhibitors to Chemotherapy vs Chemotherapy Alone as First-Line Treatment in Extensive-Stage Small-Cell Lung Carcinoma: A Systematic Review and Meta-Analysis. Oncol Ther. 2022 [Epub ahead of print], doi: 10.1007/s40487-021-00182-0, indexed in Pubmed: 35032007.
46. Chen J, Wang J, Xu H. Comparison of atezolizumab, durvalumab, pembrolizumab, and nivolumab as first-line treatment in patients with extensive-stage small cell lung cancer: A systematic review and network meta-analysis. Medicine (Baltimore). 2021; 100(15): e25180, doi: 10.1097/MD.0000000000025180, indexed in Pubmed: 33847617.
47. Paz-Ares L, Chen Y, Reinmuth N, et al. LBA61 Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the phase III CASPIAN study. Ann Oncol. 2021; 32: S1338, doi: 10.1016/j.annonc.2021.08.2142.
48. Elegbede AA, Gibson AJ, Fung AS, et al. A Real-World Evaluation of Atezolizumab Plus Platinum-Etoposide Chemotherapy in Patients With Extensive-Stage SCLC in Canada. JTO Clin Res Rep. 2021; 2(12): 100249, doi: 10.1016/j.jtocrr.2021.100249, indexed in Pubmed: 34877555.
49. Lee S, Shim HS, Ahn BC, et al. Efficacy and safety of atezolizumab, in combination with etoposide and carboplatin regimen, in the first-line treatment of extensive-stage small-cell lung cancer: a single-center experience. Cancer Immunol Immunother. 2021 [Epub ahead of print], doi: 10.1007/s00262-021-03052-w, indexed in Pubmed: 34568975.
50. Tsui D, Polito L, Madhavan S, et al. 1650P Adoption and early clinical outcomes of atezolizumab (atezo) + carboplatin and etoposide (CE) in patients with extensive-stage small cell lung cancer (ES-SCLC) in the real-world (RW) setting. Ann Oncol. 2021; 32: S1164, doi: 10.1016/j.annonc.2021.08.234.
51. Paz-Ares L, Arriola E, Campelo M, et al. 1667TiP Durvalumab plus platinum-etoposide in first-line treatment of extensive-stage small cell lung cancer (CANTABRICO): A Spanish phase IIIb single arm, real-world study. Ann Oncol. 2021; 32: S1171–S1172, doi: 10.1016/j.annonc.2021.08.251.
52. Chen Y, Paz-Ares L, Dvorkin M, et al. First-line durvalumab plus platinum-etoposide in extensive-stage (ES)-SCLC (CASPIAN): Impact of brain metastases on treatment patterns and outcomes. J Clin Oncol. 2020; 38(15_suppl): 9068–9068, doi: 10.1200/jco.2020.38.15_suppl.9068.
53. European Medicines Agency. Tecentriq (atezolizumab): Annex I. Summary of product characteristics. https://www.ema.europa.eu (01.12.2021).
54. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J Clin Oncol. 2017; 35(34): 3823–3829, doi: 10.1200/JCO.2017.72.5069, indexed in Pubmed: 28813164.
55. Chung H, Lopez-Martin J, Kao SH, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. J Clin Oncol. 2018; 36(15_suppl): 8506–8506, doi: 10.1200/jco.2018.36.15_suppl.8506.
56. Chung H, Piha-Paul S, Lopez-Martin J, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J Thorac Oncol. 2020; 15(4): 618–627, doi: 10.1016/j.jtho.2019.12.109.

57. Rudin CM, Awad MM, Navarro A, et al. KEYNOTE-604 Investigators. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J Clin Oncol. 2020; 38(21): 2369–2379, doi: 10.1200/JCO.20.00793, indexed in Pubmed: 32468956.
58. Leal T, Wang Y, Dowlati A, et al. Randomized phase II clinical trial of cisplatin/carboplatin and etoposide (CE) alone or in combination with nivolumab as frontline therapy for extensive-stage small cell lung cancer (ES-SCLC): ECOG-ACRIN EA5161. J Clin Oncol. 2020; 38(15_suppl): 9000–9000, doi: 10.1200/jco.2020.38.15_suppl.9000.
59. Ready N, Farago AF, de Braud F, et al. Third-Line Nivolumab Monotherapy in Recurrent SCLC: CheckMate 032. J Thorac Oncol. 2019; 14(2): 237–244, doi: 10.1016/j.jtho.2018.10.003, indexed in Pubmed: 30316010.
60. Bristol Myers Squibb withdraws nivolumab indication for treatment of SCLC. 2021. https://www.cancernetwork.com/view/bristol-myers-squibb-withdraws-nivolumab-indication-for-treatment-of-sclc.
61. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol. 2013; 24(1): 75–83, doi: 10.1093/annonc/mds213, indexed in Pubmed: 22858559.
62. Reck M, Luft A, Szczesna A, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol. 2016; 34(31): 3740–3748, doi: 10.1200/JCO.2016.67.6601, indexed in Pubmed: 27458307.
63. Landre T, Chouahnia K, Des Guetz G, et al. First-line immune-checkpoint inhibitor plus chemotherapy chemotherapy alone for extensive-stage small-cell lung cancer: a meta-analysis. Ther Adv Med Oncol. 2020; 12: 1758835920977137, doi: 10.1177/1758835920977137, indexed in Pubmed: 33343721.
64. Wu J, Zhang A, Li Lu, et al. Meta-analysis of the Efficacy and Tolerability of Immune Checkpoint Inhibitors Combined With Chemotherapy in First-line Treatment of Small Cell Lung Cancer. Clin Ther. 2021; 43(3): 582–593.e2, doi: 10.1016/j.clinthera.2020.12.017, indexed in Pubmed: 33509647.
65. Yu H, Chen P, Cai X, et al. Efficacy and safety of PD-L1 inhibitors versus PD-1 inhibitors in first-line treatment with chemotherapy for extensive-stage small-cell lung cancer. Cancer Immunol Immunother. 2022; 71(3): 637–644, doi: 10.1007/s00262-021-03017-z, indexed in Pubmed: 34297160.
66. Hellmann MD, Callahan MK, Awad MM, et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. Cancer Cell. 2018; 33(5): 853–861.e4, doi: 10.1016/j.ccell.2018.04.001, indexed in Pubmed: 29731394.
67. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021; 39(3): 346–360.e7, doi: 10.1016/j.ccell.2020.12.014, indexed in Pubmed: 33482121.
68. Qi WX, Xiang Yi, Zhao S, et al. Assessment of systematic inflammatory and nutritional indexes in extensive-stage small-cell lung cancer treated with first-line chemotherapy and atezolizumab. Cancer Immunol Immunother. 2021; 70(11): 3199–3206, doi: 10.1007/s00262-021-02926-3, indexed in Pubmed: 33796915.
69. Iams WT, Porter J, Horn L. Immunotherapeutic approaches for small-cell lung cancer. Nat Rev Clin Oncol. 2020; 17(5): 300–312, doi: 10.1038/s41571-019-0316-z, indexed in Pubmed: 32055013.
70. Gristina V, Galvano A, Castellana L, et al. Is there any room for PD-1 inhibitors in combination with platinum-based chemotherapy as frontline treatment of extensive-stage small cell lung cancer? A systematic review and meta-analysis with indirect comparisons among subgroups and landmark survival analyses. Ther Adv Med Oncol. 2021; 13: 17588359211018018, doi: 10.1177/17588359211018018, indexed in Pubmed: 34646363.
71. Longo V, Catino A, Montrone M, et al. What Are the Biomarkers for Immunotherapy in SCLC? Int J Mol Sci. 2021; 22(20), doi: 10.3390/ijms222011123, indexed in Pubmed: 34681779.

VIA MEDICA

REVIEW ARTICLE

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What is new about germ cell ovarian tumors?

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0013

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Germ cell tumors of the ovary are the second most frequently found ovarian neoplasms following epithelial ovarian cancers. It is a heterogeneous group with an origin in a primitive germ cells. Therefore, germ cell tumors arise typically in the gonads- ovaries, and testicles. Neoplasms that develop from germ cells in other parts of the body are very rare. Among ovarian germ cell tumors, the most common is a mature teratoma. Tumors such as immature teratoma, dysgerminoma, embryonal carcinoma, or yolk sac tumor appear less frequently. Surgical treatment and chemotherapy, especially a protocol BEP (bleomycin, etoposide, cisplatin) play the most crucial role in the treatment of germ cell malignancies. Before the introduction of systemic chemotherapy, treatment of malignant germ cell tumors of the ovary tended to be poor. The prognosis has improved recently and fertility-conserving surgeries are being performed to enable patients to become pregnant. Additionally, it reduces the risk of late side effects. However, more and more emphasis is placed on developing new methods of treatment and on improving current methods. Some studies showed a therapeutic potential of SOX2 silencing for embryonal carcinoma. The aim of our study was to review the literature to analyze the latest and most effective treatments for embryonic ovarian tumors.

Key words: germ cell tumors, ovary, teratoma, dysgerminoma, embryonal carcinoma

Oncol Clin Pract 2022; 18, 2: 115–118

Introduction

Non-epithelial neoplasm is a rare malignancy and consists of germ cell tumors (GCT), sex-cord stromal tumors, and the most infrequent tumors of mesenchymal origin [1]. Germ cell neoplasms, besides epithelial ovarian cancers, are the second most common group — they account for approximately 10% of all ovarian malignancies [2]. GCTs include a broad set of histologic subtypes, such as teratoma, seminoma (known as dysgerminoma in the ovary and germinoma in the pineal gland), yolk sack tumor, choriocarcinoma, embryonal cell carcinoma, and mixed GCT [3].

Germ cell tumors are a distinctive group originating from the primitive germ cell. They usually arise in gonads – ovaries and testicles (over 90% of cases) — but may also arise in the anterior mediastinum, retroperitoneum, brain, pineal gland, and neurohypophysis [4–6]. The extragonadal GCTs might be derived from the primitive germ cells, which are separated during their migration to the primitive gonadal glands in the urogenital ridge [6].

Malignant germ cell tumors occur mainly in women and are usually found in younger patients [7].

Among ovarian germ cell tumors, the most common is a mature teratoma. Malignant tumors such as immature teratoma, dysgerminoma, embryonal carcinoma, or yolk sac tumor appear less frequently [8]. Malignant ovarian GCTs (MOGCTs) are subdivided into dysgerminomatous tumors (the most frequent type) and non-dysgerminomatous tumors [5] (Tab. 1).

Received: 09.11.2021 Accepted: 24.01.2022 Early publication date: 24.03.2022

Table 1. Classification of malignant embryonic tumors of the ovary, based on the classification of tumors of the World Health Organization [4, 6]

Germ Cell Tumors	Tumor Type
Primitive germ cell tumors	Dysgerminoma
	Yolk sac tumor
	Polyvescicular vitelline tumor
	Glandular variant
	Hepatoid variant
	Embryonal carcinoma
	Polyembryoma
	Non-gestational choriocarcinoma
	Mixed germ cell tumor
Biphasic or triphasic teratoma	Immature teratoma
	Mature teratoma

Surgical treatment and chemotherapy [bleomycin, etoposide, cisplatin (BEP)] play the most critical role in the case of germinal and gonadal neoplasms. Avoiding surgery is often possible because most diagnoses are at an early stage. In recent years, however, more and more effort is put into modernizing ways of treating ovarian malignancies.

The study aimed to analyze and discuss the latest methods of treatment of germ cell tumors. The articles published from 1976 to 2020 in the Pubmed and Elsevier databases were analyzed. The authors concentrated on the analysis of possible neoplasm therapies, and methods of improving the quality of life (including preserving fertility after treatment). The focus of the article was in particular: immature teratoma, dysgerminoma, and embryonal carcinoma of the ovary (ECO).

Immature teratoma

Immature teratoma (IT) accounts for approximately 1% of all ovarian tumors. IT can occur in both children and adults (range 1.5–60 years of age) [9]. Immature teratoma consists of all the embryonic tissues: endoderm, mesoderm, and ectoderm [10]. The five-year survival rate of patients with stage I immature teratoma is 98.3%, but in stage IV of the disease, the survival drops to 72%, thus early detection seems significant [11]. Due to the small number of patients (especially among adults), there are obstacles with an extensive follow-up and research, so it appears challenging to find the best IT therapy.

The treatment of choice for immature teratoma is surgical tumor excision. In the situation of incomplete tumor resection, 3 BEP cycles are recommended. Chemotherapy is also used in most adult patients with stages II or III or in the case of IT relapses, which, however, do not happen commonly [9, 12].

Shinkai et al. [13] reported, based on the experience of treating their patients between 2000 and 2016, that pediatric patients should be treated only surgically and chemotherapy should be mainly used in case of relapse. Therefore, children's situation is entirely different from adult women's, in whom adjuvant chemotherapy is recommended if the tumor advancement level exceeds stage I. Although adjuvant chemotherapy is prescribed routinely among adult women, no data have confirmed its responsiveness. Additionally, Imran et al. [9] pointed out that using chemotherapy in recurrent IT may lead to the transformation of IT into a mature teratoma [growing teratoma syndrome (GTS)]. Mature teratoma is, undoubtedly, a disease that can be cured by surgery alone; however, we must be aware of the further enlargement of the mass that might make surgery difficult. Since mature teratoma shows high expression of the retinoblastoma protein (cyclin-dependent kinase 4/6), it opens a new, non-operable treatment for GTS [9, 14].

GTS is a rare condition that may occur in patients with IT who had already undergone surgery. It is characterized by normal tumor marker levels, while tumor mass or implants can be observed on imaging studies or during laparoscopy [15]. The incidence of GTS is unknown, but it is more common among patients with testicular germ cell tumors than with ovarian ones [16]. The benefit of radical intervention in asymptomatic cases of GTS has not been proven. The disease can be stable for a long period of time [17]. One of the longest and most well-documented studies about GTS was conducted by Rathod et al. [18] from 2000 to 2020. During this period, 303 cases of germ cell tumor ovarian cancers were treated, and 8 cases recurred as GTS. All the cases were managed with optimal surgical cytoreduction, some of the cases more than once. The study claims that prolonged survival and possible recovery in patients with GTS depend on optimal cytoreduction [18].

Dysgerminoma

Dysgerminoma is a malignant germ cell tumor that accounts for less than 1% of all ovarian tumors [19]. Dysgerminoma most commonly occurs in children and young women. Bleomycin, etoposide, and platinum are the main chemotherapy drugs for germ cell tumors, including dysgerminomas [20]. Almost all patients with stage IA dysgerminoma are treated only by surgery, while potential relapses respond well to the chemotherapy [21]. Additionally, chemotherapy is also given in the case of incomplete tumor resection [21, 22].

Duhil de Benaze et al. [23] described 45 patients treated for dysgerminoma over 20 years. Pediatric

patients were treated with unilateral ovariectomy. Over the years, the strategy for managing lymph nodes has changed. Patients were treated with strategies like prophylactic lymph nodes removal, the strategy for the prophylactic radiation of the lymph nodes, or platinum-based chemotherapy in advanced cases. Unfortunately, the common side effect of the treatment is reduced fertility, associated with ovary removal or chemotherapy. As a result of long-term observation, the authors concluded that dysgerminoma presents an excellent prognosis, even in advanced cases, thanks to the treatment combination of surgery and platinum-based chemotherapy.

