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Guidelines and recommendations

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Diagnostic and therapeutic management of patients with ocular melanomas – recommendations of the Polish Society of Oncology

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Uveal melanoma is the most common malignant neoplasm of the eyeball, developing from melanocytes of the uveal membrane of the eye, which is significantly different from melanoma of the conjunctiva, mucous membranes and skin. The management of this disease is therefore different from that of other forms of melanoma. The disease is most often confined to the eye and its local treatment includes radiation therapy and surgery. Some patients, despite successful local treatment, develop distant metastases, most often located in the liver. The guidelines presented here cover the principles of diagnosis, prognostic evaluation and treatment of both the disease confined to the eyeball and the disease at the metastatic stage. The principles of management of conjunctival melanoma are also discussed. The recommendations are based on a review of the literature and expert opinion, and are accompanied by an assessment of their strength and reliability.

Key words: ocular melanoma, conjunctival melanoma

Introduction

According to the authors and editors, recommendations contain the most reasonable principles of diagnostic and therapeutic management. They were prepared by taking into account the value of scientific evidence and categories of recommendations. The management principles should always be interpreted in the context of the individual clinical situation. The recommendations do not always correspond to the current reimbursement rules that apply in Poland, and this is described in the text. When in doubt, current reimbursement options for particular procedures should be determined.

The quality of scientific evidence and recommendation categories were determined according to the following criteria.

1. Quality of scientific evidence:
   - I. Evidence from at least one large randomized controlled trial (RCT) of high methodological quality (low risk of bias) or meta-analysis of correctly designed RCTs without significant heterogeneity.
   - II. Small RCTs or large RCTs with risk of bias (lower methodological quality) or meta-analyses of such studies or RCTs with significant heterogeneity.
   - III. Prospective cohort studies.

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

2. Strength of recommendations:
   1. Recommendation based on high-quality evidence for which the expert panel has reached unanimity or a high level of consensus.
   2A. Recommendation based on lower-quality evidence for which the expert panel has reached unanimity or a high level of consensus.
   2B. Recommendation based on lower-quality evidence for which the expert panel reached a moderate level of consensus.
   3. Recommendation based on evidence at any level of quality, for which the expert team did not reach consensus.

Scope and purpose of the guidelines

The guidelines provide recommendations for the prevention, diagnosis and treatment of uveal melanomas and melanomas of the conjunctiva. They are addressed to those responsible for organizing and providing care for melanoma patients at all levels of health care, including physicians, nurses and pharmacists. The guidelines were created – based on available scientific evidence – to systematize and standardize clinical practice, and thus provide patients with the best possible care.

The document presents a range of diagnostic and therapeutic options that allow clinicians to choose the most appropriate management for each patient. The guidelines outline interventions that may be preferred due to their efficacy and safety profile compared to other medical technologies. In addition, the guidelines identify publicly funded methods in the Polish health care system and include an analysis of the effectiveness of alternative treatment options (including those that are not reimbursed).

Methodology

To find relevant scientific evidence, a non-systematic search of clinical practice guidelines was conducted and medical information databases were searched. The search for clinical practice guidelines included recommendations for the diagnostic and therapeutic management of uveal and conjunctival melanoma published in Polish, English and German between 2016 and 2021. Recommendations from the European Society of Medical Oncology (ESMO), American Society of Surgical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), American Academy of Dermatology (AAD) were included in the review, European Association of Dermato-Oncology (EADO), Scottish Intercollegiate Guidelines Network (SIGN), Cancer Council Australia (CCA), Japanese Dermatological Association (JDA), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) and Polish Society of Clinical Oncology (PTOK).

A non-systematic search of medical information databases (PubMed) was also conducted to obtain key literature. The review included all phase II and III clinical trials published between 1990 and 2021, which included the keywords ocular melanoma, uveal melanoma and conjunctival melanoma. The recommendations in the guidelines are derived from a critical appraisal of the evidence, combined with the clinical expertise and consensus of a multidisciplinary panel of specialists. They were written in accordance with the principles for formulating and adopting recommendations described in the document Consensus on Methodology for Developing Clinical Practice Guidelines in Oncology under the auspices of the National Cancer Institute and the Agency for Health Technology Assessment and Tarification [1]. The panel of specialists worked together on the final document in the form of consensus (no dissenting opinions were submitted), and the document was available to all panel members at all times. All panelists completed conflict of interest disclosure statements, and potential conflicts of interest were presented.

