Ophthalmic Research

Review Article

Ophthalmic Res 2023;66:14–26
DOI: 10.1159/000524372

Received: October 1, 2021
Accepted: March 22, 2022
Published online: March 31, 2022

Outcome Measures of New Technologies in Uveal Melanoma: Review from the European Vision Institute Special Interest Focus Group Meeting

Jan-Willem M. Beenakker[a, b] Niels J. Brouwer[a] Cindy Chau[a] Sarah E. Coupland[c] Miltiadis Fiorentzis[d] Heinrich Heimann[e] Jens Heufelder[f] Antonia M. Joussen[g] Jens F. Kiilgaard[h] Tero T. Kivelä[i] Sophie Piperno-Neumann[j] Elina S. Rantala[i] Bozena Romanowska-Dixon[k] Carol L. Shields[l] Gregor D. Willerding[m] Thomas Wheeler-Schilling[n, o] Hendrik P.N. Scholl[p, q] Martine J. Jager[a] Bertil E. Damato[r]
in collaboration with the European Ocular Oncology Group and the International Society of Ocular Oncology

[a]Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands; [b]Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands; [c]University of Liverpool, Institute of Systems, Molecular and Integrative Biology, Liverpool, UK; [d]Universitätsklinikum Essen Klinik für Augenheilkunde, Essen, Germany; [e]Royal Liverpool University Hospital, Liverpool, UK; [f]Charité – Universitätsmedizin Berlin, Berlin, Germany; [g]Charité – Universitätsmedizin Berlin, Klinik für Augenheilkunde, Berlin, Germany; [h]Department of Ophthalmology, Rigshospitalet and Glostrup Hospital, Copenhagen University Hospital, Copenhagen, Denmark; [i]Ocular Oncology Service, Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [j]Department of Medical Oncology, Institut Curie, PSL Research University, Paris, France; [k]Klinika Okulistyki i Onkologii Okulistycznej, Uniwersytet Jagiellonski, Kraków, Poland; [l]The Ocular Oncology Service, Wills Eye Hospital, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA; [m]DRK Kliniken Berlin Westend, Klinik für Augenheilkunde, Berlin, Germany; [n]European Vision Institute EEIG, Brussels, Belgium; [o]Institute for Ophthalmic Research, Tübingen, Germany; [p]Department of Ophthalmology, University of Basel, Basel, Switzerland; [q]Institute of Molecular and Clinical Ophthalmology (IOB), Basel, Switzerland; [r]Nuffield Laboratory of Ophthalmology, University of Oxford, John Radcliffe Hospital, Oxford, UK

Keywords
Uveal melanoma · Ocular oncology · Outcome measures · Eye diseases

Abstract
Uveal melanoma (UM) is the most common primary intraocular tumor in adults. New diagnostic procedures and basic science discoveries continue to change our patient management paradigms. A recent meeting of the European Vision Institute (EVI) special interest focus group was held on "Outcome Measures of New Technologies in Uveal Melanoma," addressing the latest advances in UM, starting with genetic developments, then moving on to imaging and treatment of the primary tumor, as well as to investigating the most recent developments in treating metastases, and eventually taking care of the patient's well-being. This review highlights the meeting's presentations in the context of the published literature.

Karger@karger.com
www.karger.com/ore

Correspondence to:
Jan-Willem M. Beenakker, j.w.m.beenakker@lumc.nl

Introduction

Staying informed is essential for physicians who treat patients with cancer as new developments occur continuously. This is certainly true of ocular oncology, where new diagnostic procedures and basic science discoveries continue to change our patient management paradigms [1]. The identification of a subgroup of patients with uveal melanoma (UM) who carry a germline pathogenic variant in the BRCA1 associated-protein 1 (BAP1) gene in all cells has led to discussions about the need for genetic testing of patients and their family members. Diagnostic tests may help to differentiate between truly benign melanocytic fundus lesions and early UMs, which may progress into metastasis-producing lesions. Early treatment of such lesions may perhaps prevent their outgrowth. Furthermore, advances in ocular imaging may not only help to improve diagnosis but may also open new paths to improve radiotherapy. Stratifying patients with UM into well-defined metastatic risk groups may provide a more effective way for evaluating new drugs.

These are just a few examples of new developments in managing UM and an analysis of the outcomes of these novel approaches will help to determine their value and applicability. A workshop was held with clinicians and researchers who work at the forefront of new developments in this disease. This paper summarizes these latest advances, starting with genetic developments, then moving on to the realm of imaging and treatment of the primary tumor, as well as to investigating the most recent developments in treating metastases, and eventually taking care of UM patients' well-being.

BAP1 Tumor Predisposition Syndrome – Detection of Germline BAP1 in Patients with UM and Detection of Other Tumors

Occasional papers in the past described familial occurrence of UM, sometimes associated with cutaneous melanoma. A decade ago, the genetically defined BAP1 tumor predisposition syndrome emerged (BAP1-TPDS, OMIM 614327). This syndrome is caused by a pathogenic variant in the *BAP1* gene, which is associated with an increased risk of developing UM, cutaneous melanoma, renal-cell carcinoma, malignant mesothelioma, meningioma, and benign skin tumors known as MBAITS (melanocytic BAP1-mutated atypical intradermal tumors) or BAP1-inactivated melanocytic tumors [2–5].

Table 1. BAP1 screening protocol as applied by the Leiden University Medical Center [7]

Eyes: age 15 years
Annual dilated eye exams by ophthalmologist
Skin: age 15 years
Monthly self-examination of the skin
Annual screening of the skin by a dermatologist
Kidneys, pulmonary pleurae, peritoneum: age 30 years
Annual imaging of the thorax/abdomen

Tero Kivelä and colleagues [6] shared their systematic evaluation of new patients with UM in Finland. A total of 432 consecutive patients were screened for germline BAP1 variants. Pathogenic germline variants were detected in 9 of 433 (2%) patients overall and in 4 of 16 (25%) patients from Finnish UM families [6]. Of 21 rare variants, five were identified as likely pathogenic by their effect on splicing, nuclear localization, or deubiquitination activity, and four carried variants in exon 13 with no apparent effect on these functions, classified as likely benign but pending reassessment given the many suggested roles of *BAP1* in the cell. According to the standards of the American College of Medical Genetics [7], functional data are needed in addition to documenting a fitting phenotype and segregation in the family in order to define a variant as pathogenic. In addition to testing the effect of likely pathogenic coding region variants on BAP1's deubiquitinating activity, the group is developing further assays that might more directly measure the effect of BAP1 variants on cell proliferation and motility.

Several BAP1-TPDS families have similarly been identified in the Netherlands [8]. Chau et al. [8] screened 878 patients with UM for the presence of this syndrome. In a recent paper, Chau et al. [8] recommended genetic analysis in patients with ≥2 BAP1-TPDS-associated tumors in their medical history or family history, as well as in patients diagnosed with UM under the age of 40 years, with skin melanoma under the age of 18 years, malignant mesothelioma under the age of 50 years, or renal-cell carcinoma under 46 years of age. A study was set up to identify potential "BAP1 families." Starting in 2016, questionnaires were provided to newly and previously treated UM patients, which asked for the occurrence of other malignancies in the patient and their family members. A total of 246 patients were eligible for referral for germline testing, of which 206 consented. This led to 182 genetic tests, through which three new BAP1 families were identified.