In 2019, an article presenting the observation of 180 patients diagnosed with dysgerminoma was published. This study confirmed the difference in 5-year survival between the optimal and suboptimal groups receiving cytoreduction. The groups receiving optimal cytoreduction benefit most. Factors associated with optimal cytoreduction at all stages of the disease were higher levels of lactate dehydrogenase, higher levels of CA125, receiving adjuvant chemotherapy, or the patient being under treatment in a specialized facility. Authors of the study also underlie the importance of maintaining fertility, especially among young women [22, 24]. Although surgical treatment is still the basis for treating dysgerminoma, chemotherapy also plays a crucial role in therapy (among others in cases like: incomplete resection, relapses, lymph node metastases) [22].

Kilic et al. [25] conducted a retrospective study that analyzed 18 patients diagnosed with pure ovarian dysgerminoma, who underwent staging surgeries with retroperitoneal lymph node dissection between 1993 and 2019. Adjuvant therapy was added according to the guidelines of the tumor board. It consisted of chemotherapy or radiotherapy or combined chemotherapy with radiotherapy. All patients were followed up. The number of patients was low; however, the study group was homogeneous. That led to the conclusion that the treatment of choice in patients with pure dysgerminoma should be fertility-sparing surgery. Additionally, besides staging surgery, retroperitoneal lymph node dissection is obligatory for identifying stage IA patients, who are exempt from adjuvant therapy [25].

Embryonal carcinoma of the ovary (ECO)

In 1976, Kurman and Norris described embryonal carcinoma of the ovary (ECO) as a separate entity that often occurs together with other types of germ cell tumors. The most common cancer symptoms are hormonal disorders, such as premature puberty or irregular periods [26]. ECO can be managed with fertility-preserving treatments, such as a staging laparotomy and unilateral adnexectomy, followed by chemotherapy [27]. In embryonal carcinoma, 3 cycles of BEP are used for chemotherapy. Chemotherapy with surgery has been the gold standard in the treatment of embryonal carcinoma of the ovary for years [27–29].

Although the majority of patients with advanced ovarian germ cell cancer are successfully treated by platin-based chemotherapy, one-third of patients relapse and half of them develop resistance to platin-based therapy. The treatment of this group of patients is challenging, and the disease is often fatal [5]. Some studies showed a therapeutic potential of SOX2 silencing for embryonal carcinoma [30]. SOX2 is a core transcription factor, that controls embryonal stem cells' self-renewal and pluripotency [31]. Silencing of SOX2 with SOX2-siRNA in a mouse model resulted in cell cytotoxicity and growth inhibition. However, the authors of the study claim that SOX2-siRNA delivery to the tumor should be improved [30].

Conclusions

Even though GCTs constitute an extremely rare group of neoplastic diseases in women, most patients can be successfully cured. Treatment in germ cell tumors has not changed much over the years — surgery, possibly with chemotherapy, is still the gold standard in treatment. Maintaining fertility and reducing the risk of late side effects must also be an important treatment goal.

Conflict of interest

The authors declare no conflict of interest.

References

1. Bennetsen AKK, Baandrup L, Aalborg GL, et al. Non-epithelial ovarian cancer in Denmark - Incidence and survival over nearly 40 years. Gynecol Oncol. 2020; 157(3): 693–699, doi: 10.1016/j.ygyno.2020.03.021, indexed in Pubmed: 32223987.
2. Ray-Coquard I, Morice P, Lorusso D, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org, ESMO Guidelines Committee. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4): iv1–iv18, doi: 10.1093/annonc/mdy001, indexed in Pubmed: 29697741.
3. Peterson CM, Buckley C, Holley S, et al. Teratomas: a multimodality review. Curr Probl Diagn Radiol. 2012; 41(6): 210–219, doi: 10.1067/j.cpradiol.2012.02.001, indexed in Pubmed: 23009771.
4. Sadiq Q, Khan FA. Germ Cell Seminoma. StatPearls. StatPearls Publishing LLC, Treasure Island (FL) 2021.
5. De Giorgi U, Casadei C, Bergamini A, et al. Therapeutic Challenges for Cisplatin-Resistant Ovarian Germ Cell Tumors. Cancers (Basel). 2019; 11(10), doi: 10.3390/cancers11101584, indexed in Pubmed: 31627378.
6. Ueno T, Tanaka YO, Nagata M, et al. Spectrum of germ cell tumors: from head to toe. Radiographics. 2004; 24(2): 387–404, doi: 10.1148/rg.242035082, indexed in Pubmed: 15026588.

7. Nogales FF, Dulcey I, Preda O. Germ cell tumors of the ovary: an update. Arch Pathol Lab Med. 2014; 138(3): 351–362, doi: 10.5858/arpa.2012-0547-RA, indexed in Pubmed: 24576031.
8. Euscher ED. Germ Cell Tumors of the Female Genital Tract. Surg Pathol Clin. 2019; 12(2): 621–649, doi: 10.1016/j.path.2019.01.005, indexed in Pubmed: 31097117.
9. Imran H, Siddiqui AH, Wilson F, et al. Growing Teratoma Syndrome After Chemotherapy For Ovarian Immature Teratoma. J Pediatr Hematol Oncol. 2020; 42(7): e630–e633, doi: 10.1097/MPH.0000000000001525, indexed in Pubmed: 31205224.
10. Cochrane E, Frost K, Dinobile C, et al. Immature teratoma diagnosed and treated during pregnancy and later complicated by growing teratoma syndrome: A case review with clinical considerations. Gynecol Oncol Rep. 2020; 32: 100566, doi: 10.1016/j.gore.2020.100566, indexed in Pubmed: 32300632.
11. Jorge S, Jones NL, Chen L, et al. Characteristics, treatment and outcomes of women with immature ovarian teratoma, 1998-2012. Gynecol Oncol. 2016; 142(2): 261–266, doi: 10.1016/j.ygyno.2016.05.024, indexed in Pubmed: 27222024.
12. Faure-Conter C, Pashankar F. Immature Ovarian Teratoma: When to Give Adjuvant Therapy? J Pediatr Hematol Oncol. 2017; 39(7): 487–489, doi: 10.1097/MPH.0000000000000950, indexed in Pubmed: 28859031.
13. Shinkai T, Masumoto K, Chiba F, et al. Pediatric ovarian immature teratoma: Histological grading and clinical characteristics. J Pediatr Surg. 2020; 55(4): 707–710, doi: 10.1016/j.jpedsurg.2019.04.037, indexed in Pubmed: 31130350.
14. Vaughn DJ, Flaherty K, Lal P, et al. Treatment of growing teratoma syndrome. N Engl J Med. 2009; 360(4): 423–424, doi: 10.1056/NEJMc0808558, indexed in Pubmed: 19164198.
15. Taşkın S, Turgay B, Şükür YE, et al. Laparoscopic and imaging findings of growing teratoma syndrome. J Turk Ger Gynecol Assoc. 2021; 22(2): 158–160, doi: 10.4274/jtgga.galenos.2020.2019.0034, indexed in Pubmed: 32517427.
16. Logothetis CJ, Samuels ML, Trindade A, et al. The growing teratoma syndrome. Cancer. 1982; 50(8): 1629–1635, doi: 10.1002/1097-0142(19821015)50:8<1629::aid-cncr2820500828>3.0.co;2-1, indexed in Pubmed: 6288220.
17. Bentivegna E, Gonthier C, Uzan C, et al. Gliomatosis peritonei: a particular entity with specific outcomes within the growing teratoma syndrome. Int J Gynecol Cancer. 2015; 25(2): 244–249, doi: 10.1097/IGC.0000000000000345, indexed in Pubmed: 25594144.
18. Rathod PS, Singh A, Punyashree RM, et al. Growing Teratoma Syndrome a Rare Clinical Entity: Two Decades Management Experience from the Regional Cancer Institute. Indian J Surg Oncol. 2021; 12(1): 31–38, doi: 10.1007/s13193-020-01224-1, indexed in Pubmed: 33814829.
19. Behtash N, Karimi Zarchi M. Dysgerminoma in three patients with Swyer syndrome. World J Surg Oncol. 2007; 5: 71, doi: 10.1186/1477-7819-5-71, indexed in Pubmed: 17587461.
20. Lee CW, Song MJ, Park ST, et al. Residual tumor after the salvage surgery is the major risk factors for primary treatment failure in malignant ovarian germ cell tumors: a retrospective study of single institution. World J Surg Oncol. 2011; 9: 123, doi: 10.1186/1477-7819-9-123, indexed in Pubmed: 21988930.
21. Mangili G, Sigismondi C, Lorusso D, et al. The role of staging and adjuvant chemotherapy in stage I malignant ovarian germ cell tumors (MOGTs): the MITO-9 study. Ann Oncol. 2017; 28(2): 333–338, doi: 10.1093/annonc/mdw563, indexed in Pubmed: 27803008.
22. Bandala-Jacques A, Estrada-Rivera F, Cantu D, et al. Role of optimal cytoreduction in patients with dysgerminoma. Int J Gynecol Cancer. 2019; 29(9): 1405–1410, doi: 10.1136/ijgc-2019-000632, indexed in Pubmed: 31594835.
23. Duhil de Bénazé G, Pacquement H, Faure-Conter C, et al. Paediatric dysgerminoma: Results of three consecutive French germ cell tumours clinical studies (TGM-85/90/95) with late effects study. Eur J Cancer. 2018; 91: 30–37, doi: 10.1016/j.ejca.2017.11.030, indexed in Pubmed: 29331749.
24. Chen Y, Luo Y, Han C, et al. Ovarian dysgerminoma in pregnancy: A case report and literature review. Cancer Biol Ther. 2018; 19(8): 649–658, doi: 10.1080/15384047.2018.1450118, indexed in Pubmed: 29580145.
25. Kilic C, Cakir C, Yuksel D, et al. Ovarian Dysgerminoma: A Tertiary Center Experience. J Adolesc Young Adult Oncol. 2021; 10(3): 303–308, doi: 10.1089/jayao.2020.0087, indexed in Pubmed: 32762565.
26. Kurman RJ, Norris HJ. Embryonal carcinoma of the ovary: a clinicopathologic entity distinct from endodermal sinus tumor resembling embryonal carcinoma of the adult testis. Cancer. 1976; 38(6): 2420–2433, doi: 10.1002/1097-0142(197612)38:6<2420::aid-cncr2820380630>3.0.co;2-2, indexed in Pubmed: 63319.
27. Cerovac A, Ljuca D, Nevacinovic E, et al. Giving Birth After Fertility Sparing Treatment of Embrional Carcinoma Figo III C: Case Report and Literature Review. Med Arch. 2018; 72(5): 371–373, doi: 10.5455/medarh.2018.72.371-373, indexed in Pubmed: 30524172.
28. Rana S, Gill MK, Kalhan S, et al. Immature Teratoma with Embryonal Carcinoma; a Rare Malignant Mixed Germ Cell Tumor in a 13-Year-Old Girl. Iran J Pathol. 2016; 11(1): 66–70, indexed in Pubmed: 26870146.
29. Ray-Coquard I, Morice P, Lorusso D, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org, ESMO Guidelines Committee. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4): iv1–iv18, doi: 10.1093/annonc/mdy001, indexed in Pubmed: 29697741.
30. Ushida H, Chano T, Minami K, et al. Therapeutic potential of SOX2 inhibition for embryonal carcinoma. J Urol. 2012; 187(5): 1876–1881, doi: 10.1016/j.juro.2011.12.058, indexed in Pubmed: 22425046.
31. Boer B, Kopp J, Mallanna S, et al. Elevating the levels of Sox2 in embryonal carcinoma cells and embryonic stem cells inhibits the expression of Sox2:Oct-3/4 target genes. Nucleic Acids Res. 2007; 35(6): 1773–1786, doi: 10.1093/nar/gkm059, indexed in Pubmed: 17324942.

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REVIEW ARTICLE

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Response assessment in cancer immunotherapy. Cooperation between the oncologist and the radiologist

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2020.0028
Translation: prof. Ewa Bartnik

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

One of the paradigms of clinical oncology is systemic treatment on the condition that the patient obtains a therapeutic benefit. The evaluation of the benefit from treatment should be based on clinical premises together with a radiological evaluation of the response. Evidently, this implies the need for a collaboration between the clinician and the radiologist. The diversity of responses to treatment, in particular, the occurrence of the so-called atypical responses to immunotherapy requires strict cooperation between clinicians and radiologists.

Key words: criteria of response evaluation, immunotherapy, pseudoprogression, atypical response

Oncol Clin Pract 2022; 18, 2: 119–127

Significance of response evaluation in oncology

One of the paradigms in clinical oncology is systemic treatment on the condition that the patient obtains a therapeutic benefit [1]. In the case of the metastatic disease this can be measured by the prolongation of the progression-free time, obtaining a response (which is of fundamental importance in symptomatic patients, in whom a decrease in tumor mass may lead to a decrease of the intensity of symptoms), or — the most desirable — a prolongation of the overall survival time [2]. At the same time the potential undesirable effects of a given therapy, which can negatively affect the patient's quality of life, should be kept in mind. The evaluation of the treatment benefits should be based on clinical premises, such as the performance status, intensity of symptoms or the need for analgesic drugs, together with a radiological evaluation of the response. This evidently implies the need for cooperation between the clinician and the radiologist, who should have access to the requisite clinical data concerning individual patients. They concern above all the histopathological diagnosis, the type of systemic treatment, the effects of previous treatment lines and their duration, the undergone surgical treatment or other forms of local treatment (particularly radiotherapy or ablation methods such as e.g. thermoablation). The next extremely important aspect is to provide the radiologist with the documentation of previously performed imaging tests if they were performed in another center. Only thus can the evolution of changes found in imaging studies be evaluated as well as the dynamics of the disease. The direct contact of the radiologist with the attending physician is also important.