Ocular melanoma

Uveal melanoma

Epidemiology and etiology

Uveal melanoma is the most common malignant primary intraocular neoplasm in adults [2–6]. It is significantly different from melanoma of the conjunctiva, mucous membranes, and skin [7]. According to 2018 data from the National Cancer Registry (KRN – Krajowy Rejestr Nowotworów), ocular malignancies (C69) account for 0.3% of all cancers in Poland (523 cases), most of which are uveal melanoma. The mortality for this was 0.1% (121 deaths) [8]. Its incidence varies by race and latitude. The incidence is highest among Caucasians (98% of all patients) and at higher latitudes. In Mediterranean countries it is 2 new cases per 1 million inhabitants per year, while in Scandinavian countries it is 8–11/1 million inhabitants. In the United States, there is an average of 4.3 new cases per year per 1 million people [4, 6, 9, 10].

Children rarely develop this type of cancer, and their prognosis is significantly better (5- and 10-year survival rates are 97% and 92%) [11, 12].

Uveal melanoma develops from melanocytes of the uveal membrane, occupying different parts of it with varying frequencies. It is found in the iris in about 4–6%, in the ciliary body in 6–9%, and most often in the choroid in 85–90% [2, 13, 14].

Staging and prognostic factors

The prognosis of uveal melanoma depends on many factors. One of them is the size of the primary tumor (largest base diameter and height). Larger tumors offer a lower chance of survival. Increasing the height of the tumor by 1 mm increases the risk of metastasis by 5% over 10 years [3, 15]. Based on the assessment of thickness (height), tumors were divided into small (small; 0–3 mm), medium (medium; 3.1–8.0 mm)

and large (large; >8 mm). The 5-, 10- and 20-year mortality rates were 6%, 12% and 20% in each group, followed by 14%, 26% and 37%, and 35%, 49% and 67% in the last group, respectively [3, 15]. Another factor that negatively affects prognosis is tumor involvement of the ciliary body. In this case, 33% of patients develop metastases within 10 years of follow-up. When the tumor involves the iris, metastasis occurs in 7% of patients, and when it involves the choroid – in 25%.

Other factors that worsen the prognosis and are associated with a higher propensity for metastasis are the following histopathological features:

- epithelioid type of melanoma,
- deep infiltration of the eyeball wall (sclera),
- presence of extraocular infiltration,
- high mitotic index,
- infiltration of the optic nerve,
- intrinsic vascularization of the tumor with a tendency to form arches, branches, closed loops and vascular networks,
- inflammatory infiltration in the tumor mass (especially T lymphocytes and macrophages) [2, 16, 17].

Genetic disorders such as monosomy of chromosome 3, multiple copies of 1q, 6p and 8q, loss of 1p, 6q and 8p, and mutations of the BAP1, GNAQ and GNA11 genes are associated with a high risk of metastasis [2, 18]. In contrast, mutation in the EIF1AX gene is associated with a good prognosis [2, 18]. Genetic testing is not recommended for routine use, although it may influence the pattern of follow-up testing after local treatment (IV, 2B).

Local control after treatment of ocular choroidal melanoma is very high (86–98%) and is achieved by various conservative treatments, such as brachytherapy, proton therapy, transpupillary thermotherapy (TTT), endo- or exoresection of the tumor, and various combinations of these (II, 2A) [2, 19]. In very large tumors, i.e., those with a base diameter greater than 20 mm or a height greater than 12 mm, and if the neoplasm substantially occupies the optic nerve disc, the best treatment is still surgery to remove the eyeball [20] (III, 2A). A big problem in this condition is still the approximately 50% mortality rate due to generalized dissemination, for which treatment options are still limited [2, 21]. In more than 90% of cases, metastasis localizes to the liver, despite good local treatment [2, 21]. This is due to the propensity of uveal melanoma to form micro-metastases in the early stages and the presence of tumor cells in the vascular bed before treatment [2, 21].

The AJCC TNM classification developed by the American Joint Committee on Cancer is used in the staging and prognosis of uveal melanoma, which takes into account the size of the largest tumor base, its thickness (height), involvement of the ciliary body, the presence and size of extraocular infiltration, and the presence of metastases [22]. Regional lymph node involvement in uveal melanoma is extremely rare [23] (tab. I). To assess the risk of metastasis, the genetic analyses mentioned above should also be considered, with chromosome 3 monosomy and BAP1 mutations [2] being the first consideration (III, 2B).