In addition, family members and patients with a pathogenic BAP1 variant were offered screening for early de-

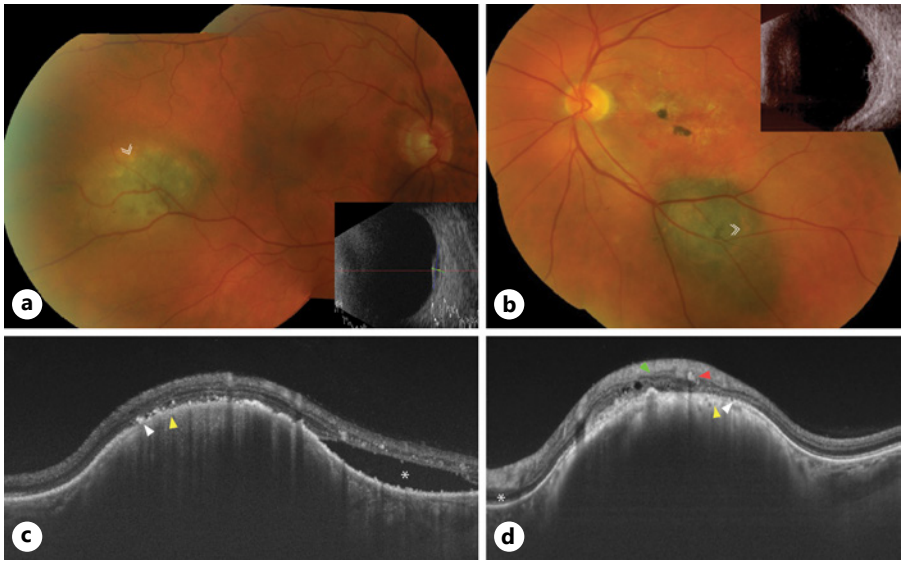

Fig. 1. OCT imaging in suspicious melanocytic fundus lesions. **a**, **c** show small peripheral lesions, which on US (**inset**) is 1.7 mm thick, while (**b**, **d**) show a small pigmented midperipheral lesion which is 2.0 mm thick. On both fundus photographs, lipofuscin (double arrowhead) can be seen, and both lesions have a low reflectivity on US. On OCT, RPE changes (white arrow), choriocapillaris compression (yellow arrow), and subretinal fluid (asterix) can be seen for both lesions. The lesion of **d** furthermore shows "shaggy" photoreceptors (red arrow) and irregularities in the ganglion layer (green arrow).

tection of other tumors. Within the first 3 years, this protocol led to the detection of two new mesotheliomas, two renal-cell carcinomas, and two cutaneous melanomas. Screening guidelines have been published by several groups [5, 9, 10]. Based on clinical experience, Chau et al. [8] made recommendations, as shown in Table 1, to perform yearly ophthalmological and dermatological examinations, starting at age 15 years, with annual imaging of the thorax and abdomen added in patients ≥30 years of age.

Differentiating between Nevi and Melanoma

As choroidal nevi are a common finding in the healthy population (10–15%) and UM is rare [11], an accurate differentiation of nevi from UM and knowledge of predictive factors of malignant transformation are of great clinical importance.

Characteristic Differences on OCT

Bozena Romanowska-Dixon reported how different morphological features in optical coherence tomography (OCT) can aid in the differentiation between small (<2.5 mm thick) choroidal nevi and melanomas. Although studies have shown no difference in melanoma-specific mortality between delayed and promptly treated small melanocytic fundus lesions, these lesions carry a risk of malignant transformation, upon which early treatment could be beneficial [12, 13]. However, treating a stable nevus might result in unnecessary loss of vision, especially for centrally located lesions. Therefore, additional clues to detect potential for malignant transformation would be valuable.

Romanowska-Dixon showed different OCT image features (Fig. 1), which can suggest malignant transformation, in particular, compression of the choriocapillaris, retinal pigment epithelial (RPE) changes, "shaggy" photoreceptors, and the presence of subretinal fluid [14–17]. On OCT angiography (OCT-A), she furthermore showed a hyperreflectivity in the choriocapillaris in these patients. However, because the same features were also found in some apparently stable choroidal nevi, they unfortunately do not provide an unequivocal diagnosis. She therefore concluded that OCT presently could have a supporting role in the differentiation between a choroidal nevus and a small melanoma and in making the decision to treat or closely follow the lesion over time.

Oximetry and OCT-A of Choroidal and Iris Tumors

Niels Brouwer showed results of two new modalities of imaging blood vessels, oximetry (using the Oxymap technique) and OCT-A, for the diagnosis of choroidal and iris melanomas. Oximetry measures the oxygen saturation of the arterial and venous blood in the retinal vessels and could therefore be a potential biomarker of tumor metabolism [18, 19]. In a cohort of 45 UM patients, an increase in oxygen consumption was found in the tumor eye in comparison to the fellow eye, while in 42 patients with a choroidal nevus, no difference in oxygen consumption occurred between the affected and fellow eye [20]. Although this finding is in agreement with ear-

lier studies in showing an increased metabolic activity in UM [21, 22], the variation between subjects was too wide to use this technique to directly differentiate between a choroidal melanoma and nevus.

Furthermore, Brouwer shared images obtained using anterior segment OCT-A in ten iris melanomas and 42 iris nevi [23]. Although this new technique is still susceptible to different types of artefacts, good images were obtained in 80% of the eyes. In all iris melanomas, vessels were observed in the tumor, whereas vessels could only be detected in 71% of the nevi. The vessels in both tumors displayed irregular patterns and a high tortuosity, which helped to differentiate the tumor vessels from the normal iris vasculature. OCT-A proved to be less suitable in pigmented lesions because the pigmentation absorbed the light from the OCT. For lightly pigmented tumors, however, it provided an elegant noninvasive method to visualize the vasculature of iris lesions. This technique is currently studied in both melanocytic lesions [24], as well as other tumors such as ocular surface squamous neoplasia [25].

The TFSOM System for Predicting Growth of Melanocytic Choroidal Tumors

Carol Shields described the updated TFSOM-DIM (To Find Small Ocular Melanoma – Doing Imaging) mnemonic for estimating the risk of growth in melanocytic choroidal tumors, which she considers to be an indicator of malignant transformation of a nevus to melanoma [26–29]. TFSOM-DIM stands for "Thickness >2 mm, Fluid under the retina, Symptoms, Orange pigment, Melanoma-hollow-on-ultrasonography and Diameter >5 mm." She provided evidence to show that imaging identifies nevi that show risk factors for growth to melanoma, with outcomes varying according to various combinations of risk factors, increasing from 1% in the absence of any risk factors to 55% if five predictors are present. In particular, the 5-year rate of growth increased from 0.8% if the tumor thickness was <1 mm to 25% if the thickness was 2–3 mm. Importantly, race did not influence these rates [30].

The MOLES System for Differentiating Choroidal Nevi from Melanomas

Bertil Damato described the MOLES system to help nonexperts in estimating the likelihood of malignancy in melanocytic choroidal tumors and to manage patients accordingly [31]. The MOLES acronym stands for "Mushroom shape, Orange pigment, Large size, Enlargement, and Subretinal fluid." Each of these is scored from 0 to 2, and tumors can subsequently be categorized ranging from "common nevus" and "low-risk nevus" to "high-risk nevus" and "probable melanoma." The MOLES system was retrospectively evaluated by Harby et al. [32] in 222 tumors. All 81 tumors diagnosed as melanoma were correctly identified as "probable melanoma," with 135 of 141 diagnosed nevi having a MOLES score <3 (97% specificity). A similar, but larger, study by Roelofs et al. [31] confirmed the high sensitivity of the MOLES system.

Furthermore, Damato highlighted the differences between the MOLES and TFSOM-DIM systems [26, 27]. Although TFSOM-DIM is intended for specialists with access to ultrasonography, MOLES is designed for nonspecialists without such imaging. Accordingly, each item in the MOLES scoring system has an intermediate/uncertain category. Another difference is that TFSOM-DIM predicts growth, whereas in MOLES, this feature is an indicator of malignancy. As a result, the most important application of the MOLES system is the efficient and appropriate referral of patients with melanocytic choroidal tumors to an ocular oncology specialist.

Biopsy of Small Choroidal Tumors

Heinrich Heimann reported on his experience with biopsies of small, melanocytic choroidal tumors. He highlighted that small UM are now treated more urgently than before because it is with these tumors that the window of opportunity for preventing metastatic spread is the greatest [33]. He suggested that early treatment improves survival, reporting several studies, including his own investigation of 132 patients with small choroidal melanomas detected during screening for diabetic retinopathy [34–36].

Heimann described his technique for trans-retinal tumor biopsy, performed with a vitreous cutter, without vitrectomy, gas tamponade, or laser treatment [37]. He also described his technique for trans-scleral biopsy, performed under a lamellar scleral flap and using tissue glue to seal the sclerotomy [38].