Received: 30.04.2020 Accepted: 03.07.2020 Early publication date: 03.02.2022

Immunotherapy in treating tumors on the example of renal cell carcinoma

Renal cell carcinoma (RCC) constitutes about 3% of malignant tumors [3]. In about 50% of patients, the disease is discovered accidentally during imaging tests of the abdominal cavity performed for other reasons [4]. In about 20% of patients with an RCC diagnosis synchronous distant metastases are detected and in a further 30%, this occurs during observation [4]. Clear cell renal cell carcinoma is a tumor which is resistant to treatment using cytostatics [5]. Cytokine-based immunotherapy — interleukin-2 or interferon alpha (IFN-α) turned out to be an effective form of treatment in selected groups of patients [6]. Interferon alpha has antiangiogenic, antiproliferative and immunomodulating activity. Immunotherapy using this cytokine was found to extend the median survival of RCC patients by 25 months in comparison with medroxyprogesterone [7]. The greatest benefits of this treatment were observed in patients with a favorable prognosis according to the Memorial Sloan Kettering Cancer Center (MSKCC) scale [8], with good performance status and with metastases limited to the lungs. Advances in molecular biology [9, 10] has led to the use in RCC treatment of drugs inhibiting angiogenesis — bevacizumab (anti-VEGF antibody) in combination with IFN-α [11, 12], multikinase inhibitors — sorafenib, sunitinib and pazopanib [13–15]. In the group with an unfavorable prognosis according to MSKCC temsirolimus was registered (mTOR inhibitor) [16]. Then the possibilities of second and successive treatment lines arose after the failure of antiangiogenic treatment. For this indication, an mTOR inhibitor (everolimus) [17] and next-generation multikinase inhibitors — axitinib [18] and cabozantinib (also inhibiting MET and AXL kinases) [19] were registered. Basic research allowing a better understanding of immunological mechanisms led to the elaboration of drugs from the group of immune checkpoint inhibitors (ICI). They affect the regulation of lymphocyte activation, differentiation and also inhibition of their apoptosis [20]. In phase III clinical trials in RCC patients ICI was found to be effective in monotherapy [21], a combination of anti-PD-1 and anti-CTLA4 antibodies [22, 23], and also in combined therapy of ICI z with a multikinase inhibitor [24, 25].

The European Medicines Agency (EMA) has registered the following drugs for treating metastatic renal cell carcinoma: nivolumab (anti-PD-1 antibody; in monotherapy or in combination with ipilimumab), ipilimumab (anti-CTLA4 antibody) in combination with nivolumab, avelumab (anti-PD-L1 antibody) in combination with axitinib and pembrolizumab (anti-PD-1 antibody) in combination with axitinib.

The use of immunotherapy in treating patients with clear cell renal cell carcinoma is recommended by scientific societies in first-line treatment [combined ICI/ICI therapy in the group with intermediate and unfavorable prognosis according to the International Metastatic RCC Database Consortium (IMDC) and TKI-VEGFR/ICI regardless of the prognosis] and in second or third-line treatment (ICI monotherapy) [26, 27].

In Poland currently only nivolumab is reimbursed as second-line treatment, used after failure of earlier antiangiogenic treatment using a multikinase inhibitor. Nivolumab for this indication was registered on the basis of the CheckMate 025 trial [21]. This was a randomized phase III trial in which patients after one or two lines of antiangiogenic treatment were randomized (at a 1:1 ratio) to immunotherapy with nivolumab (3 mg/kg body weight) or molecularly targeted treatment with the mTOR inhibitor — everolimus (10 mg/d.). During the 2020 Genitourinary Cancers Symposium organized under the auspices of the American Society of Clinical Oncology (ASCO) the final results of this trial were presented (after 60 months of follow-up). Median overall survival in the group of patients receiving immunotherapy was 25.8 months (95% CI 22.2–29.8) *vs.* 19.7 months (95% CI 17.6–22.1) in the control arm, the hazard ratio (HR) of death was 0.73; $p < 0.0001$. Median progression-free survival was 4.2 months *vs.* 4.5 months, respectively, HR for progression 0.84 (0.72–0.99), $p = 0.03$. Responses were evaluated on the basis of RECIST 1.1 (Response Evaluation Criteria In Solid Tumors). Objective responses were found in 23% *vs.* 4% patients. Progression as the best response was found in 35% of patients treated with nivolumab and in 26% receiving everolimus. According to the protocol continuation of the treatment after progression was allowed if patient derived benefit. Taking into consideration the possibility of occurrence of the pseudoprogression phenomenon, this is an extremely important aspect, as in this situation treament termination based on only on the basis of observing progression in imaging studies could deprive the patient of the effects of the treatment. In this context, the evaluation of the clinical state of the patient receiving immunotherapy is of particular importance. In the case of pseudoprogression the patient's status, in general, remains stable whereas in the case of real progression it worsens [28].

Radiological response evaluation criteria in oncology

An objective evaluation of the response to treatment (regardless of clinical data) is possible on the basis of imaging studies. The first criteria introduced in 1979 were those of the World Health Organization (WHO) (Miller et al. [29]). Many radiological methods of evaluation appeared in successive years, among

them the RECIST criteria are commonly accepted in everyday practice and in clinical trials. These criteria published in 2000 and then modified in 2009 [30] as version 1.1 are still in force in the evaluation of standard cytotoxic therapies used in the treatment of most solid tumors. There are many papers on this subject (i.a. Płużański [31]), to which the interested reader may refer. However, the basic principles on which these criteria are based should be underlined. These are anatomical criteria, evaluating exclusively the size of the leasions (primary tumor and/or metastases). Computed tomography (CT) it the preferred imaging method for evaluation in RECIST 1.1 but in some cases, MR is also used. One linear dimension of the tumor is measured (the largest perpendicular dimension or the size of the short axis in the case of lymph nodes). RECIST criteria define measurable and non-measurable lesions in a precise fashion. Among the former target, lesions are selected. The remaining lesions (both measurable and non-measurable) are non-target lesions. We propose using these terms which have been accepted in everyday practice and are better at conveying their meaning than the terms „addressed and non-addressed lesions", sometimes used in the literature. RECIST criteria assume 4 response categories: complete regression, partial regression, stabilization and disease progression. It is worth stressing that the interpretation (radiological description) of a successive CT analysis performed during treatment should finish with the conclusion to which category of response this analysis can be qualified. The decision about continuing or interrupting the treatment should, of course, be made by the oncologist on the basis of the whole clinical picture and additional analyses, but it is the radiologist who must provide precise information derived from imaging studies.

Critical evaluation of disease progression

The radiologist has a particular responsibility if the progression of the disease is suspected (on the basis of the evaluation of imaging studies). RECIST 1.1. criteria use the following definitions of disease progression [30]:

— an increase of the sum of target lesions by 20% or more (at least 5 mm in absolute values) in relation to the examination in which this sum was the smallest (nadir) and/or
— the appearance or one or more new lesions and/or
— evident (not doubtful) increase in the size of non-target lesions.

It is very important to compare the current examination not only with the previous one but also with earlier analyses: the initial one and (this is key for detecting disease progression) with the examination in which the sum of the dimensions was the smallest (nadir).

If new lesions appear it is important to be certain that they represent symptoms of malignancy. For instance, the appearance of (or increase of the volume of) fluid in the pleural or peritoneal cavity may be a symptom of a reaction to treatment (inflammatory reaction, fluid retention in the organism), and not the disease itself [32, 33].

In turn, the appearance of blastic (sclerotic) foci observed in successive CT analyses during the treatment most commonly indicates an osteoblastic reaction (calcification of metastatic foci in bone marrow, not visible in previous CT analyses) and cannot be treated as a symptom of disease progression – on the contrary, it is a beneficial reaction to treatment [34] (Fig. 1). The examples given above require particular attention during the interpretation of imaging studies and should be appropriately described and evaluated, together with the clinical status of the patient.

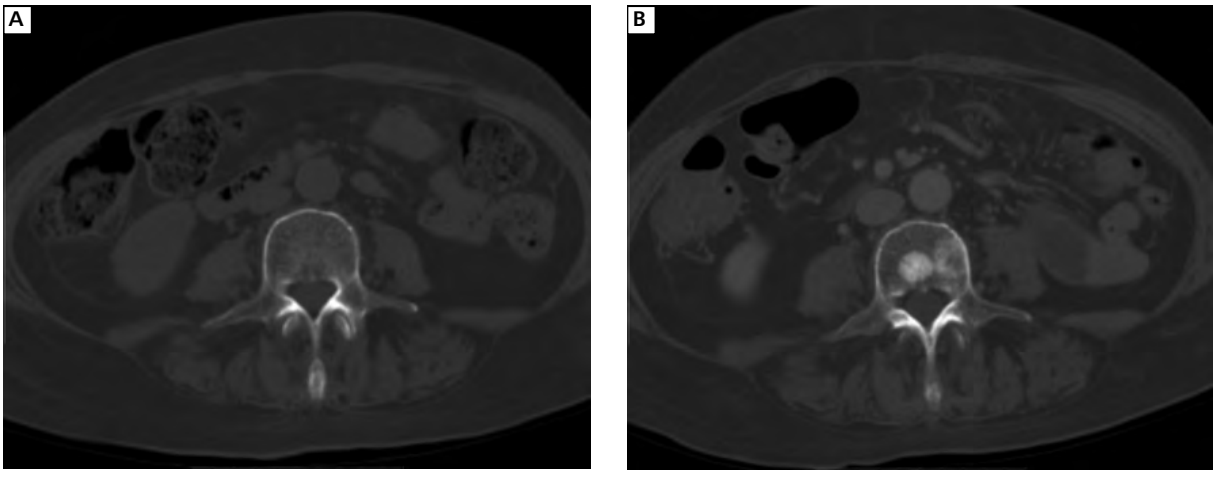

Figure 1. Osteoblastic reaction. CT analysis in a patient with non-small cell lung cancer during chemotherapy. (**A**) image before initiation of treatment — no lesions in bones visible; (**B**) image after a successive cycle of chemotherapy — appearance of blastic foci in the vertebral body corresponds to calcification of metastases which were present but not visible in the initial TK examination

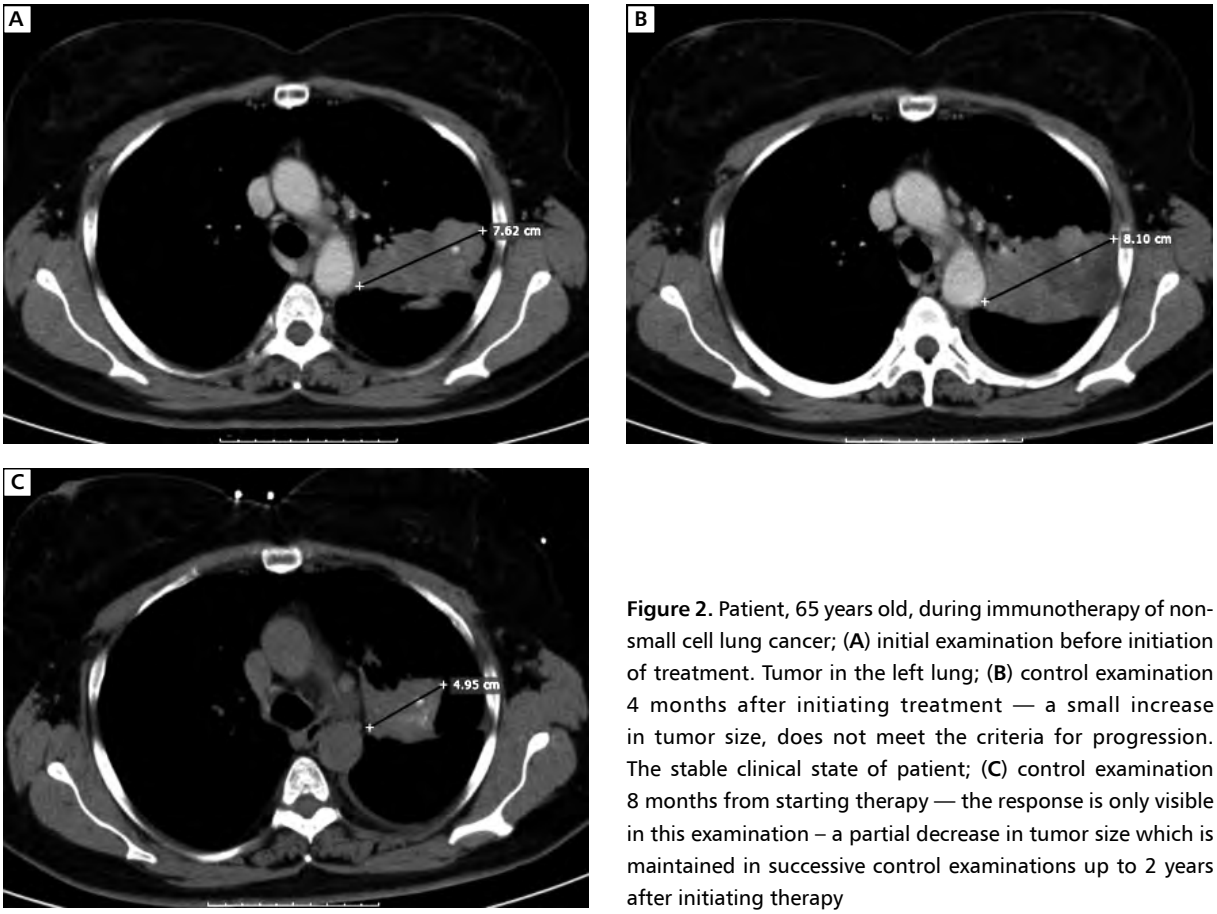

Figure 2. Patient, 65 years old, during immunotherapy of non-small cell lung cancer; (**A**) initial examination before initiation of treatment. Tumor in the left lung; (**B**) control examination 4 months after initiating treatment — a small increase in tumor size, does not meet the criteria for progression. The stable clinical state of patient; (**C**) control examination 8 months from starting therapy — the response is only visible in this examination – a partial decrease in tumor size which is maintained in successive control examinations up to 2 years after initiating therapy

Evaluation of response immunotherapy. New response criteria(irRC, irRECIST, iRECIST)

RECIST criteria were elaborated and introduced into common usage in 2000, thus during the period when cytostatic drugs were the basis of chemotherapy in oncology. The development of new therapies, especially the increasingly frequent use of immunotherapy, gives rise to the question of whether these criteria are reliable to evaluate the response in new types of therapy. Since immunotherapy is based on a completely different mechanism of action than standard cytotoxic therapies, different responses to treatment can be expected than those which have been observed so far. A reaction to treatment may occur (and be observed in imaging studies) with a longer delay, sometimes lasting even up to several months after initiating treatment (Fig. 2). It can also be maintained longer, even after termination of the treatment [35].

Atypical reactions

Reactions have been also observed which did not occur during standard therapies. The phenomenon of pseudoprogression should particularly be mentioned. This is based on the initial increase in the size of the lesions and/or the appearance of new lesions after initiating treatment, and then subsequent decrease in the further course of therapy (Fig. 3). This phenomenon was observed for the first time during immunotherapy of patients with metastatic melanoma, and subsequently during the therapy of other malignancies [36].

The mechanism of the increase in the size of the tumor or metastases can be explained by infiltration by the immune cells (mainly T lymphocytes) of the tumor, which leads to a transient increase of its volume visible in imaging studies or clinical examinations. This has been confirmed in histopathological analyses of resected melanoma lung metastases. Lesions invisible in the initial examination (because they were too small) can appear in the course of immunotherapy also because of their transient increase in size (immune infiltration and necrosis within the tumor) which makes them visible in imaging studies (Fig. 4). In the case of pseudoprogression, this increase in size is not caused by an increase in the number of cancer cells which distinguishes this phenomenon from true progression.