Symptoms

About $^{1}/_{3}$ of patients with uveal melanoma report no symptoms, or if any occur, they are uncharacteristic [24]. Among the most common are decreased visual acuity and visual field abnormalities. There may also be pain due to elevated intraocular pressure values, and there may be a "veil" in front of the eye or distorted vision [24].

Diagnostic examinations

1. Anterior ophthalmoscopic examination under a slit lamp (III, 2A).
2. Fundus examination after pupil dilation (indirect ophthalmoscopy preferred) (III, 2A).
3. Ultrasound examination (III, 2A):
   a) ultrabiomicroscopy – ultrasonography of the anterior segment of the eyeball, ciliary body and anterior choroid,
   b) ultrasonography of the posterior segment of the eyeball (finding a mycotic tumor shape is a typical feature of uveal melanoma).
4. Optical coherence tomography (OCT) (III, 2A).
5. Photography of the observed lesion to determine possible progression (III, 2A).
6. Gonioscopy – when a lesion is suspected to occupy or reach the iridocorneal angle (III, 2A).
7. Diaphanoscopy, or transillumination (makes the base of the tumor visible) (III, 2A).
8. Additional examinations (performed when there is diagnostic doubt) (III, 2B):
   a) fluorescein angiography,
   b) indocyanine angiography,
   c) computed tomography of the orbits,
   d) magnetic resonance imaging of the orbits,
   e) autofluorescence [19].
9. Tumor biopsy, is still controversial due to the increased risk of tumor dissemination and the high rate of false negative results [25] (III, 2A) [26] (NCCN Guidelines. Uveal Melanoma. Version 3.2020).

Differential diagnosis

Uveal melanoma needs to be differentiated from metastatic tumors of other locations and from pigmented nevi [19, 27]. It is very important to distinguish an atypical pigmented nevus from a small melanoma (TFSOM rule developed by Shields et al.) [28] (III, A). Less commonly considered in the differential diagnosis are:

- choroidal hemangioma (limited or diffuse),
- intraocular lymphoma,
- retinal hemangiomas,
- osteoma,

Table I. Primary tumors – T feature

T (primary tumor)	Disease staging
all uveal membrane melanomas of the eyeball	
TX	primary tumor cannot be evaluated
T0	no primary tumor is found
iris	
T1	tumor limited to the iris
T1a	tumor limited to the iris, not more than 3 clock hours in size
T1b	tumor limited to the iris more than 3 clock hours in size
T1c	tumor limited to the iris with secondary glaucoma
T2	tumor confluent with or extending into the ciliary body, choroid or both
T2a	tumor of the iris involving the ciliary body, without secondary glaucoma
T2b	iris tumor involving the choroid, without secondary glaucoma
T2c	iris tumor involving the ciliary body and/or choroid, with secondary glaucoma
T3	iris tumor involving the ciliary body and/or choroid with scleral infiltration
T3a	iris tumor involving the ciliary body and/or choroid with infiltration of the sclera and secondary glaucoma
T4	melanoma with extrascleral extension
T4a	tumor with extrascleral extension less than or equal to 5 mm in diameter
T4b	tumor with extrascleral extension more than 5 mm in diameter
ciliary body and choroid	
T1	tumor size category 1
T1a	tumor size category 1 without ciliary body involvement and extraocular extension
T1b	tumor size category 1 with ciliary body involvement
T1c	tumor size category 1 without ciliary body involvement, and with extraocular extension less than or equal to 5 mm in diameter
T1d	tumor size category 1 with involvement of the ciliary body and with extraocular extension less than or equal to 5 mm in diameter
T2	tumor size category 2
T2a	tumor size category 2 without ciliary body involvement and extraocular extension
T2b	tumor size category 2 with ciliary body involvement
T2c	tumor size category 2 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T2d	tumor size category 2 with involvement of the ciliary body and with extraocular extension less than or equal to 5 mm in diameter
T3	tumor size category 3
T3a	tumor size category 3 without ciliary body involvement and extraocular extension
T3b	tumor size category 3 with ciliary body involvement
T3c	tumor size category 3 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T3d	tumor size category 3 with ciliary body involvement and with extraocular extension less than or equal to 5 mm in diameter
T4	tumor size category 4
T4a	tumor size category 4 without ciliary body involvement and extraocular extension
T4b	tumor size category 4 with ciliary body involvement
T4c	tumor size category 4 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T4d	tumor size category 4 with ciliary body involvement and with extraocular extension less than or equal to 5 mm in diameter
T4e	any tumor size category with extraocular extension more than 5 mm in diameter

To determine the T-feature for ciliary body and choroidal melanoma, it is necessary to first classify the tumor into the appropriate size category based on the height and largest diameter of the tumor base (fig. 1)

- retinal-vascular calcifications,
- staphyloma (astrocytoma),
- age-related macular degeneration (AMD), especially the exudative form [19, 27].