In 100 eyes with a UM with a thickness ≤2 mm, histological diagnosis was obtained in 85 and genetic typing in 67 tumors, with monosomy 3 observed in 16% of these. In a cohort of 232 cases, complications were rare and included episcleral seeding (one case), endophthalmitis (one case), subretinal hemorrhage (5–8%), and vitreous hemorrhage in 1% of 101 trans-scleral and 13% of 131 trans-retinal biopsies [39]. Heimann predicted that tumor biopsy will become mandatory when effective treatment for metastatic disease becomes available.

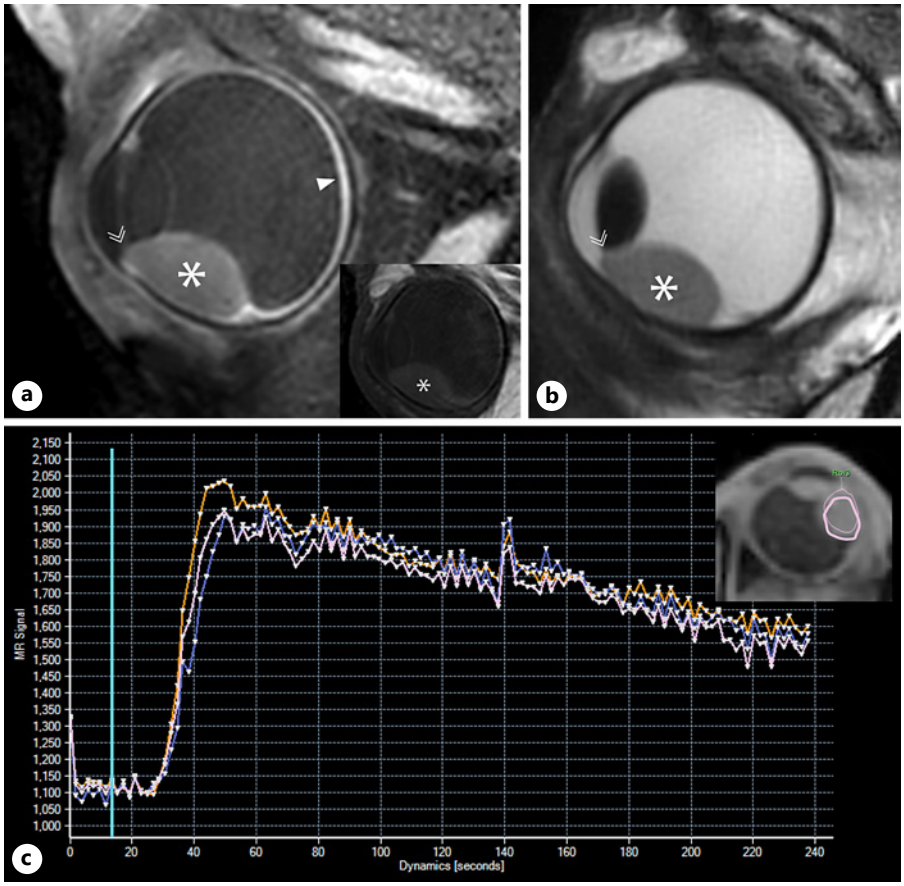

Fig. 2. MRI of UM. Contrast enhanced T1-weighted (**a**) and T2-weighted MR-image of a UM-containing eye (**b**), showing an enhancing UM (asterix) and choroid (arrowhead) compared to the native T1-weighted image (**inset**). Note that the UM has grown through the iris (double arrow). **c** PWI showing a rapid uptake of the gadolinium contrast agent, followed by a gradual decrease. This so-called wash-out curve is seen in two-thirds of UM. PWI, perfusion-weighted imaging.

Imaging UM

Modern ocular imaging technologies not only aid in the diagnosis of UM but are also increasingly applied to improve treatment and to provide promising new biomarkers to enable early assessment of the efficacy of a therapy.

Magnetic Resonance Imaging

Jan-Willem Beenakker presented the possibilities of magnetic resonance imaging (MRI) of UM, which has become feasible using regular clinical imaging [40–42]. He showed how MR images, of which some can be seen in Figure 2, can accurately assess the involvement of adjacent structures, such as the optic nerve or ciliary body [43]. In terms of size measurements, the MRI-based prominence and basal diameter measurements showed a good agreement with ultrasound (US) for small- and medium-sized UM, with generally <0.5 mm differences. For large UM, however, larger differences were found, and MRI was preferred over conventional US because the three-dimensional visualization of MRI proved to be beneficial to assess an irregularly shaped UM [44]. Furthermore, he showed how MRI is being used to improve the target definition for proton beam therapy of UM [45, 46].

Beenakker continued with describing the two main functional MRI techniques: diffusion- and perfusion-weighted imaging. Different studies have shown how diffusion-weighted imaging can differentiate between various intraocular lesions because they have a different diffusivity, a biomarker for their cellularity [47–50]. Furthermore, perfusion-weighted imaging shows changes in pharmacokinetic parameters of the tumor after radiotherapy, before size changes are apparent on US, making it a promising technique to assess treatment responses early. Additionally, these biomarkers seem to be associated with prognostic markers, such as monosomy 3 [43, 47]. Beenakker expected that, similar to other tumor sites, these functional MRI techniques will soon play a more prominent role in both clinical practice and ophthalmic research as they assess noninvasively multiple elements of the biology of UM [43, 51].

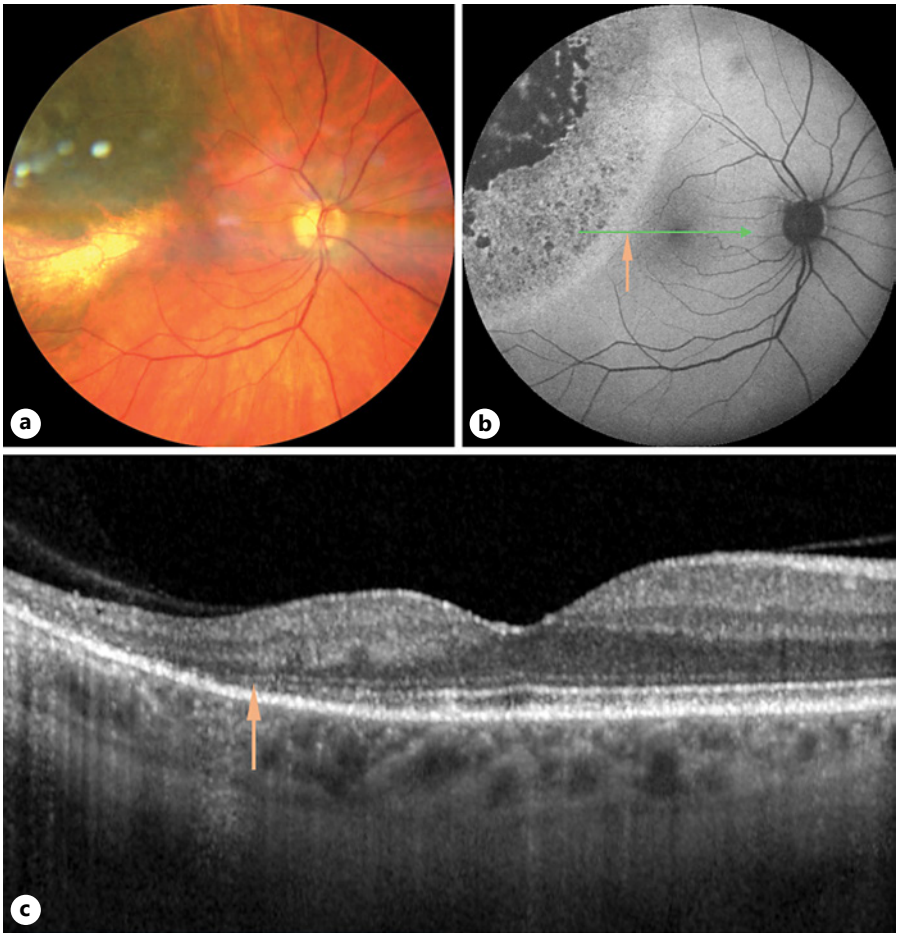

Fig. 3. Autofluorescence imaging of UM. Fundus photograph (**a**), blue-light fundus autofluorescence image (**b**), and SD-OCT image (**c**) of a UM in a male patient, 60 months after ruthenium-106 brachytherapy. The initial tumor thickness was 3.5 mm, and the prescribed scleral dose was 480 Gy. Laminar autofluorescence mottling and a rim of increased autofluorescence visualize the central irradiation field. The corresponding SD-OCT scan shows retinal thinning with loss of the ellipsoid zone and loss of the external limiting membrane directly adjacent to the rim of increased autofluorescence (orange arrows).