The frequency of pseudoprogression for metastatic melanoma attains 10% of patients observed during immunotherapy [37]. In non-small cell lung cancer it is

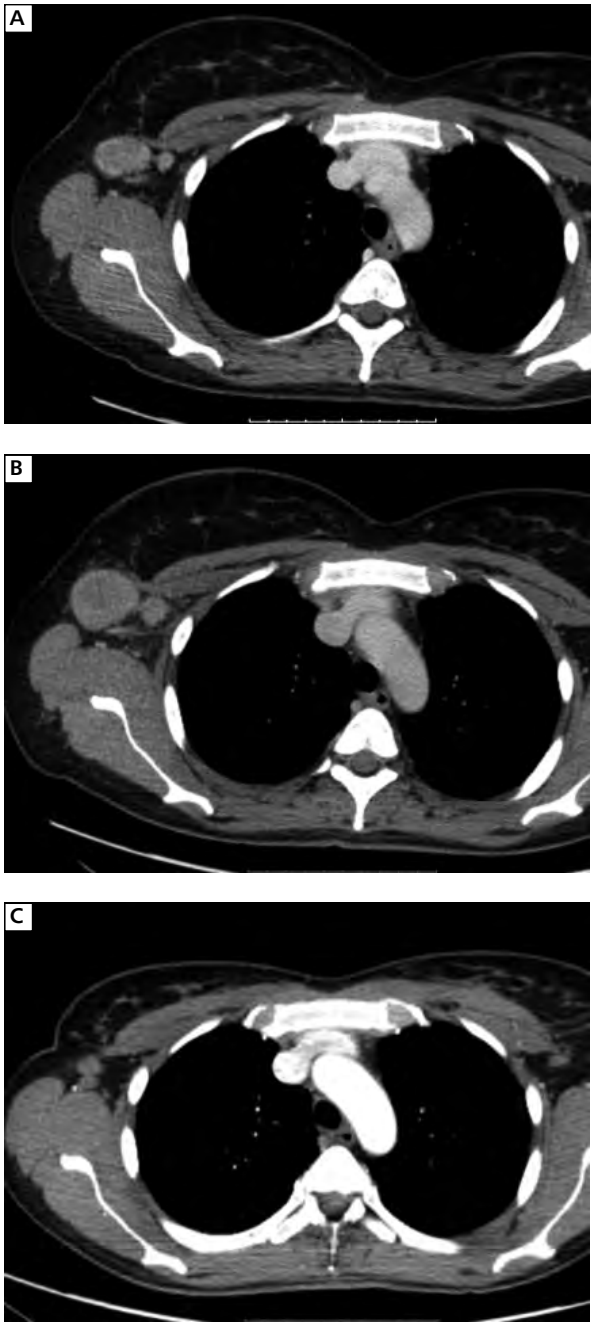

Figure 3. The pseudoprogression phenomenon. Woman, 30 years old, with metastatic melanoma of trunk skin; (**A**) initial examination — enlarged right axillar node (target lesion); (**B**) the first scan after the initiation of immunotherapy — clear increase in size, meets progression criteria (RECIST 1.1.); (**C**) CT scan after 2 successive cycles of immunotherapy — clear decrease of the size of the lymph node to normal dimensions — complete regression

less frequent — up to 5% [38]. The frequency of this phenomenon during immunotherapy of other malignancies is not known and requires further observations. The phenomenon of pseudoprogression during immunotherapy, though infrequent, can be a cause of diagnostic errors, which lead to premature termination of treatment. Hence proposals have appeared during clinical trials not to interrupt treatment after progression is observed in imaging studies if the clinical status of the patient is stable. This phenomenon has also been the basis of different criteria for evaluating response in immunotherapy.

Hyperprogression is a second very important atypical phenomenon. This phenomenon described relatively recently in the course of immunotherapy [39] describes a sudden increase in tumor size after initiating therapy. The tumor growth rate (TGR) is important here as it can rapidly accelerate after applying immunotherapy, which is associated with a clear deterioration of the patient's status. An over twofold increase in TGR in the last examination in comparison with the tumor growth rate in previous examinations suggests hyperprogression. This aggressive and unfavorable mechanism of response to immunotherapy has been described in 9% of patients treated for various types of malignancies (Fig. 5).

The next type of atypical response to immunotherapy is a dissociated response (Fig. 6). It occurs in case when during treatment some of the lesions become smaller, and some larger [40]. So far this phenomenon has been poorly described. There are no precise definitions of how to detect it and what criteria should be used in imaging studies in this situation. Tazdait et al. observed this type of response in 7.5% of patients with non-small cell lung cancer during immunotherapy and associated it with better survival than in the group of patients with real progression [41]. The possibility of using radiotherapy in selected cases for foci which increase in size during immunotherapy (e.g. metastases in the brain or bones) with a good response to treatment and an increase in overall survival was pointed out [42].

Criteria of response evaluation to immunotherapy

Different response evaluation criteria have been proposed for immunotherapy, which takes into consideration atypical reactions to treatment. The first proposal was criteria elaborated for evaluation of immunotherapy of metastatic melanoma [36]. These criteria called immune-related response criteria (irRC) were based on WHO criteria. They are two-dimensional criteria (two dimensions of the lesion size) in which the sum of the products of perpendicular sizes of lesions which are considered as targets is evaluated. If new lesions appear their dimensions are added to the sum of the dimensions of the measured lesions. Progression is defined as an increase in the sum of the lesion dimensions ≥ 25%. It

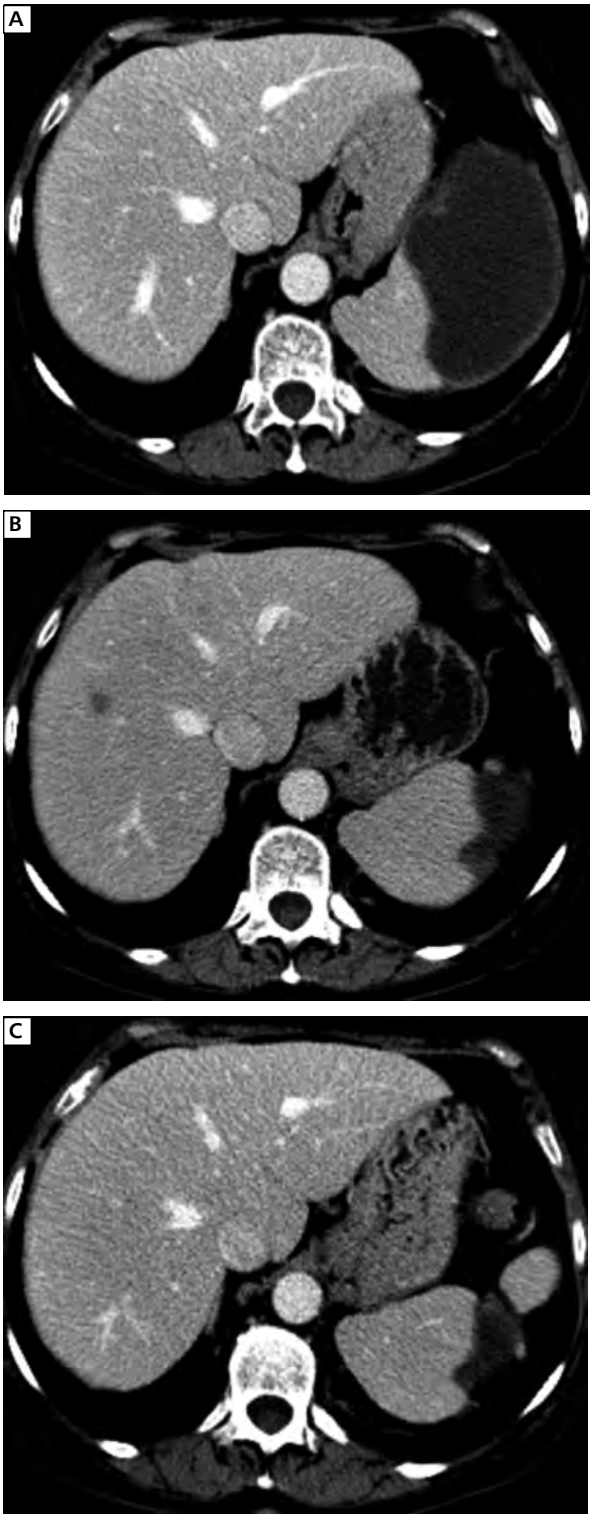

Figure 4. Pseudoprogression phenomenon — the appearance of new foci. Woman, 75 years old, with non-small cell lung cancer; (**A**) initial examination before starting immunotherapy — normal appearance of the liver; (**B**) first control examination during immunotherapy. A focus with the appearance of metastasis has appeared in the liver; (**C**) next control examination — the focus has undergone complete regression

is indispensable to confirm the increase in lesion size in a control examination performed not earlier than 4 weeks after the recent examination. This method of measurement allows the continuation of treatment even if progression criteria are fulfilled in examination studies in the absence of clinical symptoms of disease progression. Only the confirmation of the increase in the dimensions of the lesions ≥ 25% in two successive examinations can be the basis for stopping the treatment.

irRECIST criteria. The next proposal for evaluating immunotherapy were criteria based on RECIST 1.1. principles (one-dimensional, evaluating the sum of the largest sizes of the target lesions), but maintaining basic irRC principles if disease progression (PD, *progressive disease*) was suspected. These criteria, described as immune-related RECIST (irRECIST), require confirmation of PD in two successive control examinations and include the dimensions of new measurable lesions into the total sum of target lesions. They were introduced in 2013 [43] in clinical trials of new immunotherapy drugs. These authors demonstrated the high agreement of irRECIST and irRC criteria in response evaluation in a group of patients with advanced melanoma, however, irRECIST criteria were characterized by better reproducibility which allows comparison of treatment effectiveness with earlier clinical trials, where methodology was based on standard RECIST 1.1. criteria [43]. It is also worth underlining that these criteria are simpler and less time-consuming to use than irRC.

iRECIST criteria. One of the last proposals are criteria elaborated for the requirements of immunotherapy by the RECIST working group [44]. They are based on RECIST 1.1. principles concerning the measurements and selection of target and non-target lesions, but they introduce modifications in order to adapt the response evaluation to atypical reactions encountered in immunotherapy. The concept of immune unconfirmed progressive disease (iUPD) is introduced; this requires confirmation in a control examination performed during the next 4–8 weeks. iUPD is based on RECIST 1.1. principles, but confirmed progression (iCPD, immune confirmed progressive disease) occurs in the situation when in the next control examination additional new lesions appear or previously observed new lesions become larger, or the sum of the target lesions increases by an additional size ≥ 5 mm or (qualitatively evaluated) any increase of the size of non-target lesions is observed. If this does not happen the result of the examination is still described as unconfirmed progression and treatment is continued (in correlation with the clinical picture). It should be stressed that a small increase in the sum of target lesions (≥ 5mm) or any increase in the size of non-target lesions is sufficient to confirm disease progression. Detailed principles of using iRECIST criteria are given on the

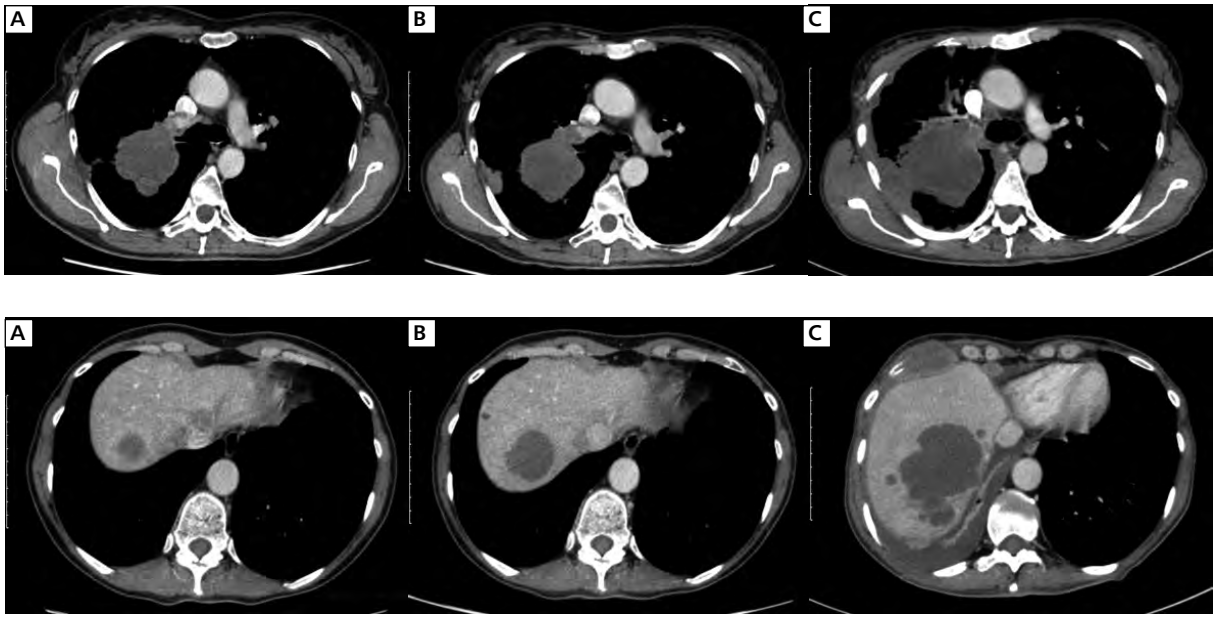

Figure 5. Hyperprogression. Woman, 54 years old, diagnosed with non-small cell lung cancer; (**A**) examination during chemotherapy — lung tumor (upper row) and liver metastases (lower row); (**B**) disease progression was observed during the next examination (increase in the size of liver metastases). Immunotherapy was initiated; (**C**) first control examination during immunotherapy — a considerable increase in the size of the lung tumor and liver metastases. New metastases have appeared in the pleura and bones. Clear deterioration of the patient's status