The TNM staging classification according to AJCC revision 8 is shown in tables I–IV. Table V shows the histological grade [22].

Tumor features such as largest diameter and thickness (height) are used to determine the size category (tab. I, fig. 1 – T-feature). Determination of pT is required for the ciliary body and choroidal melanomas, but is only feasible if the primary treatment was ocular excision (enucleation). In these situations, proper technique is essential to visualize the greatest base diameter and thickness (height) of the tumor in the removed eyeballs. To achieve this, the eyeball should be illuminated with a strong light source to map the tumor's shadow on the sclera and determine its position in relation to the optic nerve. The eyeball should be cut so that the plane of the section contains the largest diameter of the tumor base, rests on the shadow, and passes through the center of the disc as well as the optic nerve.

Table II. Regional lymph nodes – N feature

N (regional lymph nodes)	Disease staging
Nx	regional lymph nodes cannot be assessed*
N0	no regional lymph node metastasis
N1	metastasis in regional lymph nodes or separate tumor infiltration in the orbit is found
N1a	metastasis in one or more regional lymph nodes
N1b	separate tumor infiltration in the orbit without continuity with the eyeball, without metastasis to regional lymph nodes

*Regional lymph nodes include the preauricular, submandibular and cervical lymph nodes

Table III. Distant metastasis – M feature

M (distant metastasis)	Disease staging
M0	no distant metastasis
M1	distant metastasis
M1a	diameter of the largest distant metastasis ≤3 cm
M1b	diameter of the largest metastasis is between 3.1–8.0 cm
M1c	diameter of the largest metastasis >8 cm

Table IV. Tumor stage

Stage	T	N	M
I	T1a	N0	M0
IIA	T1b–d	N0	M0
	T2a	N0	M0
IIB	T2b	N0	M0
	T3a	N0	M0
IIIA	T2c–d	N0	M0
	T3b–c	N0	M0
	T4a	N0	M0
IIIB	T3d	N0	M0
	T4b–c	N0	M0
IIIC	T4d–e	N0	M0
IV	any T	N1	M0
	any T	any N	M1 a–c

Table V. Evaluation of histological structure (grading) – G feature

G (histological grade)	Histological structure of melanoma
GX	histologic type cannot be assessed
G1	spindle cell melanoma (>90% spindle cells)
G2	mixed cell melanoma (>10% epithelioid cells and <90% spindle cells)
G3	epithelioid cell melanoma (>90% epithelioid cells)

Primary tumor thickness	Size (mm)						
>15	4	4	4	4	4	4	4
12.1–15.0	3	3	3	3	3	4	4
9.1–12	3	3	3	3	3	3	4
6.1–9.0	2	2	2	2	3	3	4
3.1–6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
	≤3.0	3.1–6.0	6.1–9.0	9.1–12	12.1–15.0	15.1–18.0	>18.0
	Largest dimension of the tumor base (mm)						

Figure 1. Classification of ciliary body and uveal melanoma based on the thickness and size of the primary tumor

In the past, in the clinical evaluation of tumor dimensions, the largest base diameter was expressed in multiples of the optic disc diameter (DD) (average 1 DD = 1.5 mm), and the thickness (height) of the tumor in diopters (average 3 diopters = 1 mm). Nowadays, the standard is to determine the size of intraocular tumor parameters in millimeters based on ultrasound measurements (T-feature determination) [22]. As the majority of patients with uveal melanoma are treated conservatively, so ultrasonography remains the only method to assess tumor size.

Treatment

Local treatment of uveal melanoma can be divided into two main types.