Requirements for Proton Beam Radiotherapy

Jens Heufelder discussed requirements for successful proton beam therapy, based on his experience [52–54]. He started his presentation by emphasizing that precise positioning of the eye, with an accuracy of at least 0.2 mm, is essential during treatment. Modern treatment planning systems, such as Ocular Tumour Planning UtilitieS (an inhouse-developed treatment planning software jointly developed by the German Cancer Research Center and the Helmholtz-Zentrum Berlin) [55, 56] or RayOcular, a module within the RayStation treatment planning system (RaySearch Laboratories, Sweden), can combine information from different imaging modalities, including CT, MRI, ophthalmoscopy, ultrasonography, OCT, to complement the conventional intraoperative measurement of fiducial marker locations with respect to the tumor. Patients must be able to look steadily at the fixation target and must not have intraocular gas or a tumor diameter exceeding that of the maximum beam width.

The main indications for proton beam radiotherapy include unsuitability for brachytherapy because of large tumor size or a juxtapapillary location and recurrence after other forms of treatment. He suggested that neoadjuvant proton beam radiotherapy may also be useful before enucleation in eyes with optic nerve invasion. Studies consistently report high rates of local tumor control and ocular conservation so that treatment of UM with proton beam radiotherapy is increasing around the world [57–59].

Blue-Light Autofluorescence Imaging after Plaque Radiotherapy

Gregor Willerding reported on the scope of autofluorescence imaging (excitation wavelength 488 nm, detection of emission >500 nm) after ruthenium-106 brachytherapy for choroidal melanoma [60–62]. This imaging allows for visualization of autofluorescence originating from (melano-)lipofuscin at the level of the RPE as is shown in Figure 3. Willerding reported results in 31 eyes receiving a scleral radiation dose of 390–690 Gy. Apart

from preexisting changes overlying the tumor apex, the irradiation field was characterized by irregular increased autofluorescence with spots of decreased autofluorescence (*mottling*). The margin of the irradiation field was defined by a rim of markedly increased autofluorescence corresponding to loss of the external limiting membrane layer and the ellipsoid zone in the presence of an intact pigment epithelium on SD-OCT. RPE changes like clumping, migration, and atrophy corresponded to areas with autofluorescence mottling. This imaging is useful for highlighting the irradiated area when this is not evidence ophthalmoscopically. Limitations are poor image quality when media are opaque and lack of quantitative autofluorescence imaging in routine clinical practice. Furthermore, it is not known whether changes of the autofluorescence signal indicate a tumoricidal dose of radiation.

Outcomes after Treatment

Although the various treatment options for the primary UM have high degrees of tumor control, these patients often develop complications post radiotherapy, some of which can be treated surgically. It is important to include recent insights in the patients' quality of life after ocular radiotherapy in the determination of the optimal treatment strategy.

Local Treatment Results

Miltiadis Fiorentzis discussed outcomes after plaque radiotherapy, proton beam radiotherapy, and local resection, reporting high rates of local tumor control, especially with smaller tumors and those not involving the ciliary body. Rates of radiation-induced optic neuropathy increased from around 40% to almost 100% as radiation dose increased from <20 Gy to ≥40 Gy. Fiorentzis concluded by highlighting the need for further studies to determine which therapeutic modality is best for each tumor and to determine whether molecular genetics should influence the choice of treatment.

Endoresection of Choroidal Melanoma

Antonia Joussen emphasized that endoresection can conserve eyes that are likely to develop "toxic tumor syndrome" after radiotherapy and that careful surgical planning and follow-up are necessary for obtaining the best results. Joussen described her surgical technique of endoresection, which involves neoadjuvant radiotherapy, total vitrectomy, tumor resection with a low cutting rate, use of heavy liquid and endolaser, and finally filling the eye with silicone oil, which is removed after 3–6 months. Contraindications include optic-disc and/or foveal involvement and ciliary body involvement of more than 3–4 clock hours (relative contra indication). Following reports of fatal air embolism, the use of air has been replaced by heavy liquid and any vortex veins in the quadrant of the tumor are now cauterized at the start of the operation, which may also decrease the risk of dissemination of tumor cells into the general circulation, even though the tumor had been completely irradiated prior to irradiation [63].

The main complications are postoperative hemorrhage, pressure decompensations, and angle closure by silicone prolapse. Long-term complications include retinal detachment with proliferative vitreoretinopathy, radiation-induced ocular morbidity, ciliary body insufficiency, and disturbed wound healing [64–66]. As endoresection should only be performed after a complete irradiation of the tumor, local tumor recurrences are rare [59].

Joussen concluded by drawing attention to the lack of standardized procedures and perioperative management for tumor resection surgery, with lack of consensus regarding the need for a neoadjuvant radiotherapy prior to surgery and the optimal type of radiation. Successful local resection requires a highly skilled team, careful case selection, and good preparation of the patient.

Quality of Life after Treatment for UM

Bertil Damato discussed quality-of-life outcomes after treatment for UM, emphasizing that because ocular oncologists and patients expend much effort and expense to conserve the eye and vision with the aim of improving quality of life, it is essential to measure quality of life and factors influencing this outcome, to improve care. These studies should help decide which patients should undergo eye-conserving treatment and what therapeutic modality provides the best well-being in a particular patient. These studies should also indicate the impact of long-term monitoring of suspicious nevi and treated melanomas on quality of life.

A study of 1,596 patients treated at the Liverpool Ocular Oncology Centre investigated patient-reported outcomes, anxiety, depression, and well-being after enucleation or radiotherapy [67, 68]. Self-reported quality of life was generally good. Only 10% reported poor quality of life, with only 10% of these patients attributing this to their ocular tumor and its treatment. The main causes of loss of well-being were poor social support, poor general health, and unemployment/financial difficulties, which were beyond the control of ocular oncologists. Similarly,

a study in the USA identified factors within the control of ocular oncology teams that influenced well-being [69]. These included patient education on all aspects their disease, its treatment and likely outcomes and consequences, informed consent for treatment and prognostic biopsy, and psychological support.

Prognostication of UM

As the survival from UM varies greatly from patient to patient, different models have been developed to not only accurately estimate the patient's life expectancy but also to predict metastatic death after tumor dissemination. This information is not only valuable for the patient but also clinically relevant as it can be used to determine the optimal screening frequency. Furthermore, this staging is essential in stratifying UM patients in clinical trials.

Prognostication of Primary UM

Sarah Coupland highlighted in her talk on prognostication in UM that this should be based on the combination of clinical parameters as well as histologic and genetic features of the primary tumors. Such combined multivariable prognostication enables refined stratification of UM patients into metastatic risk groups. This enables targeted surveillance of high-risk UM patients and also enhanced opportunities for clinical trials and meeting patients' demands for accurate estimation of life expectancy [70, 71]. The Liverpool UM Prognosticator Online (LUMPO) has been implemented in clinical care for close to a decade at the supraregional ocular oncology center in Liverpool, UK, and is used by around the world. The latest version of LUMPO – i.e., LUMPO3 – was validated by a recent multicenter study [72].

Bespoke next-generation sequencing techniques, designed for UM, have improved the detection of lethal genetic aberrations in UM [73–75]. Novel technologies, such as digital pathology with artificial intelligence promises to detect loss of BAP1 protein expression, associated with high mortality, in hematoxylin-and-eosin sections [76]. These advances will enhance our understanding of UM biology, improve prognostication, and enable clinical trials evaluating systemic adjuvant therapy.