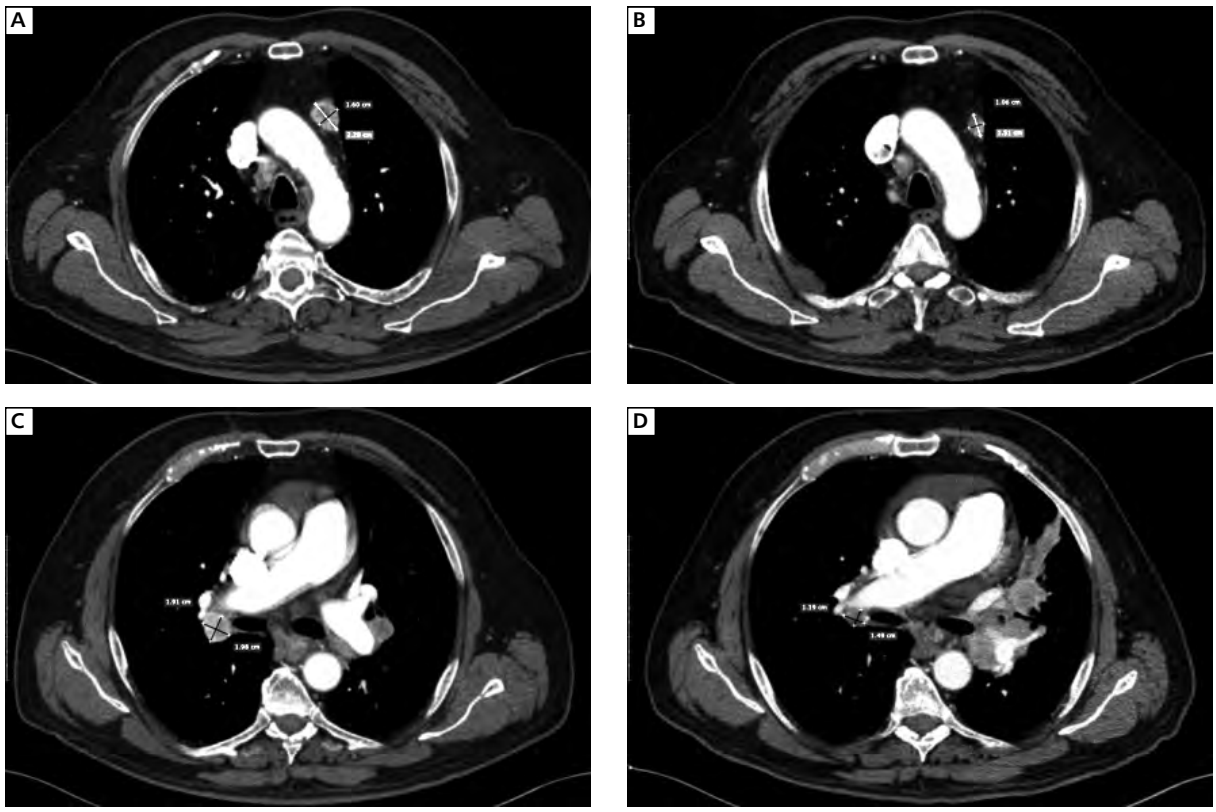

Figure 6. Example of a dissociated response. Man, 60 years old, in the course of immunotherapy for metastatic clear cell renal cell carcinoma carcinoma. Left side (**A**, **C**) — CT scan before initiating treatment. Enlarged mediastinum and internal right and left lung lymph nodes. Right side (**B**, **D**) — CT scan after initiating immunotherapy. A clear decrease in size of the mediastinum and internal right lung nodes with a simultaneous increase in the size of the internal right lung lymph nodes

web page https://recist.eortc.org/irecist/. irRECIST and iRECIST criteria are based on RECIST 1.1. criteria and the difference consists in the evaluation in the case of suspected disease progression. All of them — irRC, irRECIST as well as iRECIST require a subsequent imaging examination performed after 4–8 weeks in order to confirm disease progression.

The criteria for evaluating response to immunotherapy described above are applied mainly in clinical trials. They have not yet been introduced into everyday clinical practice nor into drug reimbursement programs. The increasing frequency of therapies based on checkpoint inhibitors gives rise to the risk of an incorrect evaluation of response to treatment with strict adherence to RECIST 1.1. principles. Most drug reimbursement programs are based on RECIST 1.1. criteria. If an increase in the size of the target lesions occurs (fulfilling progression criteria) or new lesions appear such a result of the examination obligatorily causes an interruption of treatment. There is a high probability that in some of the patients' interruption of treatment is premature and may exclude them from a therapy which could lead to improved survival. The radiologist performs the examination in an objective fashion in agreement with the principles and provides the oncologist with information on the basis of which he makes a decision. Observation of disease progression in CT imaging currently does not require its confirmation in a subsequent control examination which excludes the possibility of verifying what is the real effect of the treatment. The aim should be to change the Polish National Drug Reimbursement Program Guidelines, in a fashion taking into consideration the possibility of atypical reactions in the course of immunotherapy and allow the continuation of treatment until an examination confirming or excluding progression can be performed after 4–8 weeks.

Analysis of imaging studies (CT) should be performed by radiologists familiar with the response evaluation criteria in oncology and experienced in their application. The evaluation of subsequent control examinations is necessary, together with the initial examination. It is important to determine the examination in which the sum of the target lesions is the smallest (nadir), this will be the basis for the eventual evaluation of disease progression. A situation when the current examination is only compared with the previous one is inadmissible.

The radiologist evaluating the patient's results must know his basic clinical data, but also basic data concerning treatment (a type of treatment, the administered drug, when was the therapy started, undergone surgeries and other types of treatment). The constant collaboration between the oncologist and the radiologist is indispensable. Similarly, as radiologists should be required to be able to apply treatment response evaluation criteria, oncologists should be required to include basic clinical information in the referral to imaging studies and the possibility of contacting them directly if there are any suspicions during the interpretation of the result. Situations (unfortunately frequent) are inadmissible when the referral only contains the patient's name and the statistical number of the disease. At the same time, the oncologist referring the patient to examination in the course of treatment (marking on the referral that the description should be according to RECIST 1.1. criteria) should obtain an interpretation of the image and a final conclusion — to which category of response does the result of this examination belong. The increasingly frequent use of advanced therapies, in which evaluation of the response is based on objective information provided by imaging studies, requires the use of a "common language" understandable for oncologists and radiologists. RECIST criteria and their modifications (especially used in immunotherapy) can and should be such a language. To attain this a strict cooperation between oncologists and radiologists is required — especially in the frame of scientific societies, joint conferences and workshops.

Conflict of interest

Authors declare that they have no conflict of interest.

References

1. Krzakowski M, Wyrwicz L. Leczenie systemowe. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P (ed.). Onkologia Kliniczna. Tom I. Via Medica, Gdańsk. 2014: 107–134.
2. Płużański A, Sacha T. Ocena wartości przeciwnowotworowego leczenia. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P (ed.). Onkologia Kliniczna. Tom I. Via Medica, Gdańsk. 2014: 400–411.
3. Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev. 2008; 34(3): 193–205, doi: 10.1016/j.ctrv.2007.12.001, indexed in Pubmed: 18313224.
4. Pantuck A, Zisman A, Rauch M, et al. Incidental renal tumors. Urology. 2000; 56(2): 190–196, doi: 10.1016/s0090-4295(00)00655-5.
5. Makhov P, Joshi S, Ghatalia P, et al. Resistance to Systemic Therapies in Clear Cell Renal Cell Carcinoma: Mechanisms and Management Strategies. Mol Cancer Ther. 2018; 17(7): 1355–1364, doi: 10.1158/1535-7163.MCT-17-1299, indexed in Pubmed: 29967214.
6. Rini BI, Battle D, Figlin RA, et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of renal cell carcinoma. J Immunother Cancer. 2016; 4(1): 81, doi: 10.1186/s40425-016-0180-7, indexed in Pubmed: 27891227.
7. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. Lancet. 1999; 353(9146): 14–17, indexed in Pubmed: 10023944.
8. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol. 1999; 17(8): 2530–2540, doi: 10.1200/JCO.1999.17.8.2530, indexed in Pubmed: 10561319.
9. Mittal K, Koon H, Elson P, et al. Dual VEGF/VEGFR inhibition in advanced solid malignancies: clinical effects and pharmacodynamic biomarkers. Cancer Biol Ther. 2014; 15(8): 975–981, doi: 10.4161/cbt.29187, indexed in Pubmed: 24842548.
10. Escudier B, Pluzanska A, Koralewski P, et al. AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet.

2007; 370(9605): 2103–2111, doi: 10.1016/S0140-6736(07)61904-7, indexed in Pubmed: 18156031.
11. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010; 28(13): 2137–2143, doi: 10.1200/JCO.2009.26.5561, indexed in Pubmed: 20368558.
12. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009; 27(20): 3312–3318, doi: 10.1200/JCO.2008.19.5511, indexed in Pubmed: 19451442.
13. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27(22): 3584–3590, doi: 10.1200/JCO.2008.20.1293, indexed in Pubmed: 19487381.
14. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010; 28(6): 1061–1068, doi: 10.1200/JCO.2009.23.9764, indexed in Pubmed: 20100962.
15. Hudes G, Carducci M, Tomczak P, et al. Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007; 356(22): 2271–2281, doi: 10.1056/NEJMoa066838, indexed in Pubmed: 17538086.
16. Motzer R, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008; 372(9637): 449–456, doi: 10.1016/s0140-6736(08)61039-9.
17. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011; 378(9807): 1931–1939, doi: 10.1016/S0140-6736(11)61613-9, indexed in Pubmed: 22056247.
18. Choueiri TK, Escudier B, Powles T, et al. METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016; 17(7): 917–927, doi: 10.1016/S1470-2045(16)30107-3, indexed in Pubmed: 27279544.
19. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology. 2012; 1(8): 1223–1225, doi: 10.4161/onci.21335, indexed in Pubmed: 23243584.
20. Motzer RJ, Escudier B, McDermott DF, et al. CheckMate 025 Investigators. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015; 373(19): 1803–1813, doi: 10.1056/NEJMoa1510665, indexed in Pubmed: 26406148.
21. Motzer RJ, Tannir NM, McDermott DF, et al. CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018; 378(14): 1277–1290, doi: 10.1056/NEJMoa1712126, indexed in Pubmed: 29562145.
22. Motzer RJ, Rini BI, McDermott DF, et al. CheckMate 214 investigators. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019; 20(10): 1370–1385, doi: 10.1016/S1470-2045(19)30413-9, indexed in Pubmed: 31427204.
23. Rini BI, Plimack ER, Stus V, et al. KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019; 380(12): 1116–1127, doi: 10.1056/NEJMoa1816714, indexed in Pubmed: 30779529.
24. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019; 380(12): 1103–1115, doi: 10.1056/NEJMoa1816047, indexed in Pubmed: 30779531.
25. Escudier B, Porta C, Schmidinger M, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019; 30(5): 706–720, doi: 10.1093/annonc/mdz056, indexed in Pubmed: 30788497.
26. Albiges L, Powles T, Staehler M, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma. Eur Urol. 2019; 76(2): 151–156, doi: 10.1016/j.eururo.2019.05.022, indexed in Pubmed: 31151678.
27. Vrankar M, Unk M. Immune RECIST criteria and symptomatic pseudoprogression in non-small cell lung cancer patients treated with immunotherapy. Radiol Oncol. 2018; 52(4): 365–369, doi: 10.2478/raon-2018-0037, indexed in Pubmed: 30367809.
28. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer. 1981; 47(1): 207–214, doi: 10.1002/1097-0142(19810101)47:1<207::aid-cncr2820470134>3.0.co;2-6, indexed in Pubmed: 7459811.
29. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228–247, doi: 10.1016/j.ejca.2008.10.026, indexed in Pubmed: 19097774.
30. Płużański A. Kryteria oceny odpowiedzi na leczenie RECIST 1.1. Nowotwory. Journal of Oncology. 2014; 64(4): 331–335, doi: 10.5603/njo.2014.0055.
31. Kim WK, Shingare AB, Ramaiya NH, et al. Fluid Retention Associated with Imatinib Treatment in Patients with GIST. Korean J Radiol. 2015; 16(2): 304–313.
32. Howard SA, Krajewski KM, Thornton E, et al. Decade of molecular targeted therapy: abdominal manifestations of drug toxicities--what radiologists should know. AJR Am J Roentgenol. 2012; 199(1): 58–64, doi: 10.2214/AJR.11.7432, indexed in Pubmed: 22733894.
33. Stattaus J, Hahn S, Gauler T, et al. Osteoblastic response as a healing reaction to chemotherapy mimicking progressive disease in patients with small cell lung cancer. Eur Radiol. 2009; 19(1): 193–200, doi: 10.1007/s00330-008-1115-6, indexed in Pubmed: 18677488.
34. Dromain C, Beigelman C, Pozzessere C, et al. Imaging of tumour response to immunotherapy. Eur Radiol Exp. 2020; 4(1): 2, doi: 10.1186/s41747-019-0134-1, indexed in Pubmed: 31900689.
35. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009; 15(23): 7412–7420, doi: 10.1158/1078-0432.CCR-09-1624, indexed in Pubmed: 19934295.
36. Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol. 2016; 34(13): 1510–1517, doi: 10.1200/JCO.2015.64.0391, indexed in Pubmed: 26951310.
37. Gettinger SN, Horn L, Gandhi L, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2015; 33(18): 2004–2012, doi: 10.1200/JCO.2014.58.3708, indexed in Pubmed: 25897158.
38. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res. 2017; 23(8): 1920–1928, doi: 10.1158/1078-0432.CCR-16-1741, indexed in Pubmed: 27827313.
39. Borcoman E, Kanjanapan Y, Champiat S, et al. Novel patterns of response under immunotherapy. Ann Oncol. 2019; 30(3): 385–396, doi: 10.1093/annonc/mdz003, indexed in Pubmed: 30657859.
40. Tazdait M, Mezquita L, Lahmar J, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer. 2018; 88: 38–47, doi: 10.1016/j.ejca.2017.10.017, indexed in Pubmed: 29182990.
41. Liniker E, Menzies AM, Kong BY, et al. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. Oncoimmunology. 2016; 5(9): e1214788, doi: 10.1080/2162402X.2016.1214788, indexed in Pubmed: 27757312.
42. Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013; 19(14): 3936–3943, doi: 10.1158/1078-0432.CCR-13-0895, indexed in Pubmed: 23743568.
43. Seymour L, Bogaerts J, Perrone A, et al. RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017; 18(3): e143–e152, doi: 10.1016/S1470-2045(17)30074-8, indexed in Pubmed: 28271869.

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CASE REPORT

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Small cell neuroendocrine carcinoma of the bladder with synchronous Warthin's tumor of the parotid gland: A rare case and overview of the literature

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0002

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. Neuroendocrine tumors (NETs) develop from the epithelium rich in enterochromaffin cells. NETs most commonly originate from the gastrointestinal and respiratory tract. NETs rarely occur in the urinary bladder. Synchronous tumor is defined as having two different tumors growing at the same time in an organ. NETs are frequently associated with synchronous or metachronous second-primary malignancies. In this paper, we describe a synchronous tumor: a small cell neuroendocrine carcinoma (SCNEC) of the bladder and a Warthin's tumor (WT) of the parotid gland, both of which are highly rare in the literature.

Case report. A 79-year-old male patient was admitted to the hospital with gross hematuria and nodular mass involving the wall of the urinary bladder. The bladder neck resection and transurethral bladder resection (TURB) were performed. The tumor consisted of small, uniform, round, and spindled-shaped cells with chromatin dark nuclei and numerous mitotic figures. The cells were immunoreactive for CD56, synaptophysin (diffuse), and keratin (focal). The diagnosis of SCNEC with focal urothelial carcinoma in situ component was established. PET-CT was performed for staging purposes, and it showed a residual/recurrent tumor behind the lumen of the bladder floor and two nodular lesions with metabolic activity in the left parotid. After the biopsy of the parotid gland, it was diagnosed as WT. No metastasis of SCNEC was found at the time of diagnosis, and the patient received four cycles of induction chemotherapy (Etoposide combined with carboplatin chemotherapy) followed by chemoradiotherapy.

Conclusion. In this case report, an extremely rare case of primary SCNEC of the bladder with synchronous of the parotid gland is presented, along with a discussion on the clinical presentation, immunohistochemical and cytomorphological characteristics, management, biological behavior, and prognosis.