1. Eye-sparing treatment, which preserves the eyeball and even useful visual acuity in some cases

Radiation therapy (II, 2A):

- Brachytherapy (used most often) with various radioactive elements, which allows very good local tumor control of 95–98% [29, 30]. Commonly used are the isotopes ruthenium-106 (Ru-106) and iodine-125 (I-125). Palladium (Pd-103) and iridium (Ir-192) are used much less frequently due to their short half-life and the associated high cost of therapy. Ru-106 is effective in treating tumors up to 5 mm in height, or up to 6 mm, but in combination with transpupillary thermotherapy (TTT). I-125 is used to treat tumors that are 5 mm and above, but not more than 10–12 mm. The base of the tumor is also an important determinant in the use of applicators, which should not exceed the diameter of the applicator and can be no more than 18 mm to maintain a safe margin [31]. The dose to the top of the tumor should not be less than 70 Gy, and ideally for I-125 it should be around 82.5 Gy [31–35].
- Proton beam therapy – a positive local result is achieved in 95-98% of cases. The therapy uses a collimated beam of protons or helium nuclei. Irradiation is performed for 4 consecutive days with a total dose to the tumor apex of 60 Gy (4 × 15 Gy) [36].
- Stereotactic radiotherapy.

Local sparing surgical treatment (II, 2A):

- Exoresection – this is used to treat lesions located in the iris, ciliary body, or anterior choroid [2]. The tumor is removed under the scleral flap, in combination with brachytherapy [2].
- Endoresection – can be performed after prior radiation therapy. The tumor is removed during pars plana vitrectomy [37–39].

Laser treatment:

- Transpuppilary thermal therapy (TTT) is designed to treat small melanomas. It is most commonly used with brachytherapy, especially in the parathyroid localization of the tumor, the so-called sandwich therapy method (III, 2B).
- Photodynamic therapy – an experimental and controversial therapy, using a photosensitizing dye (verteporfin), for the treatment of amelanotic small melanomas [40, 41] (IV, C) – this type of therapy is currently not reimbursed in Poland.

2. Radical surgical treatment

Enucleation, or removal (excision) of the eyeball. Recommended when the tumor is more than 12 mm thick and more than 20 mm in base, and when the tumor infiltrates the optic nerve or secondary glaucoma is present [20] (III, 2A). It is recommended that an orbital implant be placed at the same time, after removal of the eyeball – provided there are no features of extraocular infiltration, and and orbital prosthesis up to 14 days after the procedure.

Exenteration, or evisceration of the orbit, is indicated when there is massive extraocular infiltration.

Both diagnosis and qualification for treatment, as well as treatment of uveal melanoma, should be carried out in ophthalmic oncology centers by specialists experienced in the subject.

Treatment at the generalized stage

Treatment of generalized uveal melanoma of the eyeball makes it possible to prolong survival by several months, especially if local treatment of liver metastases is possible.

The key element determining the length of survival of patients with uveal membrane melanoma is the presence of liver metastases. The liver is the most common site of metastasis – 70-90% of cases, with the liver being the only site of metastasis in about 50%. Metastases of ocular choroidal melanoma spread via the bloodstream. Survival after finding metastatic lesions in the liver is usually short, with a median of 2–3 months. Metastases of this cancer to the liver are classified as:

- stage 1: ≤50 μm in diameter,
- stage 2: 51–500 μm,
- stage 3: >500 μm,

In the latter stage, two types of metastatic growth occur:

- infiltration and replacement of hepatic lobules with peri--lobular fibrous septa,
- formation of large islands of tumor cells adjacent to small portal veins.

During progression, the tumor becomes vascularized and mitotically active [42, 43].

To date, there are no established, agreed-upon methods for the management of such patients. Various methods of surgical treatment are described in the literature, including:

- liver resection,
- isolated liver perfusion,
- intraarterial chemoinfusion,
- transarterial chemoembolization,
- immunoembolization,
- selective radiotherapy,
- thermoablative methods (radiofrequency ablation – RFA, microwave ablation – MWA).

There are more than a dozen publications in the literature, most of them retrospective, that analyze the outcomes of patients undergoing liver resection. A significant number of publications either do not include a comparison group or compare with a historical group of patients undergoing surgery, or with patients treated conservatively. A systematic review published in 2020 includes a group of nearly 800 operated patients with an overall survival of 10 to 35 months, compared with a survival of 9 to 15 months in the group treated with systemic chemotherapy [44]. In the largest group in the retrospective analysis – 255 patients undergoing resection – median survival was 14 months, compared to 8 months in the group treated conservatively.

Surgical treatment usually consisted of classical resection of the liver parenchyma along with the focal lesion. Sometimes the resection was supplemented by intraarterial chemotherapy, chemoembolization or thermoablation.