Algorithms Combining Genetic Data with AJCC Staging

Jens Folke Kiilgaard presented data showing how mortality from metastases increases with higher stages of the Tumor, Node, Metastasis (TNM) American Joint Committee on Cancer (AJCC) system and with chromosome 3 and 8 aberrations [77, 78]. It has been known for a long time that these aberrations are associated with development of metastases from UM, but these chromosomal markers specifically indicate the potential to develop metastases not the survival time. The AJCC stages are built up by combining the anatomic extent of the tumor (thickness, largest basal diameter, involvement of the ciliary body, and extraocular extension), with the presence of lymph node metastases (hardly ever seen in UM), and the presence of distant metastases [77]. Combining information on chromosome aberrations with the anatomical AJCC stage predicted metastatic death differently in patients whose tumor had or did not have abnormal chromosome 3 and/or 8 (Fig. 4) [79]. A nomogram developed by Bagger et al. [64, 80] estimates one-year and five-year survival probability according to AJCC stage and chromosome 3 and 8 status.

Predicting Metastatic Death (after Dissemination)

Kivelä and colleagues [81] explained the importance of an accurate prediction model for survival of patients already known to have clinical metastases. Because UM is a rare cancer, a randomized trial to compare treatments is difficult to conduct. Staging to allow a meaningful comparison of nonrandomized studies and stratification in trials are essential [81]. Different management approaches are otherwise hard to compare: palliative care, systemic therapy, and local treatment are all being used but selection of patients to each of them differ, making results without staging essentially impossible to compare. The Helsinki University Hospital Working Formulation (HUH-WF) showed that the performance index (such as the Karnofsky or WHO score), the largest dimension of the largest metastasis, and serum alkaline phosphatase levels provide independent strong predictors of survival [82]. A subsequent multicenter validation of this staging method successfully separated a cohort of 249 patients into three stages with distinct survival times (an online calculator is available at http://www.prognomics.org/huhwf.aspx) [83]. Two other staging systems created by an Italia-American team and a French team can also be considered [84, 85].

Rantala et al. [86] subsequently showed how the HUH WF differentiates by overall survival also patients managed with best supportive care (BSC) and that using these data, the effectiveness of systemic treatments, and local treatments, such as liver surgery, could be compared [87]. This example clearly showed the importance of stratification, given that the effect of treatment depended

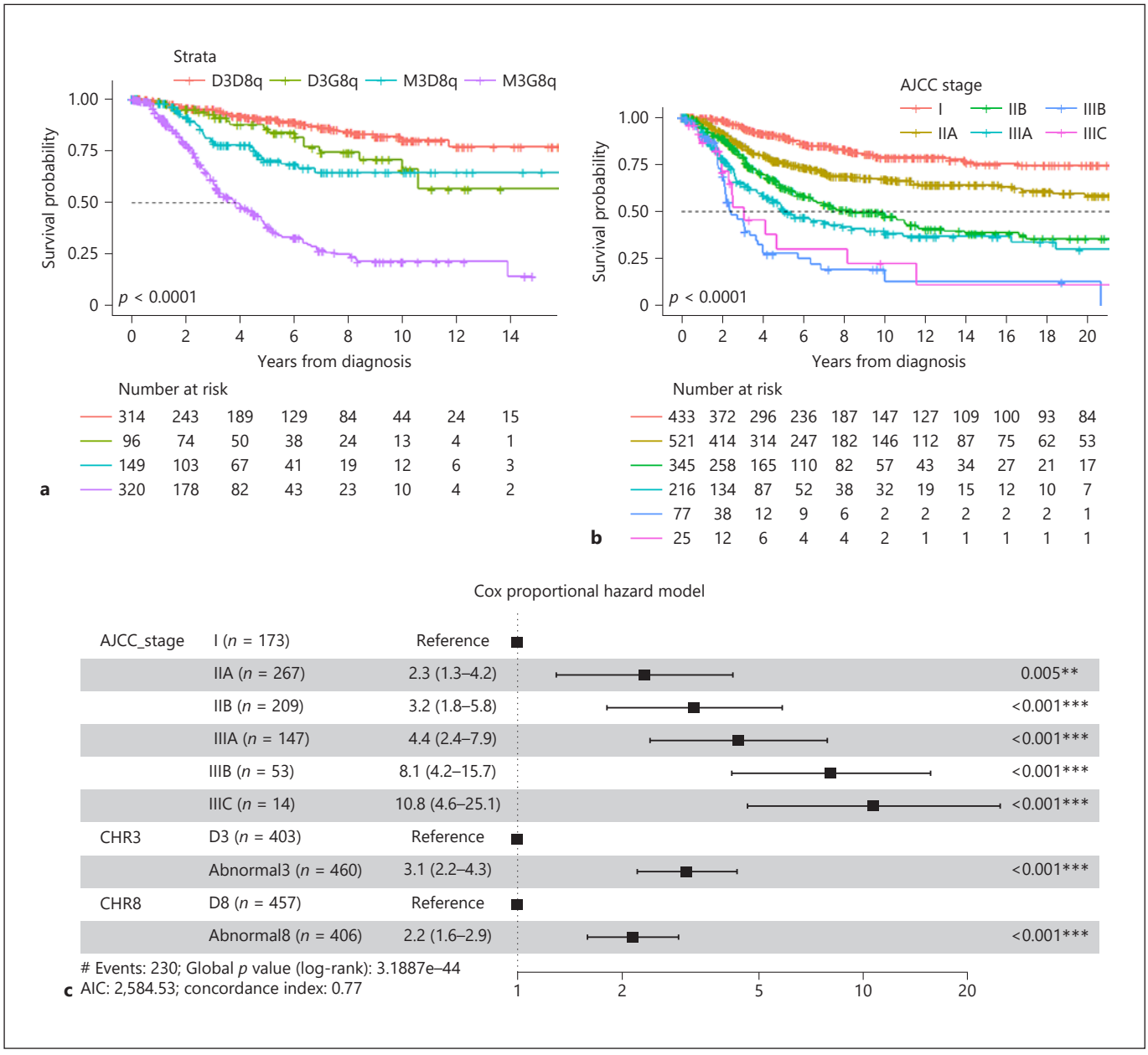

Fig. 4. Kaplan-Meier survival plots of the combined UM populations in Leiden (n = 1,210) and Copenhagen (n = 1,370), with up to 50 years follow-up. **a** Chromosomal status and survival for the pooled populations. **b** Survival plots for the pooled populations stratified for the AJCC staging (8th edition). **c** Forest plot based on Cox proportional regression (R i386 3.6.1). The plot shows that the chromosomal status for CHR3 and CHR8 is independent of the AJCC staging. D3, disomi 3; D8q, disomi 8q; M3, monosomi 3; G8q, gain of chromosome 8q.

strongly on stage, e.g., compared to BSC, and only surgical resection for stage IVa disease provided longer overall survival in the Finnish national cohort. This means that a stage-specific comparison of novel treatments against BSC data is informative because the results would otherwise strongly depend on patient selection and case mix [88, 89]. Selecting only patients in the best prognostic stage would lead to biased conclusion as regards outcomes of treatments. She emphasized that the HUH-WF and other staging systems must continue to evolve, e.g., by including metastasis-free survival time in the model [85, 90].

Treatment of Metastases

Piperno-Neumann et al. [91] mentioned the collaboration within the International Rare Cancers Initiative (IRCI) and the European Reference Network for Rare Adult Cancers (ERN-EURACAN), which stimulate multicenter worldwide trials in collaboration with patient association groups within a reasonable timescale. A meta-analysis of trial data provided an overview of overall survival and progression-free survival of patients treated for metastases of UM with local and systemic treatments and may be used as a benchmark to select patients for future studies [92]. Objectives and endpoints need to be clearly defined in a practice-changing perspective, and adaptive or alternative designs should be considered to optimize the study duration and the sample size [93]. Basket trials based on molecular screening are ongoing, targeting patients with GNAQ/11 mutated tumors (NCT03947385) [87].