Key words: small cell bladder carcinoma, small cell carcinoma, synchronous cancers, Warthin's tumor, urothelial carcinoma in situ

Oncol Clin Pract 2022; 18, 2: 128–133

Introduction

Neuroendocrine tumors (NETs) develop from the epithelium rich in enterochromaffin cells. NETs comprise small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC), well-differentiated neuroendocrine tumor, and paragangliomas [1]. NETs most commonly originate from the gastrointestinal and respiratory tract. NETs rarely occur in the urinary bladder.

NETs are frequently associated with synchronous or metachronous second primary malignancies [2].

Received: 12.08.2021 Accepted: 30.08.2021 Early publication date: 20.01.2022

Though the cause and developmental mechanisms of multiple primary tumors are not fully understood, various factors including immune deficiency, genetic instability, increased use of systemic chemotherapy and radiotherapy, increased survival, elderliness, and smoking have been implicated. SCNEC of the bladder is a quite rare neoplasm and comprises less than 1% of all bladder malignancies [1, 3].

SCNEC of the bladder has a strong male predilection and most commonly presents in the seventh decade, with a mean age of presentation at approximately 67 years [3].

Risk factors are not well-defined; however, these tumors are more prominent in smokers suffering from longstanding cystitis and bladder stones [4–5].

SCNEC of the bladder is a highly aggressive tumor, nevertheless, these tumors are chemotherapy-sensitive and are often managed with a multi-disciplinary approach due to their highly malignant potential.

The Warthin's tumor (WT) is the second most common benign salivary gland tumor and is located almost exclusively in the parotid gland [6]. Like SCNEC of the bladder, WT occurs between the sixth and seventh decades when the male gender is dominant and is associated with smoking [7].

Nonetheless, the cases of small cell cancer of the bladder and synchronous tumors are rarely reported in the literature [2, 8–9].

In the present study, this rare case of SCNEC+ in situ urothelial carcinoma (UCI) of the bladder with synchronous WT of the parotid gland is presented, along with a discussion on the clinical presentation, immunohistochemical (IHC), and cytomorphological characteristics, management, biological behavior, and prognosis of this disease.

Case report

A 79-year-old ex-smoker man who had complained for 6 months of intermittent painful gross hematuria was admitted to the hospital in December 2020. A 60 x 30 mm homogeneously contrasted mass extending to the ureterovesical junction at the bladder floor and right grade-3/4 hydroureteronephrosis were detected in Ultrasonography and contrast-enhanced computed tomography (CT). Bladder neck resection and transurethral bladder resection (TURB) with deep muscle biopsy were performed because the bladder neck was completely closed at cystoscopy. Histopathological (HP) examination revealed tumor tissue infiltrating into the lamina propria and deep muscles in all sections (Fig. 1A). A tumor is composed of nests of small round malignant cells with pyknotic round to oval nuclei and evenly dispersed salt and pepper chromatin and a scant amount of cytoplasm (Fig. 1B). Few comedo necrosis foci and increased atypical mitosis were also noted (Fig. 1C). Lymphovascular and perineuronal tumor invasion was observed. IHC studies showed positivity for CD56 (Fig. 1D) and synaptophysin (Fig. 1E). However, the tumor was negative for chromogranin, CD45, TTF-1, and GATA3. Ki-67 labeling index showed a very high proliferation fraction of virtually 95% (Fig. 1F).

In addition, UCI, which is the second lesion consisting of cells with large irregular hyperchromatic nuclei in one area, was observed. Significant nuclear pleomorphism, a high N/C ratio, and mitotic figures in the upper epithelium were observed in this area. There was full-thickness atypia (Fig. 2A). IHC studies showed positivity for CK20 full-thickness (Fig. 2B–2C), and Ki-67 positivity was seen extending to the upper

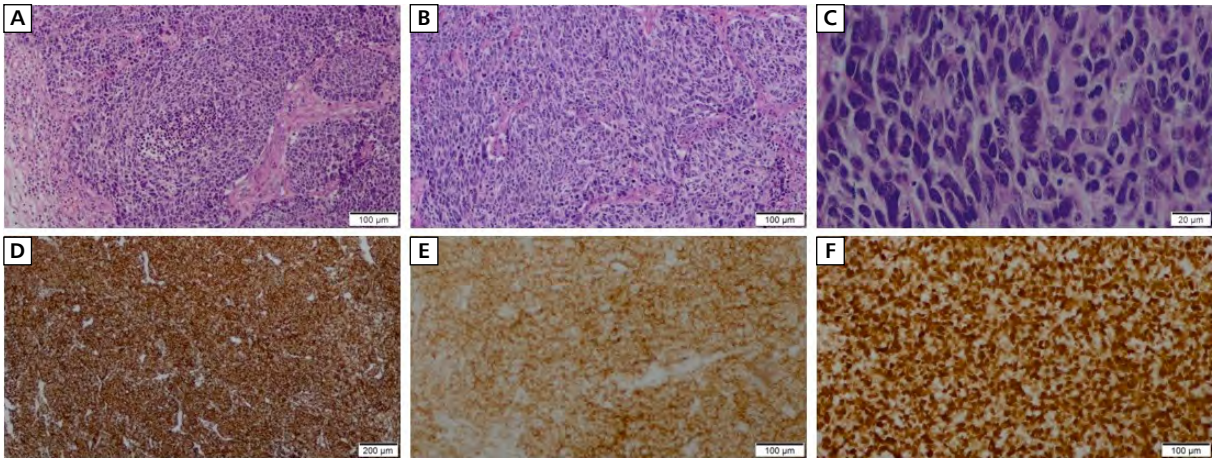

Figure 1. SCNEC of bladder; **A.** Comedonecrosis, apopitoticdebris,muscleinvasion (H&E ×10); **B.** Tumor composed of nests of malignant small round/spindle cells arranged in sheets (H&E, ×10); **C.** High power showing oval to spindle-shaped nucleus with salt and pepper chromatin with many pyknotic nucleiandatipikmitoticfigures (H&E × 40); **D.** Tumor cells with synaptophysin positivity (×4); **E.** CD 56 positivity (×10) and **F.** Ki-67 labelling index of 95%

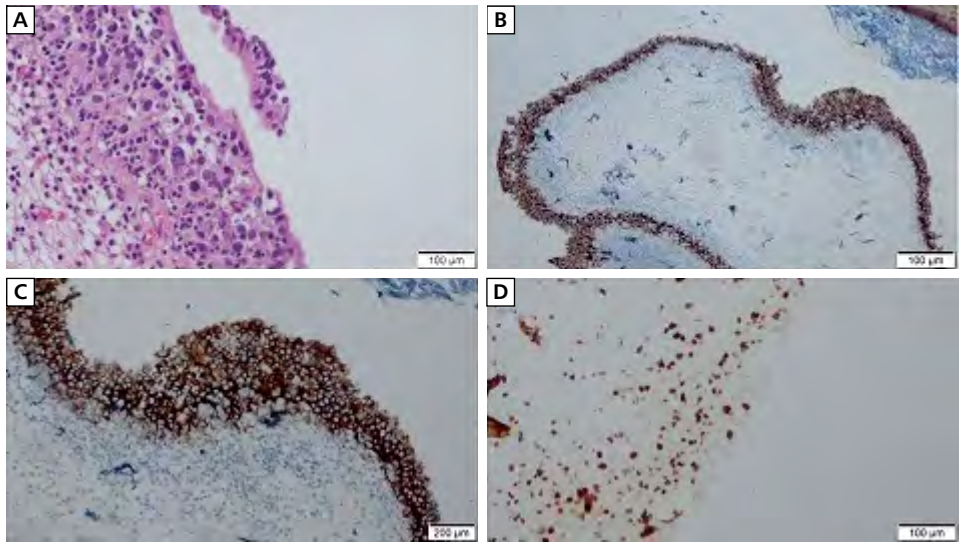

Figure 2. Carcinoma in situ; **A.** H&E; **B, C.** CK20; **D.** Ki–67

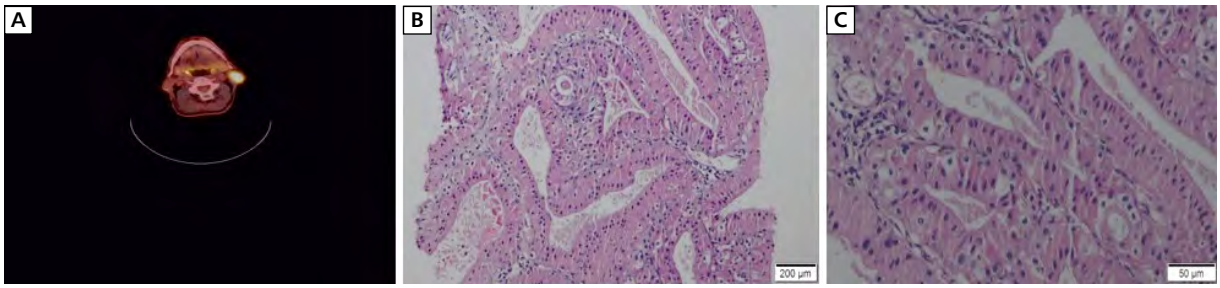

Figure 3. Warthin's tumor; **A.** Parotid gland PET-CT; **B.** Tubular masses of cells; **C.** With a two rows of pink (eosinophilic) epithelial cells (with cuboidal basal cells and columnar luminal cells)

level of the epithelium (Fig. 2D). The final pathological outcome was diagnosed as muscle-invasive SCNEC of the bladder.

PET-CT was performed for staging purposes for the patient. Residual/recurrent tumor growing posteriorly to the lumen of the bladder floor, approximately 3 cm in diameter (SUVmax: 16.06) (Fig. 4A–4B), two nodular lesions in the left parotid gland (SUVmax: 20.76) with metabolic activity (SUVmax: 20.76) (Fig. 3A), the left preauricular 9 mm diameter (SUVmax: 5.67), and the left parotid gland inferior to 9 mm diameter (SUVmax: 7.28) nodular lesions were detected on the PET-CTNo metastasis was identified in on other organ systems.

A tumor consisting of papillary and tubular structures containing cystic spaces was observed in the biopsy of the parotid gland. The tumor consisted of papillary structures lined by bi-layered oncocytic epithelium and enclosing a scant amount of lymphocytic infiltrate (Fig. 3B–3C).

The multidisciplinary tumor board planned induction chemotherapy followed by concurrent chemoradiotherapy treatment for the non-metastatic SCNEC of the bladder, and it was decided to follow the synchronous WT of the parotid gland.

Etoposide combined with carboplatin chemotherapy was planned for the patient with ECOG (Eastern Coope--rative Oncology Group), the performance status was 2.

After 3 cycles of chemotherapy, the mass in the bladder in the previous PET-CT disappeared, and other findings were stable (Fig. 4C–4D). After 4 courses of chemotherapy were completed, definitive weekly carboplatin (AUC: 2) concurrent radiotherapy was started and the patient's treatment is still ongoing. After finishing the bladder treatment, if there is still no progression, parotid tumor surgery will be planned.

Discussion

SCNEC of the bladder is a rare aggressive malignant neoplasm with a high incidence of local recurrence and metastasis. Smoking is the most important risk factor [3]. No consensus exists regarding the origin and

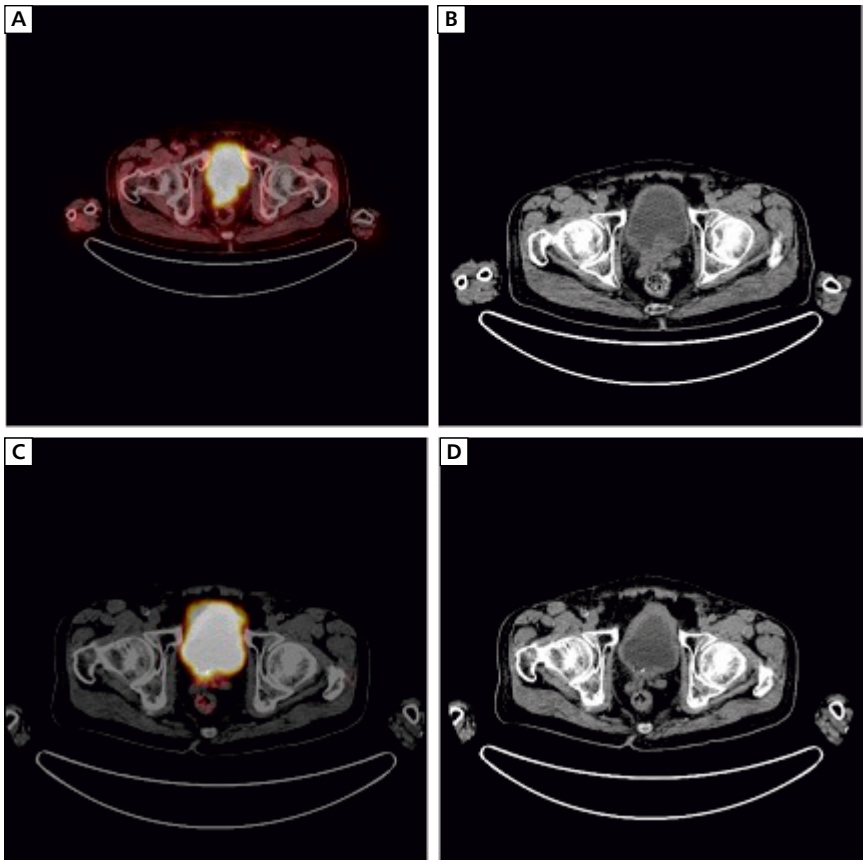

Figure 4. Positron emission tomography-computed tomography (PET-CT) mass in the posterior wall of the urinary bladder; **A.** PET-CT with FDG; B. PET-CT without FDG, the image where the mass in the bladder disappeared after post-chemotherapy treatment; **C.** PET-CT with FDG; **D.** PET-CT without FDG

histogenesis of SCNEC of the urinary bladder. Yet, metaplastic differentiation from transitional cell carcinoma has been suggested. The most common clinical presentation is hematuria, which might be accompanied by pain and dysuria.

Diagnosis of primary SCNEC of the bladder mainly depends on histopathology, immunohistochemistry, and cytomorphological characteristics, which is similar to SCNEC in the lung and other tissues. The differential diagnosis includes high-grade urothelial carcinoma (lymphoma-like variant), lymphoma, and metastatic malignant neoplasms.

Our case was an elderly male smoker, who presented with hematuria and dysuria as reported in the literature. HP and IHC findings were similar to small cell lung cancer. Cancers included in the differential diagnosis were ruled out with IHC findings, and the final diagnosis was made as SCNEC of bladder including UCI of the bladder.

Wang et al. performed clinicopathological and IHC analysis of 81 cases of SCNEC of the bladder. They reported 66% of SCNEC to be mixed with other carcinomas, most commonly urothelial carcinoma (UC) (40%) and UCI (32%) [3].

Chen et al. [10] found these rates as UC 56.3% and UCI 5.3% in the 128 Chinese patients with SCNEC of the bladder. On the other hand, in the report of Nicholas W. et al. [11], 61.4% of forty-four patients with primary bladder SCNEC had pure SCNEC.