There are reports of the successful use of laparoscopic techniques for resection and/or complementary thermoablation. This method is relatively safe, with no perioperative mortality, and a morbidity rate of 19%. Median survival in this group is 35 months [44]. Typically, patients with metastatic melanoma undergo small resections – no more than 1–2 liver segments.

The aforementioned surgical results may be subject to patient selection bias, as patients with favorable tumor biology and less advanced liver metastatic foci in number and volume are qualified for resection.

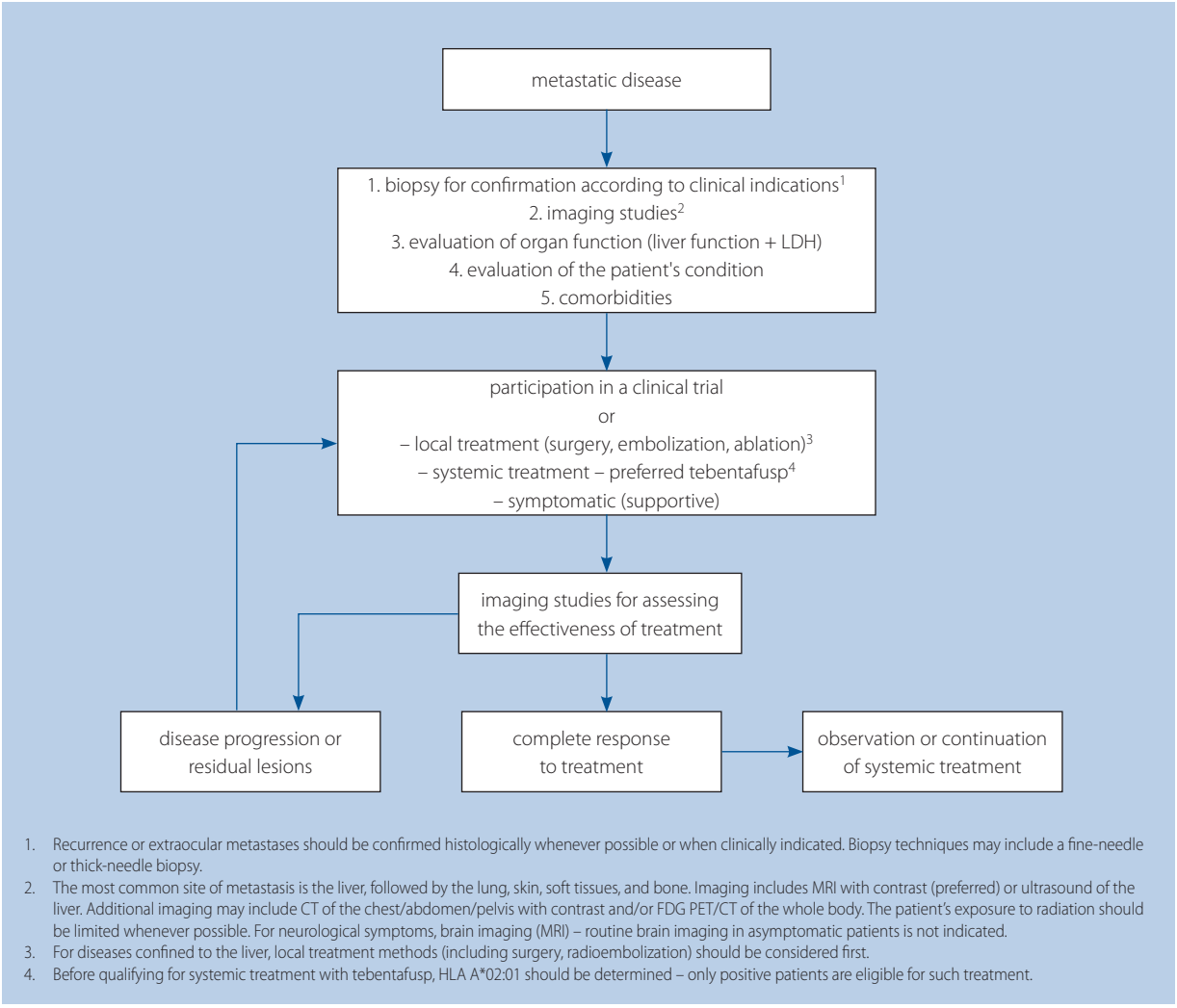
Thus, in view of the low quality of evidence, it is difficult to recommend surgical treatment in this group of patients. However, resection of liver metastases should be considered in a carefully selected group of patients in whom:

- a long survival period is anticipated,
- no extrahepatic lesions are found,
- there are technically radical resectable (R0) focal lesions.