Adjuvant trials have stimulated great interest because prediction of metastatic disease is now quite accurate. In such trials, the tumor mutation status should be taken into account because it not only affects survival but potentially also the effectiveness of the treatment. The best outcome parameters are yet to be determined, e.g., overall or metastasis-free survival. Furthermore, given that UM is a rare disease, one may ask what level of evidence is needed to get regulatory approval for a drug.

Conclusion

This workshop, which was supported by the European Vision Institute (EVI), featured numerous new technologies for outcome measures for UM. With the advancement of diagnostic tests, new genetic and imaging biomarkers, and especially potential treatments of metastatic disease, exciting new strategies to improve the care for patients with UM are being developed and integrated into clinical practice.

Conflict of Interest Statement

Beenakker: reports research support from Philips Healthcare. Scholl: editor-in-chief of *Ophthalmic Research*. All other authors report no conflicts of interest.

Funding Sources

Beenakker: part of the research shown is funded by the Dutch Cancer Society (KWF). Brouwer reports funding from the European Commission Horizon 2020 program UMCure (667787) and a MD/PhD program grant from Leiden University Medical Center, Leiden, the Netherlands. Coupland reports funding from the European Commission Horizon 2020 program UMCure (667787). Chau reports grants from Oogfonds, ANVVB, and LSBS that contributed through UitZicht and Wealtheon. Jager reports grants from the European Commission Horizon 2020 program UMCure (667787), Oogfonds, ANVVB, LSBS, and Wealtheon. Kivuh elä reports support from the Finnish Cancer Foundation and the Helsinki University Hospital (Grant No. 2020315), both in Finland. Rantala reports support from the Eye Foundation, the Finnish Medical Foundation, the Mary and Georg C. Ehrnrooth Foundation, the Eye and Tissue Bank Foundation, the Evald and Hilda Nissi Foundation, and the Helsinki University Hospital (Grant No. 2020315) all in Finland. Scholl reports support from the Swiss National Science Foundation, the National Center of Competence in Research Molecular Systems Engineering "Molecular Systems Engineering" and project funding in biology and medicine (#310030_201165), the Wellcome Trust (PINNACLE study), the Translational Research Acceleration Program Award by the Foundation Fighting Blindness (#TA-NMT-0621-0805-TRAP), and the Foundation Fighting Blindness Clinical Research Institute (ProgStar study).

Author Contributions

Beenakker, Wheeler-Schilling, Scholl, Jager, and Damato initiated and organized the EVI meeting. Beenakker, Brouwer, Chau, Coupland, Fiorentzis, Heimann, Heufelder, Joussen, Kiilgaard, Kivuh elä, Piperno-Neumann, Rantala, Romanowska-Dixon, Shields, Willerding, Jager, and Damato presented results at the EVI meeting. Beenakker wrote the manuscript with support from Jager and Damato. All the authors revised the manuscript and approved the final version of the manuscript.

References

1 Jager MJ, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern M-H, et al. Uveal melanoma. Nat Rev Dis Primers. 2020;6(1):24.
2 Abdel-Rahman MH, Pilarski R, Cebulla CM, Massengill JB, Christopher BN, Boru G, et al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. J Med Genet. 2011;48(12):856–9.
3 Carbone M, Ferris LK, Baumann F, Napolitano A, Lum CA, Flores EG, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. J Transl Med. 2012;10(1):179.
4 Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet. 2011;43(10):1022–5.
5 Rai K, Pilarski R, Cebulla CM, Abdel-Rahman MH. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. Clin Genet. 2016;89(3):285–94.
6 Repo P, Järvinen R-S, Jäntti JE, Markkinen S, Täll M, Raivio V, et al. Population-based analysis of BAP1 germline variations in patients with uveal melanoma. Hum Mol Genet. 2019;28(14):2415–26.