Cheng et al. [12] analyzed the heterozygous loss patterns of SCNEC of bladder with the comparable UC and concluded that SCNEC of bladder and UC had nearly identical allelic loss patterns, implying a common clonal precursor origin. Nevertheless, further genetic and molecular studies are required to explore the oncogenesis of bladder SCNEC.

Wang et al. [3] found no significant difference in survival rates between patients with pure SCNEC of bladder and mixed histology in their study. A similar result was reported in the 2020 review by Vericco et al. [2] On the contrary, publications are suggesting pure SCNEC of bladder is associated with a worse prognosis than SCNEC of bladder mixed with other histology [13, 14].

Since SCNEC of the bladder is a clinically rare tumor, no standard treatment exists. In the study of Wang et al., the median survival time for patients who received neoadjuvant chemotherapy before cystectomy

was longer (38 months) than for patients who did not (12 months), and longer survival (> 60 months) has been reported in patients with the bladder-localized disease who received neoadjuvant chemotherapy [3]. Similarly, Lynch et al. [15] reported in 16 patients with long-term survival that radical cystectomy after neoadjuvant chemotherapy is an effective approach in the treatment of patients with bladder-localized SCNEC. In our case, the tumor was muscle-invasive, and distant organ metastasis was not observed. In the treatment response evaluation after 3 cycles of neoadjuvant chemotherapy, the mass has disappeared and other findings were stable.

Verrico et al. showed an increased risk of second cancer following NETs in their study evaluating the incidence of additional malignancies in patients with NETs. In this single-institution retrospective review, the incidence of additional malignancies in patients with NETs was 11.4% [2]. Although few similar studies exist, these studies also reported similar results [16, 17]. However, in these studies, very few or no reports of synchronous or metachronous tumors with Neuroendocrine tumors of the bladder were reported. To date, five cases of multiple primary tumors with synchronous/metachronous with bladder NETs have been reported in the literature. Three of these case reports involved multiple primary tumors with SCNEC of bladder: one with squamous cell carcinoma of the lung and esophagus [9], one with prostatic ductal adenocarcinoma, and penile squamous cell carcinoma [8], and one with Chronic lymphocytic leukemia [18]. Two of these cases were multiple primary tumors with non-subtype specified neuroendocrine tumors [2, 17].

Although multiple primary tumors might emerge at any age, they are reported to be more common in elder patients [16]. This result can be explained by reasons such as the duration of carcinogenesis, the insensitivity of aged tissues to carcinogens, and weakening of immunity with aging [19]. Synchronous tumors are associated with organ-specific carcinogens, such as smoking and alcohol. Hence, synchronous tumors tend to involve the aerodigestive and urinary tract (head-neck, lung, and upper esophagus) and are usually associated with smoking.

In our case, the WT was present in the parotid gland as the synchronous second primary tumor. Synchronized SCNEC of bladder + UCIS/WT is not associated with any known syndrome. The causal risk factors we could identify were smoking and elderliness, which could explain synchronous bladder and WT. Although high-grade NETs of the bladder determined the prognosis and survival as in our case, second primary tumors of the bladder NETs should be kept in mind as in other organ NETs, and further diagnostic evaluations should be made in suspicious lesions.

In conclusion, SCNEC of bladder is a rare aggressive malignant neoplasm with the diagnosis mainly depending on histopathology and immunohistochemistry.

After the diagnosis of NETs, second cancer formation should be kept in mind and monitored closely.

Despite the poor prognosis associated with SCNEC of the bladder, a good response to chemotherapy is obtained.

Conflict of interest

The authors have declared no conflicts of interest.

References

1. Kouba E, Cheng L. Neuroendocrine Tumors of the Urinary Bladder According to the 2016 World Health Organization Classification: Molecular and Clinical Characteristics. Endocr Pathol. 2016; 27(3): 188–199, doi: 10.1007/s12022-016-9444-5, indexed in Pubmed: 27334654.
2. Verrico M, Rossi L, Tomao S, et al. Metachronous and Synchronous Cancers in Patients with Neuroendocrine Tumors. Oncology. 2020; 98(1): 10–15, doi: 10.1159/000502384, indexed in Pubmed: 31505502.
3. Wang G, Xiao Li, Zhang M, et al. Small cell carcinoma of the urinary bladder: a clinicopathological and immunohistochemical analysis of 81 cases. Hum Pathol. 2018; 79: 57–65, doi: 10.1016/j.humpath.2018.05.005, indexed in Pubmed: 29763719.
4. Alijo Serrano F, Sánchez-Mora N, Angel Arranz J, et al. Large cell and small cell neuroendocrine bladder carcinoma: immunohistochemical and outcome study in a single institution. Am J Clin Pathol. 2007; 128(5): 733–739, doi: 10.1309/HTREM6QYQDYGNWYA, indexed in Pubmed: 17951193.
5. Li Z, Lin C, Wang D, et al. Primary small-cell neuroendocrine carcinoma of the urinary bladder: A rare case and a review of the literature. Mol Clin Oncol. 2018; 9(3): 335–338, doi: 10.3892/mco.2018.1679, indexed in Pubmed: 30155256.
6. Dżaman K, Pietniczka-Załęska M, Piskadło-Zborowska K, et al. Parotid gland tumours in the ENT Department in Międzyleski Hospital in Warsaw between 2007 and 2014. Otolaryngol Pol. 2016; 70(1): 34–40, doi: 10.5604/00306657.1193068, indexed in Pubmed: 26926306.
7. Peter Klussmann J, Wittekindt C, Florian Preuss S, et al. High risk for bilateral Warthin tumor in heavy smokers--review of 185 cases. Acta Otolaryngol. 2006; 126(11): 1213–1217, doi: 10.1080/00016480600740605, indexed in Pubmed: 17050316.
8. Ogawa S, Yasui T, Taguchi K, et al. The probability of involvement of human papillomavirus in the carcinogenesis of bladder small cell carcinoma, prostatic ductal adenocarcinoma, and penile squamous cell carcinoma: a case report. BMC Res Notes. 2014; 7: 909, doi: 10.1186/1756-0500-7-909, indexed in Pubmed: 25512116.
9. Tamura K, Inoue K, Fukata S, et al. Small cell carcinoma of the urinary bladder with synchronous esophageal cancer and incidental lung cancer: a case report. Hinyokika kiyo Acta urologica Japonica. 2001; 47(4): 273–276.
10. Chen Z, Liu Q, Chen R, et al. Clinical analysis of small cell carcinoma of the bladder in Chinese: nine case reports and literature reviews. World J Surg Oncol. 2017; 15(1): 33, doi: 10.1186/s12957-016-1079-y, indexed in Pubmed: 28125986.
11. Choong NWW, Quevedo JF, Kaur JS. Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer. 2005; 103(6): 1172–1178, doi: 10.1002/cncr.20903, indexed in Pubmed: 15700264.
12. Cheng L, Jones TD, McCarthy RP, et al. Molecular genetic evidence for a common clonal origin of urinary bladder small cell carcinoma and coexisting urothelial carcinoma. Am J Pathol. 2005; 166(5): 1533–1539, doi: 10.1016/S0002-9440(10)62369-3, indexed in Pubmed: 15855652.
13. Pasquier D, Barney B, Sundar S, et al. Small Cell Carcinoma of the Urinary Bladder: A Retrospective, Multicenter Rare Cancer Network Study of 107 Patients. Int J Radiat Oncol Biol Phys. 2015; 92(4): 904–910, doi: 10.1016/j.ijrobp.2015.03.019, indexed in Pubmed: 26104942.
14. Cheng L, Pan CX, Yang XJ, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. Cancer. 2004;

101(5): 957–962, doi: 10.1002/cncr.20456, indexed in Pubmed: 15329903.
15. Ismaili N, Lynch SP, Shen Yu, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center. Eur Urol. 2013; 64(2): 307–313, doi: 10.1016/j.eururo.2012.04.020, indexed in Pubmed: 22564397.
16. Tsai HJ, Wu CC, Tsai CR, et al. Second cancers in patients with neuroendocrine tumors. PLoS One. 2013; 8(12): e86414, doi: 10.1371/journal.pone.0086414, indexed in Pubmed: 24392036.
17. Reina JJ, Serrano R, Codes M, et al. Second primary malignancies in patients with neuroendocrine tumors. Clin Transl Oncol. 2014; 16(10): 921–926, doi: 10.1007/s12094-014-1174-x, indexed in Pubmed: 24788817.
18. Vaidyanathan S, Mansour P, Soni BM, et al. Chronic lymphocytic leukaemia, synchronous small cell carcinoma and squamous neoplasia of the urinary bladder in a paraplegic man following long-term phenoxybenzamine therapy. Spinal Cord. 2006; 44(3): 188–191, doi: 10.1038/sj.sc.3101789, indexed in Pubmed: 16130025.
19. Balducci L, Beghe' C. Cancer and age in the USA. Crit Rev Oncol Hematol. 2001; 37(2): 137–145, doi: 10.1016/s1040-8428(00)00109-8, indexed in Pubmed: 11166587.

VIA MEDICA

CASE REPORT

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Resistance to neoadjuvant chemotherapy in breast cancer with proven intratumoral heterogeneity: a clinical case

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0015

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Breast cancer (BC) is the most common cancer in women in Bulgaria, with a frequency of 26.7% of all newly registered cancer cases in 2020 and ranks first in mortality. In recent years, research and studies have confirmed that breast cancer is a highly heterogeneous disease at the morphological, genomic, and transcriptomic levels, manifested clinically with different behavior and response to therapy. The gold standard for breast cancer diagnostic management is based upon three diagnostic methods, including clinical examination, imaging, and percutaneous biopsy. The main percutaneous biopsy method is an ultrasound-guided core-needle biopsy. It is sufficiently representative of the composition of the tumor although it represents a limited part of it, and some cellular subpopulations are often scantly represented or completely absent. We present a case of a 41-year-old breast cancer patient with primary intratumoral morphological heterogeneity diagnosed through core-needle biopsy and with primary resistance to neoadjuvant targeted therapy.

Key words: breast cancer, core-needle biopsy, intratumoral heterogeneity, non-adjuvant chemotherapy

Oncol Clin Pract 2022; 18, 2: 134–138

Introduction

Breast cancer is the most common cancer in women. In Bulgaria, it ranks first in mortality among cancers in women. In 2020, the number of new cases in the 27 countries of the European Union (EU) was 355 457, with an estimated annual frequency of 142.8/100,000 population. For Bulgaria, the frequency is 100/100 000, i.e. 26.7% of all newly registered oncological diseases in women. The mortality in Bulgaria is higher than the average for the European Union, 36.3/100,000 compared to 34.1/100,000 population [1].

In recent years, studies have confirmed that breast cancer is highly heterogeneous at the morphological, genomic, and transcriptomic levels, manifesting clinically with different behavior and different responses to therapy. Many of the therapeutic solutions, and neoadjuvant chemotherapy (NACT) in particular, are based on the possibility of a complete pathological response. Most often, it is achieved with targeted therapy, based on the molecular subtype of cancer, i.e. molecular markers expressed from the cancer cells found in the biopsy specimen. The samples taken by core-needle percutaneous biopsy (CNB) represent a limited part of the

Received: 12.12.2021 Accepted: 04.02.2022 Early publication date: 31.03.2022

tumor, where different cellular subpopulations are often scantly represented or completely absent [2]. However, a biopsy under ultrasound control is considered the gold standard in breast cancer diagnosis. The obtained biopsy samples are processed for histomorphological evaluation, including the morphological variant, degree of differentiation, invasiveness, expression of biomarkers, including steroid receptors (ER and PgR), HER 2 status, and proliferative index Ki-67. There is a statistically significant correlation between the results obtained in the pathological examination of tumor tissue taken by CNB and tissue taken by surgical excision, in which the available volume of pathological tissue is larger. Multiple authors have confirmed this view in their studies [3, 4]. The morphological heterogeneity is often accompanied by a heterogeneous expression of biomarkers, a fact that further complicates the choice of therapy. It calls into question the effect of NACT, which in some cases delays surgical intervention. Tumor heterogeneity has been associated with poorer prognosis and survival [5]. It is also the leading cause of therapeutic resistance [6].

A clinical case

We present a case of a 41-year-old breast cancer patient with core-needle biopsy-proven primary intratumoral morphological heterogeneity and primary resistance to chemotherapy.

The patient was admitted to the Surgical Oncology Clinic at Dr. Georgi Stranski University Hospital in Pleven, with complaints of a palpable mass in the left mammary gland dating back six months. The patient reported arterial hypertension and hypothyroidism as concomitant diseases treated with L-thyroxine and antihypertensive drugs. The clinical examination revealed a formation in the upper lateral quadrant of the left mammary gland near the nipple-areolar complex. It was a solid mass about 30 mm in diameter, painless, fused with the surrounding tissues, with no changes involving the skin. Enlarged solid lymph nodes of about 20 mm in diameter were also painless, palpated in the homolateral axilla. The mammography examination classified the finding as 4C according to the BI-RADS system with a recommendation for subsequent histological verification. Following a lidocaine susceptibility test, an ultrasound-guided core-needle biopsy (CNB) with local anesthesia and a fine-needle aspiration biopsy (FNA) of an enlarged homolateral axillary lymph node were performed. The samples were sent for histopathological and cytological examination. Findings from cytological examination demonstrated ductal carcinoma tumor cells arranged individually and in small groups, and the presence of lymphocytes and erythrocytes.

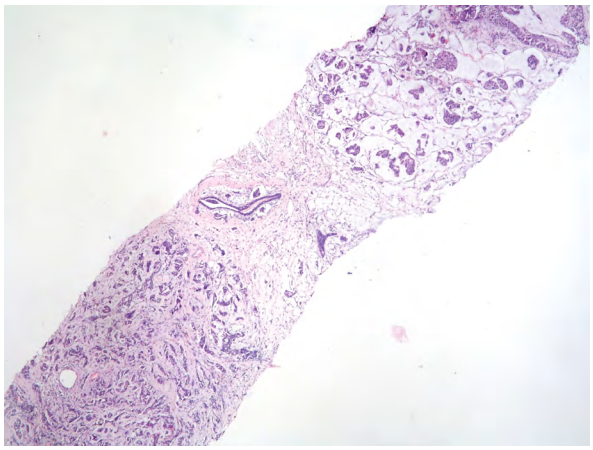

Figure 1. A heterogeneous tumor composed of two components mucinous (hypocellular variant) carcinoma and NST G2 carcinoma. HE 40×

The processing and immunohistochemical staining of the preparation was made according to the current standard laboratory protocols.

The histological evaluation of the core needle biopsy samples demonstrated 5 tissue cylinders containing mammary gland parenchyma infiltrated by tumor cells, composed of two morphologically distinct components (Fig.1).

Immunohistochemistry of the core needle biopsy demonstrated positivity for steroid receptors, HER2 was interpreted as equivocal (2+), and in situ hybridization was advised. In situ hybridization for HER2 demonstrated the presence of amplification. The proliferation index estimated by Ki-67 was about 35% (Fig. 2).