In many studies, the median overall survival of these patients was more than 20 months after resection of metastases, and the rate of R0 resection ranged from 27% to 88%.

Undoubtedly, further randomized and prospective studies that include similar patient eligibility criteria for resection, treatment protocols and endpoints are needed and necessary. Their goal should be to compare results and establish recommendations for liver resection [21]. Current treatment options for ocular melanoma patients with liver metastases are surgical resection (provided single foci are present, which is rare), chemoembolization/radioembolization or thermoablation of liver metastases, and systemic treatment [2, 45] (III, A).

Clinical trials are attempting therapies that target the PKC--MAPK pathway, modifying epigenetic mechanisms (e.g., vorinostat) or immune checkpoint inhibitors (small effects have been observed in phase II trials mainly with the combination of nivolumab and ipilimumab) [46, 47]. So far, these studies have not yielded positive results [2, 48]. One exception is the use of tebentafusp (IMCgp100), a new bispecific molecule targeting T cells in the presence of HLA-002, which allows for a benefit in overall survival (OS) time both compared to historical data (phase II study [49] – median OS 16.8 months) and the active comparator (phase III study – 1-year OS rate 73% *vs.* 58%,



1. Recurrence or extraocular metastases should be confirmed histologically whenever possible or when clinically indicated. Biopsy techniques may include a fine-needle or thick-needle biopsy.
2. The most common site of metastasis is the liver, followed by the lung, skin, soft tissues, and bone. Imaging includes MRI with contrast (preferred) or ultrasound of the liver. Additional imaging may include CT of the chest/abdomen/pelvis with contrast and/or FDG PET/CT of the whole body. The patient's exposure to radiation should be limited whenever possible. For neurological symptoms, brain imaging (MRI) – routine brain imaging in asymptomatic patients is not indicated.
3. For diseases confined to the liver, local treatment methods (including surgery, radioembolization) should be considered first.
4. Before qualifying for systemic treatment with tebentafusp, HLA A*02:01 should be determined – only positive patients are eligible for such treatment.

Figure 2. Treatment algorithm for patients with metastatic ocular melanoma

HR 0.51 [50] (I, 2A). The drug was registered in the European Union in March 2022, but is not reimbursed in Poland.

Some difficulty remains in determining the duration of treatment with tebentafusp, as improved overall survival is also observed in the treatment group after disease progression. Continuation of therapy after progression should be considered with good treatment tolerance. After the first three doses of the drug, it is necessary to observe the patient in the hospital setting with regular monitoring of vital signs for 24 hours for potential complications, including cytokine release syndrome. Treatment should be carried out in centers that have experience in the use of immunotherapy and access to an intensive care unit. Patients should be informed about the symptoms and management of cytokine release syndrome.

Data on the efficacy of chemotherapy are limited, but its use may be considered in selected situations.

Observation and treatment of local complications

After treatment of uveal melanoma, the patient should be examined ophthalmologically every 3–6 months during the first 2 years, and once every 6–12 months thereafter. The examination should be aimed at detecting potential local recurrence or complications after therapy. After conservative treatment, it should include at least:

- evaluation of visual acuity,
- measurement of intraocular pressure,
- anterior segment examination in the slit lamp and fundus examination after pupil dilation,
- ultrasound examination,
- taking photographs and OCT.

On the other hand, after the enucleation procedure, the orbit should be examined (after removal of the epiprosthesis, the orbit should be viewed and palpated) and a follow-up MR examination of the orbit should be ordered once every 6–12 months [51, 52] (III, A). In cases of suspected extraocular infiltration, palpation of regional lymph nodes is also indicated.