7 Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24.
8 Chau C, van Doorn R, van Poppelen NM, van der Stoep N, Mensenkamp AR, Sijmons RH, et al. Families with BAP1-tumor predisposition syndrome in The Netherlands: path to identification and a proposal for genetic screening guidelines. Cancers. 2019;11(8):1114.
9 Pilarski R, Cebulla CM, Massengill JB, Rai K, Rich T, Strong L, et al. Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases. Genes Chromosomes Cancer. 2014;53(2):177–82.
10 Star P, Goodwin A, Kapoor R, Conway RM, Long GV, Scolyer RA, et al. Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy. Eur J Cancer. 2018;92:48–53.
11 Qiu M, Shields CL. Choroidal nevus in the United States adult population: racial disparities and associated factors in the national health and nutrition examination survey. Ophthalmology. 2015;122(10):2071–83.
12 Murray TG, Sobrin L. The case for observational management of suspected small choroidal melanoma. Arch Ophthalmol. 2006;124(9):1342–4.
13 Augsburger JJ, Vrabec TR. Impact of delayed treatment in growing posterior uveal melanomas. Arch Ophthalmol. 1993;111(10):1382–6.
14 Tran AQ, Eadie JA, Altaweel MM. Shaggy photoreceptors with subfoveal fluid associated with a distant choroidal melanoma. Case Rep Ophthalmol Med. 2015;2015:187542–3.
15 Markiewicz A, Romanowska-Dixon B, Jakubowska B, Romanowska-Pawliczek A. Characteristic features of choroidal nevus and small choroidal melanoma in deep range imaging optical coherence tomography. Acta Ophthalmologica Polonica. 2017;119(1):12.
16 Shields CL, Materin MA, Shields JA. Review of optical coherence tomography for intraocular tumors. Curr Opin Ophthalmol. 2005;16(3):141–54.
17 Vishnevskia-Dai V, Zur D, Yaacobi S, Moroz I, Newman H, Neudorfer M. Optical coherence tomography: an adjunctive tool for differentiating between choroidal melanoma and metastasis. J Ophthalmol. 2016;2016:9803547.
18 Geirsdottir A, Palsson O, Hardarson SH, Olafsdottir OB, Kristjansdottir JV, Stefánsson E. Retinal vessel oxygen saturation in healthy individuals. Invest Ophthalmol Vis Sci. 2012;53(9):5433–42.
19 Valverde-Megías A, Say EA, Ferenczy SR, Shields CL. Differential macular features on optical coherence tomography angiography in eyes with choroidal nevus and melanoma. Retina. 2017;37(4):731–40.
20 Brouwer NJ, Marinkovic M, Bleeker JC, Filaliel M, Stefansson E, Luyten GPM, et al. Retinal oximetry is altered in eyes with choroidal melanoma but not in eyes with choroidal nevi. Retina. 2019;40(11):2207–15.
21 Papastefanou VP, Islam S, Szyszko T, Grantham M, Sagoo MS, Cohen VM. Metabolic activity of primary uveal melanoma on PET/CT scan and its relationship with monosomy 3 and other prognostic factors. Br J Ophthalmol. 2014;98(12):1659–65.
22 Calcagni ML, Mattoli MV, Blasi MA, Petrone G, Sammarco MG, Indovina L, et al. A prospective analysis of 18F-FDG PET/CT in patients with uveal melanoma: comparison between metabolic rate of glucose (MRglu) and standardized uptake value (SUV) and correlations with histopathological features. Eur J Nucl Med Mol Imaging. 2013;40(11):1682–91.
23 Brouwer NJ, Marinkovic M, Bleeker JC, Luyten GPM, Jager MJ. Anterior segment OCTA of melanocytic lesions of the conjunctiva and iris. Am J Ophthalmol. 2021;222:137–47.
24 Skalet AH, Li Y, Lu CD, Jia Y, Lee B, Husvogt L, et al. Optical coherence tomography angiography characteristics of iris melanocytic tumors. Ophthalmology. 2017;124(2):197–204.
25 Liu Z, Karp CL, Galor A, Bayyat GJA, Jiang H, Wang J. Role of optical coherence tomography angiography in the characterization of vascular network patterns of ocular surface squamous neoplasia. Ocular Surf. 2020;18(4):926–35.
26 Shields CL, Dalvin LA, Yu MD, Ancona-Lezama D, Di Nicola M, Williams BK, et al. Choroidal nevus transformation into melanoma per millimeter increment in thickness using multimodal imaging in 2355 cases: the 2019 Wendell L. Hughes lecture. Retina. 2019;39(10):1852–60.
27 Dalvin LA, Shields CL, Ancona-Lezama DA, Yu MD, Di Nicola M, Lucio-Alvarez JA, et al. Combination of multimodal imaging features predictive of choroidal nevus transformation into melanoma. Brit J Ophthalmol. 2019;103(10):1441–7.
28 Shields CL, Dalvin LA, Ancona-Lezama D, Yu MD, Nicola MD, Williams BK, et al. Choroidal nevus imaging features in 3,806 cases and risk factors for transformation into melanoma in 2,355 cases. Retina. 2019;39(10):1840–51.
29 The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma: COMS report no. 5. Arch Ophthalmol. 1997;115(12):1537–44.
30 Marous CL, Shields CL, Yu MD, Dalvin LA, Ancona-Lezama D, Shields JA. Malignant transformation of choroidal nevus according to race in 3334 consecutive patients. Indian J Ophthalmol. 2019;67(12):2035–42.
31 Roelofs KA, O'Day R, Harby LA, Arora AK, Cohen VML, Sagoo MS, et al. The MOLES system for planning management of melanocytic choroidal tumors: is it safe? Cancers. 2020;12(5):1311.
32 Harby LA, Sagoo MS, O'Day R, Hay G, Arora AK, Keane PA, et al. Distinguishing choroidal nevi from melanomas using the MOLES algorithm: evaluation in an ocular nevus clinic. Ocular Oncol Pathol. 2021;7:294–302.
33 Boldt HC, Binkley E. Treating small choroidal melanoma: smaller is better. JAMA Ophthalmol. 2018;136(12):1333–4.
34 Hussain R, Czanner G, Taktak A, Damato B, Praidou A, Heimann H. Mortality of patients with uveal melanoma detected by diabetic retinopathy screening. Retina. 2020;40(11):2198–206.
35 Jouhi S, Jager MJ, de Geus SJR, Desjardins L, Eide NA, Grange J-D, et al. The small fatal choroidal melanoma study. A survey by the European Ophthalmic Oncology Group. Am J Ophthalmol. 2019;202:100–8.
36 Shields CL, Sioufi K, Robbins JS, Barna LE, Harley MR, Lally SE, et al. Large uveal melanoma (≥10 mm thickness). Retina. 2018;38(10):2010–22.
37 Sen J, Groenewald C, Hiscott PS, Smith PA, Damato BE. Transretinal choroidal tumor biopsy with a 25-gauge vitrector. Ophthalmology. 2006;113(6):1028–31.
38 Damato BE, Afshar A, Coupland SE, Heimann H, Groenewald C. Diagnostic techniques: other biopsy techniques. Clinical ophthalmic oncology. Springer, Cham; 2019. p. 309–16.
39 Angi M, Kalirai H, Taktak A, Hussain R, Groenewald C, Damato BE, et al. Prognostic biopsy of choroidal melanoma: an optimised surgical and laboratory approach. Brit J Ophthalmol. 2017;101(8):1143–6.
40 Ferreira TA, Fonk LG, Jaarsma-Coes MG, van Haren GGR, Marinkovic M, Beenakker J-WM. MRI of uveal melanoma. Cancers. 2019;11(3):377.
41 Niendorf T, Beenakker J-WM, Langner S, Erb-Eigner K, Cuadra MB, Beller E, et al. Ophthalmic magnetic resonance imaging: where are we (heading to)? Curr Eye Res. 2021;46:1251–70.
42 Foti PV, Travali M, Farina R, Palmucci S, Spatola C, Raffaele L, et al. Diagnostic methods and therapeutic options of uveal melanoma with emphasis on MR imaging-part I: MR imaging with pathologic correlation and technical considerations. Insights Imaging. 2021;12(1):66.
43 Ferreira TA, Jaarsma-Coes MG, Marinkovic M, Verbist B, Verdijk RM, Jager MJ, et al. MR imaging characteristics of uveal melanoma with histopathological validation. Neuroradiology. 2022 Jan;64(1):171–84.
44 Beenakker J-WM, Ferreira TA, Soemarwoto KP, Genders SW, Teeuwisse WM, Webb AG, et al. Clinical evaluation of ultra-high-field MRI for three-dimensional visualisation of tumour size in uveal melanoma patients, with direct relevance to treatment planning. Magn Reson Mater Phys Biol Med. 2016;29(3):571–7.