The patient was evaluated clinically as cT2N1M0, stage IIB, and the Medical Oncology Committee referred the patient for NACT. Four courses with docetaxel, trastuzumab, and pertuzumab at intervals of 21 days were applied. After the last course, a restaging was performed and showed no response to therapy. The physical exam revealed enlargement of the tumor lesion to 35 mm in diameter. The lymph nodes persisted up to 20 mm in diameter. CT results confirmed progression for the soft tissue lesion (26 × 24 mm) in the left mammary gland, which did not increase its density in post-contrast enhancement, and the pathologically enlarged lymph nodes (21 × 10 mm) to the left side. There was no CT data for dissemination to the internal organs and bone structures. The patient was referred for radical surgical treatment. A mastectomy with axillary lymph node dissection was performed.

After the breast was surgically removed, the breast specimen was cut in a standard manner and fixed in 10% NBF. A round, gray-white nonhomogeneous, infiltrative tumor with a cartilaginous density, and partly soft consistency measuring 50 × 45 × 30 mm was found. The axillary lymph nodes harvested from the axillary dissection were enlarged up to 25 mm.

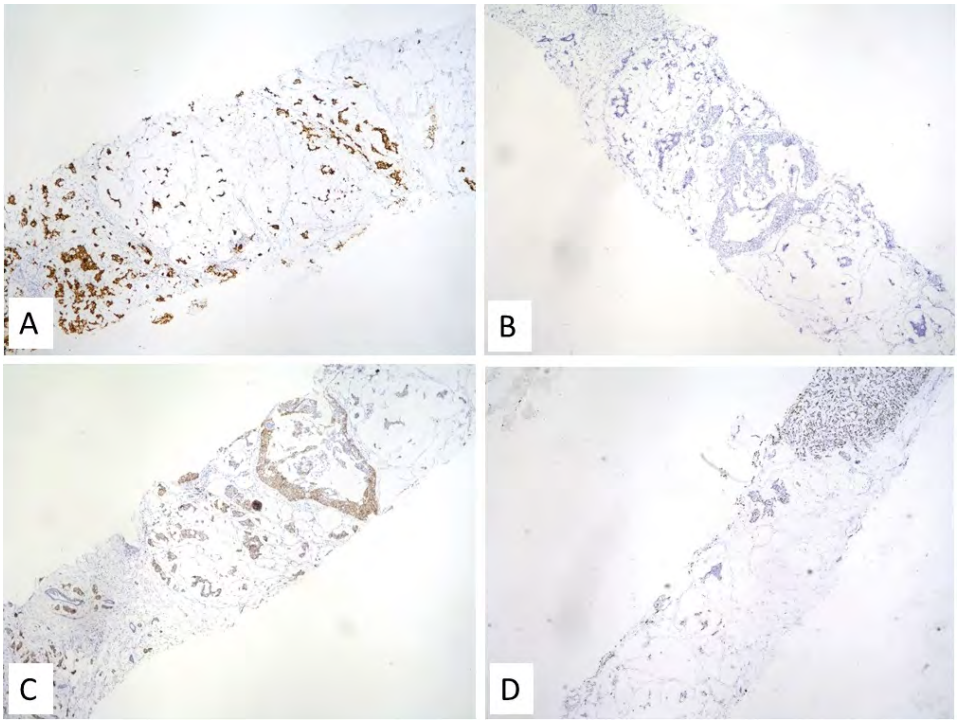

Figure 2. A. ER staining in the two components ER, 40×; **B.** PgR staining in the two components PgR, 40×; **C.** HER2 staining in the two components HER2, 40×; **D.** Ki-67 staining in the two components Ki-67, 40×

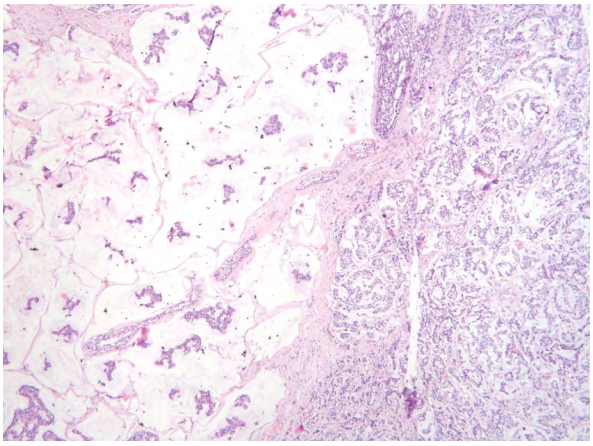

Figure 3. Heterogeneous tumor, composed of two components mucinous (hypocellular variant) carcinoma and NST G2 carcinoma. HE 40×

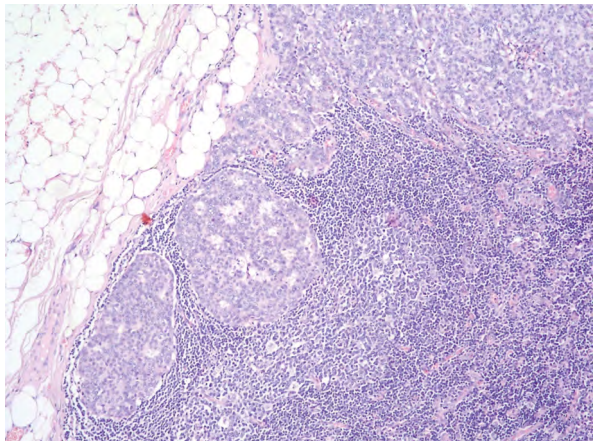

Figure 4. Lymph node metastasis HE 100×

A histopathological examination demonstrated the presence of a heterogeneous carcinoma, composed of mucinous (hypocellular variant) and NST G2 component with moderately desmoplastic stroma, vascular invasion, presence of DCIS-G2, usual ductal hyperplasia, columnar cell changes, and fibroadenomatoid hyperplasia (Fig. 3).

Metastases were obtained in 5 of the 18 evaluated lymph nodes. Additionally, focal necrosis cholesterol crystals and hemorrhages were found focally in some lymph nodes (Fig. 4).

Upon IHC retesting, the NST component demonstrated positivity for steroid receptors, equivocal (2+) result for HER2 (with amplification after in situ hybridization testing), and Ki-67 proliferation index of about 75%. The mucinous component demonstrated positivity for steroid receptors, negative (1+) result for HER2, and low Ki-67 proliferation index (Fig. 5).

The tumor response to therapy was limited. According to Sataloff criteria, it was estimated as T-D and N-D, respectively. The pathology report confirmed progression with pT3N2M0, stage IIIA.

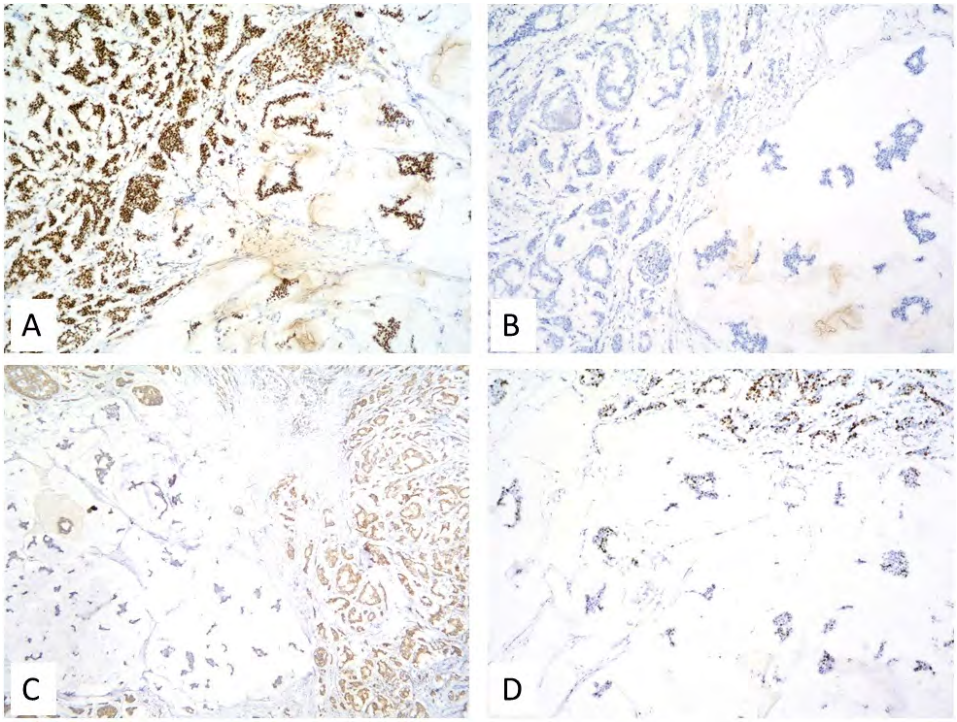

Figure 5. A. ER staining in the two components ER, 40×; **B.** PgR staining in the two components PgR, 40×; **C.** HER2 staining in the two components HER2, 40×; **D.** Ki-67 staining in the two components Ki-67, 40×

Discussion

Breast cancer is a heterogeneous disease involving many tumor subtypes characterized by different morphology, behavior, and clinical consequences [7]. Preoperative assessment of breast lesions and their histological verification are crucial for an accurate diagnosis, determining the appropriate therapeutic treatment plan and prognosis. According to the European Society for Medical Oncology (ESMO) Guidelines, the pathological diagnosis should be made after CNB under ultrasound control before starting any treatment. If preoperative systemic therapy (NACT) is required, an invasive process must be identified, and molecular biomarkers tested [8]. According to the recommendations of the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP), estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) should be routinely, immunohistochemically tested biomarkers in all primary histologically proven breast tumors [9] They are the basis of the molecular classification of breast tumors presented in 2000 by Perou et al. in an attempt to include the manifestation of genetic tumor heterogeneity in clinical practice [10].

In recent years, the proliferative index Ki-67, an element of the same classification, has also been studied. It has a predictive and prognostic value in clinical practice. It is a factor that can predict a complete pathological response in NACT [11]. Chemotherapy significantly improves survival in patients with breast cancer, and NACT has become an established first choice in the treatment of locally advanced large tumors, enhancing surgical success [12]. It is also increasingly used in patients in the early stages of the disease, with an unfavorable prognosis, mostly HER 2 positive and triple-negative breast cancers.

Neoadjuvant chemotherapy (NACT) allows evaluation of the therapy outcome and subsequent optimization of systemic therapy in the absence of response [13]. Preoperative therapy has been shown to lead to changes in tumor biomarkers, which is relevant to crucial for patients' subsequent prognosis and survival [12]. Excessively aggressive therapies select tumor cells and cell clones with a resistant phenotype. This leads to a rapid progression of the disease, making it virtually unresponsive to subsequent treatment [14].

The morphological heterogeneity is accompanied by molecular heterogeneity (heterogeneous immunomarker expression). Morphological heterogeneity is presented as different subpopulations within a single tumor and was described as early as the 1950s [15]. The existence of components with unclear morphological features or foci with different differentiation can also be attributed to morphological tumor heterogeneity and reflect different genetic aberrations [2]. They further

complicate the choice of therapy and question the effect of NACT, which can delay surgical treatment. In our case, the patient was in an advanced stage of the disease and was suitable for neoadjuvant targeted therapy with an expected complete pathological response. However, morphological heterogeneity together with the presence of heterogeneous molecular subtypes (marker expression) within the tumor mass resulted in a lack of therapeutic effect of the applied therapy, leading to prolongation of the time to surgical intervention and causing cancer progression. To optimize therapeutic effect in patients with morphological heterogeneity, additional research is required.

Conclusion

Tumor heterogeneity in breast cancer may be manifested in every characteristic of the disease, including histopathological, molecular, and functional. Additional genetic and epigenetic changes and various adaptive responses during the disease generate different cell populations that exacerbate tumor heterogeneity and lead to disease progression and drug resistance. Morphologically heterogeneous tumors and tumors demonstrating molecular heterogeneity cannot be classified and treated with established therapeutic standards. They require personalized therapy as they are often associated with therapeutic resistance and poor prognosis.

Conflict of interest

Authors declare no conflict of interest.

References

1. ECIS—European Cancer Information System. https://ecis.jrc.ec.europa.eu (21.07.2021).
2. Turashvili G, Brogi E. Tumor Heterogeneity in Breast Cancer. Front Med (Lausanne). 2017; 4: 227, doi: 10.3389/fmed.2017.00227, indexed in Pubmed: 29276709.
3. Parker SH, Jobe WE, Dennis MA, et al. US-guided automated large-core breast biopsy. Radiology. 1993; 187(2): 507–511, doi: 10.1148/radiology.187.2.8475299, indexed in Pubmed: 8475299.
4. Taki S, Kakuda K, Kakuma K, et al. US-guided core biopsy of the breast with an automated biopsy gun: comparison with an aspiration core needle device. Nihon Igaku Hoshasen Gakkai Zasshi. 1997; 57(1): 1–4, indexed in Pubmed: 9038055.
5. Baliu-Piqué M, Pandiella A, Ocana A. Breast Cancer Heterogeneity and Response to Novel Therapeutics. Cancers (Basel). 2020; 12(11): 3271, doi: 10.3390/cancers12113271, indexed in Pubmed: 33167363.
6. Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? Nat Rev Cancer. 2012; 12(5): 323–334, doi: 10.1038/nrc3261, indexed in Pubmed: 22513401.
7. Dai X, Xiang L, Li T, et al. Cancer Hallmarks, Biomarkers and Breast Cancer Molecular Subtypes. J Cancer. 2016; 7(10): 1281–1294, doi: 10.7150/jca.13141, indexed in Pubmed: 27390604.
8. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019; 30(8): 1194–1220, doi: 10.1093/annonc/mdz173, indexed in Pubmed: 31161190.
9. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med. 2020; 144(5): 545–563, doi: 10.5858/arpa.2019-0904-SA, indexed in Pubmed: 31928354.
10. Perou C, Sørlie T, Eisen M, et al. Molecular portraits of human breast tumours. Nature. 2000; 406(6797): 747–752, doi: 10.1038/35021093.
11. Fasching P, Heusinger K, Haeberle L, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer. 2011; 11(1), doi: 10.1186/1471-2407-11-486.
12. Zhou X, Zhang J, Yun H, et al. Alterations of biomarker profiles after neoadjuvant chemotherapy in breast cancer: tumor heterogeneity should be taken into consideration. Oncotarget. 2015; 6(34): 36894–36902, doi: 10.18632/oncotarget.5050, indexed in Pubmed: 26384297.
13. Candás G, García A, Ocampo M, et al. Impact of immunohistochemical profile changes following neoadjuvant therapy in the treatment of breast cancer. Ecancermedicalscience. 2021; 15: 1162, doi: 10.3332/ecancer.2021.1162, indexed in Pubmed: 33680076.
14. Cajal SR, Sesé M, Capdevila C, et al. Clinical implications of intratumor heterogeneity: challenges and opportunities. Journal of Molecular Medicine. 2020; 98(2): 161–177, doi: 10.1007/s00109-020-01874-2.
15. Heppner GH. Tumor heterogeneity. Cancer Res. 1984; 44(6): 2259–2265, indexed in Pubmed: 6372991.