As a result of conservative treatment, there is a risk of complications in the form of cataracts, secondary glaucoma, iris neovascularization, retinopathy (with maculopathy) and neuropathy. All of these complications should be treated,

Table VI. Principles of follow-up after local treatment of ocular melanoma

Risk group	Features of the risk group	Recommended management
ocular melanoma patients at low risk of distant metastasis	T1 feature and in case of known molecular abnormalities (disomy of chromosome 3, multiple copies of 6p, *EIF1AX* mutation)	imaging studies if indicated
ocular melanoma patients with intermediate risk of distant metastasis	T2 or T3 or with known molecular abnormalities (*SF3B1* mutation)	imaging studies every 6–12 months and if clinically indicated
ocular melanoma patients at high risk of distant metastasis	T4 or with known molecular abnormalities (chromosome 3 monosomy, multiple copies of 8q, *BAP1* mutation, PRAME expression)	Follow-up imaging every 3–6 months for 5 years, then every 6–12 months for up to 10 years, then if clinically indicated (physical or subjective symptoms)

but above all, they should be prevented. The best treatment for retinopathy, maculopathy and radiation neuropathy, as well as iris neovascularization, are intravitreal or anterior chamber injections of anti-VEGF preparations or steroids. In the case of anti-VEGF preparations, it is recommended to initially give 3 injections at an interval of 1–2 months (depending on the type of drug), and then depending on the clinical picture [53, 54] (III, A).

The patient should remain under follow-up after ophthalmic treatment so that possible metastases can be detected and treated. Imaging studies are recommended. If liver metastatic lesions are suspected, an MRI of the liver with contrast is recommended. It should be noted that even an MRI in some cases cannot determine the actual stage of the disease [52, 55] (III, A). Post-treatment follow-up regimens should be determined by assessing the risk of metastasis, as summarized in table VI.

Conjunctival melanoma

Conjunctival melanoma accounts for 0.25% of all melanomas and 5% of melanomas located within the eye. In recent years, there has been a significant increase in the incidence of this type of malignancy [56, 57]. Molecular aspects of the development of conjunctival melanoma include mutations of the *BRAF* and *NRAS* genes, quite different from those described in uveal melanoma [1] (III, 2A).

The vast majority i.e. 74% of conjunctival melanomas develop from primary acquired melanosis (PAM) with atypia, 7% from pre-existing nevus, and 19% arise de novo [56, 58] (III, 2A).

Local relapses occurs in 30–50% of cases within 5 years [59]. Metastasis develop in about 20–30% of patients at 10-year follow-up [56]. Factors associated with a worse prognosis are:

- location of the tumor outside the ocular conjunctiva,
- multinodular type of growth,
- rapid growth of the lesion,
- tumor thickness >2 mm,
- appearance of recurrence,
- incomplete excision,
- failure to use adjuvant therapy after excision [56, 60] (III, 2A).

The mainstay of treatment remains surgical resection of the tumor after prior occlusion of the feeding vessels, with a macroscopically preserved margin of healthy tissue, the size of which remains undetermined [56, 60] (III, 2A). Some recommend the use of cryoapplication of excision sites and the application of absolute alcohol swabs [56, 61] (IIIB). In very advanced cases, enucleation and exenteration are considered [56, 62, 63] (III, 2A).

Complementary treatment

1. Local chemotherapy:
- mitomycin C, the administration of which into the conjunctival sac is started 2 weeks after surgery [56, 64–69] – an unreimbursed recommendation with very limited clinical data (IV, 2B),
- interferon alfa-2b [56, 70, 71] (IV, 2B) – also not reimbursed with limited clinical data.

2. Radiation therapy:
- radiotherapy from external fields,
- local brachytherapy.

A sentinel node biopsy should be considered. However, it is important to remember that 50% of cases have distant metastasis without the presence of tumor cells in the regional lymph nodes [56, 72, 73] (III, 2B).

In the metastatic conjunctival melanoma, the same therapies as in advanced cutaneous melanoma are used [56] (III, 2A). Molecular testing is necessary to determine the mutation status within the *BRAF* gene.

The patient should remain under constant oncologic and ophthalmologic follow-up after treatment for conjunctival melanoma (photographic documentation of the local condition each time is important; remember to check the conjunctiva after eyelid inversion).

Conflicts of interest:

P. Rutkowski received a grant from Pfizer, lecture fees from Novartis, Pierre Fabre, Eli Lilly, Merck, Sanofi, MSD, and BMS, and participation in MSD, Pierre Fabre, Sanofi, Merck, Novartis, and BMS advisory meetings. Medison Pharma. M. Dudzisz-Śledź received honoraria for lectures from Pierre Fabre, Merck KGaA, MSD, Sanofi Aventis, Novartis, Medison Pharma, and BMS – for participation in advisory meetings from Merck KGaA and Novartis, and funding for participation in conferences from Novartis. T. Świtaj received honoraria for lectures from

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