45 Fleury E, Trnková P, Erdal E, Hassan M, Stoel B, Jaarma-Coes M, et al. Three-dimensional MRI-based treatment planning approach for non-invasive ocular proton therapy. Med Phys. 2020;48(3):1315–26.
46 Nguyen HG, Sznitman R, Maeder P, Schalenbourg A, Peroni M, Hrbacek J, et al. Personalized anatomic eye model from T1-weighted volume interpolated gradient echo magnetic resonance imaging of patients with uveal melanoma. Int J Radiat Oncol Biol Phys. 2018;102(4):813–20.
47 Kamrava M, Sepahdari AR, Leu K, Wang P-C, Roberts K, Demanes DJ, et al. Quantitative multiparametric MRI in uveal melanoma: increased tumor permeability may predict monosomy 3. Neuroradiology. 2015;57(8):833–40.
48 Sepahdari AR, Politi LS, Aakalu VK, Kim HJ, Razek AA. Diffusion-weighted imaging of orbital masses: multi-institutional data support a 2-ADC threshold model to categorize lesions as benign, malignant, or indeterminate. AJNR Am J Neuroradiol. 2014;35(1):170–5.
49 Sepahdari AR, Kapur R, Aakalu VK, Villablanca JP, Mafee MF. Diffusion-weighted imaging of malignant ocular masses: initial results and directions for further study. AJNR Am J Neuroradiol. 2012;33(2):314–9.
50 Soliman A, Aggag M, Abdelgawwad A, Aly W, Yossef A. Role of diffusion weighted MRI in evaluation of orbital lesions. Al-Azhar Int Med J 2020;1(1):331–6.
51 Jaarsma MG, Ferreira TA, van Houdt P, van der Heide UA, Luyten GPM, Beenakker JM. Eye-specific quantitative dynamic contrast-enhanced MRI analysis for patients with intraocular masses. MAGMA. 2022 Apr;35(2):311–23.
52 Denker A, Cordini D, Heufelder J, Homeyer H, Kluge H, Simiantonakis I, et al. Ion accelerator applications in medicine and cultural heritage. Nucl Instrum Methods Phys Res Sect A. 2007;580(1):457–61.
53 Hrbacek J, Mishra KK, Kacperek A, Dendale R, Nauraye C, Auger M, et al. Practice patterns analysis of ocular proton therapy centers: the international OPTIC survey. Int J Radiat Oncol Biol Phys. 2016;95(1):336–43.
54 Seibel I, Cordini D, Hager A, Tillner J, Riechardt AI, Heufelder J, et al. Predictive risk factors for radiation retinopathy and optic neuropathy after proton beam therapy for uveal melanoma. Graefe's Arch Clin Exp Ophthalmol. 2016 Jul;254(9):1787–92.
55 Dobler B, Bendl R. Precise modelling of the eye for proton therapy of intra-ocular tumours. Phys Med Biol. 2002;47(4):593–613.
56 Pfeiffer K, Bendl R. Real-time dose calculation and visualization for the proton therapy of ocular tumours. Phys Med Biol. 2001;46(3):671–86.
57 Seibel I, Cordini D, Rehak M, Hager A, Riechardt AI, Böker A, et al. Local recurrence after primary proton beam therapy in uveal melanoma: risk factors, retreatment approaches, and outcome. Am J Ophthalmol. 2015;160(4):628–36.
58 Egger E, Schalenbourg A, Zografos L, Bercher L, Boehringer T, Chamot L, et al. Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma. Int J Radiat Oncol Biol Phys. 2001;51(1):138–47.
59 Chang MY, McCannel TA. Local treatment failure after globe-conserving therapy for choroidal melanoma. Br J Ophthalmol. 2013;97(7):804–11.
60 Bindewald-Wittich A, Swenshon T, Carasco E, Dreyhaupt J, Willerding GD. Blue-light fundus autofluorescence imaging following ruthenium-106 brachytherapy for choroidal melanoma. Ophthalmologica. 2020;243(4):303–15.
61 Almeida A, Kaliki S, Shields CL. Autofluorescence of intraocular tumours. Curr Opin Ophthalmol. 2013;24(3):222–32.
62 Navaratnam J, Bærland TP, Eide NA, Faber RT, Rekstad BL, Vavvas DG, et al. Fundus autofluorescence change as an early indicator of treatment effect of brachytherapy for choroidal melanomas. Ocular Oncol Pathol. 2019;5(6):445–53.
63 Joussen AM, Wong D. Egress of large quantities of heavy liquids from exposed choroid: a route for possible tumor dissemination via vortex veins in endoresection of choroidal melanoma. Graefes Arch Clin Exp Ophthalmol. 2015;253(2):177–8.
64 Konstantinidis L, Groenewald C, Coupland SE, Damato B. Long-term outcome of primary endoresection of choroidal melanoma. Br J Ophthalmol. 2014;98(1):82–5.
65 Cassoux N, Cayette S, Plancher C, Lumbroso-Le Rouic L, Levy-Gabriel C, Asselain B, et al. Choroidal melanoma: does endoresection prevent neovascular glaucoma in patients treated with proton beam irradiation? Retina. 2013;33(7):1441–7.
66 Damato B, Groenewald C, McGalliard J, Wong D. Endoresection of choroidal melanoma. Br J Ophthalmol. 1998;82(3):213–8.
67 Damato B, Hope-Stone L, Cooper B, Brown S, Heimann H, Dunn L. Patient-reported outcomes and quality of life after treatment for choroidal melanoma. Ocul Oncol Pathol. 2019;5(6):402–11.
68 Damato B, Hope-Stone L, Cooper B, Brown SL, Salmon P, Heimann H, et al. Patient-reported outcomes and quality of life after treatment of choroidal melanoma: a comparison of enucleation versus radiotherapy in 1596 patients. Am J Ophthalmol. 2018;193:230–51.
69 Afshar AR, Deiner M, Allen G, Damato BE. The patient's experience of ocular melanoma in the US: a survey of the ocular melanoma foundation. Ocular Oncol Pathol. 2018;4(5):280–90.
70 Gomez D, Wetherill C, Cheong J, Jones L, Marshall E, Damato B, et al. The Liverpool uveal melanoma liver metastases pathway: outcome following liver resection. J Surg Oncol. 2014;109(6):542–7.
71 Marshall E, Romaniuk C, Ghaneh P, Wong H, McKay M, Chopra M, et al. MRI in the detection of hepatic metastases from high-risk uveal melanoma: a prospective study in 188 patients. Brit J Ophthalmol. 2013;97(2):159–63.
72 Rola AC, Taktak A, Eleuteri A, Kalirai H, Heimann H, Hussain R, et al. Multicenter external validation of the Liverpool Uveal Melanoma Prognosticator Online: an OOG collaborative study. Cancers. 2020;12(2):477.
73 Afshar AR, Damato BE, Stewart JM, Zablotska LB, Roy R, Olshen AB, et al. Next-generation sequencing of uveal melanoma for detection of genetic alterations predicting metastasis. Transl Vis Sci Technol. 2019;8(2):18.
74 Thornton S, Coupland SE, Olohan L, Sibbring JS, Kenny JG, Hertz-Fowler C, et al. Targeted next-generation sequencing of 117 routine clinical samples provides further insights into the molecular landscape of uveal melanoma. Cancers. 2020;12(4):1039.
75 Smit KN, van Poppelen NM, Vaarwater J, Verdijk R, van Marion R, Kalirai H, et al. Combined mutation and copy-number variation detection by targeted next-generation sequencing in uveal melanoma. Modern Pathol. 2018;31(5):763–71.
76 Zhang H, Kalirai H, Acha-Sagredo A, Yang X, Zheng Y, Coupland SE. Piloting a deep learning model for predicting nuclear BAP1 immunohistochemical expression of uveal melanoma from hematoxylin-and-eosin sections. Transl Vis Sci Technol. 2020;9(2):50.
77 Kujala E, Damato B, Coupland SE, Desjardins L, Bechrakis NE, Grange J-D, et al. Staging of ciliary body and choroidal melanomas based on anatomic extent. J Clin Oncol. 2013;31(22):2825–31.
78 Robertson AG, Shih J, Yau C, Gibb EA, Oba J, Mungall KL, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. Cancer Cell. 2017;32(2):204–20.
79 Dogrusöz M, Bagger M, van Duinen SG, Kroes WG, Ruivenkamp CAL, Böhringer S, et al. The prognostic value of AJCC staging in uveal melanoma is enhanced by adding chromosome 3 and 8q status. Invest Ophthalmol Vis Sci. 2017;58(2):833–42.
80 Bagger MM. Intraocular biopsy of uveal melanoma risk assessment and identification of genetic prognostic markers. Acta Ophthalmol. 2018;96 Suppl A112:1–28.
81 Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. Melanoma Res. 2019;29(6):561–8.
82 Eskelin S, Pyrhönen S, Hahka-Kemppinen M, Tuomaala S, Kivelä T. A prognostic model and staging for metastatic uveal melanoma. Cancer. 2003;97(2):465–75.
83 Kivelä TT, Piperno-Neumann S, Desjardins L, Schmittel A, Bechrakis N, Midena E, et al. Validation of a prognostic staging for metastatic uveal melanoma: a collaborative study of the European Ophthalmic Oncology Group. Am J Ophthalmol. 2016;168:217–26.

84 Mariani P, Dureau S, Savignoni A, Rouic LL, Levy-Gabriel C, Piperno-Neumann S, et al. Development of a prognostic nomogram for liver metastasis of uveal melanoma patients selected by liver MRI. Cancers. 2019;11(6):863.
85 Valpione S, Moser JC, Parrozzani R, Bazzi M, Mansfield AS, Mocellin S, et al. Development and external validation of a prognostic nomogram for metastatic uveal melanoma. PLoS One. 2015;10(3):e0120181.
86 Rantala ES, Hernberg MM, Lundin M, Lundin J, Kivelä TT. Metastatic uveal melanoma managed with best supportive care. Acta Oncol. 2020;60(1):1–5.
87 Rantala ES, Kivelä TT, Hernberg MM. Impact of staging on survival outcomes: a nationwide real-world cohort study of metastatic uveal melanoma. Melanoma Res. 2021;31(3):224–31.
88 Augsburger JJ, Corrêa ZM, Shaikh AH. Quality of evidence about effectiveness of treatments for metastatic uveal melanoma. Trans Am Ophthalmol Soc. 2008;106:128–7; discussion 135–7.
89 Pons F, Plana M, Caminal JM, Pera J, Fernandes I, Perez J, et al. Metastatic uveal melanoma. Melanoma Res. 2011;21(3):217–22.
90 Cassoux N, Rodrigues MJ, Plancher C, Asselain B, Levy-Gabriel C, Rouic LL-L, et al. Genome-wide profiling is a clinically relevant and affordable prognostic test in posterior uveal melanoma. Brit J Ophthalmol. 2014;98(6):769.
91 Piperno-Neumann S, Piulats JM, Goebeler M, Galloway I, Lugowska I, Becker JC, et al. Uveal melanoma: a European network to face the many challenges of a rare cancer. Cancers. 2019;11(6):817.
92 Khoja L, Atenafu EG, Suciu S, Leyvraz S, Sato T, Marshall E, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an International Rare Cancers Initiative (IRCI) Ocular Melanoma study. Ann Oncol. 2019;30(8):1370–80.
93 Bogaerts J, Sydes MR, Keat N, McConnell A, Benson A, Ho A, et al. Clinical trial designs for rare diseases: studies developed and discussed by the International Rare Cancers Initiative. Eur J Cancer. 2015;51(3):271–81.