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Metastatic uveal melanoma: The final frontier

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ABSTRACT

Treatment of primary intraocular uveal melanoma has developed considerably, its driver genes are largely unraveled, and the ways to assess its risk for metastases are very precise, being based on an international staging system and genetic data. Unfortunately, the risk of distant metastases, which emerge in approximately one half of all patients, is unaltered. Metastases are the leading single cause of death after uveal melanoma is diagnosed, yet no consensus exists regarding surveillance, staging, and treatment of disseminated disease, and survival has not improved until recently. The final frontier in conquering uveal melanoma lies in solving these issues to cure metastatic disease. Most studies on metastatic uveal melanoma are small, uncontrolled, retrospective, and do not report staging. Meta-analyses confirm a median overall survival of 10–13 months, and a cure rate that approaches nil, although survival exceeding 5 years is possible, estimated 2% either with first-line treatment or with best supportive care. Hepatic ultrasonography and magnetic resonance imaging as surveillance methods have a sensitivity of 95–100% and 83–100%, respectively, to detect metastases without radiation hazard according to prevailing evidence, but computed tomography is necessary for staging. No blood-based tests additional to liver function tests are generally accepted. Three validated staging systems predict, each in defined situations, overall survival after metastasis. Their essential components include measures of tumor burden, liver function, and performance status or metastasis free interval. Age and gender may additionally influence survival. Exceptional mutational events in metastases may make them susceptible to checkpoint inhibitors. In a large meta-analysis, surgical treatment was associated with 6 months longer median overall survival as compared to conventional chemotherapy and, recently, tebentafusp as first-line treatment at the first interim analysis of a randomized phase III trial likewise provided a 6 months longer median overall survival compared to investigator's choice, mostly pembrolizumab; these treatments currently apply to selected patients. Promoting dormancy of micrometastases, harmonizing surveillance protocols, promoting staging, identifying predictive factors, initiating controlled clinical trials, and standardizing reporting will be critical steppingstones in reaching the final frontier of curing metastatic uveal melanoma.

1. Introduction

Uveal melanoma, by far the most common primary malignant intraocular tumor in adults, shows wide variation in its incidence from 0.1 to 8.6 per million by age, ethnicity, and latitude (Abrahamsson, 1983; Kivelä, 2014; Park et al., 2015; Raivio, 1977; Singh et al., 2011; Stang et al., 2005; Virgili et al., 2007). In contrast to cutaneous melanoma – which is genetically an entirely different type of cancer but similar with conjunctival melanoma, a cancer that is not infrequently lumped with uveal melanoma as "ocular melanoma" in non-ophthalmological literature (Griewank et al., 2013; van der Kooij et al., 2019) – the age-adjusted incidence of uveal melanoma both in Europe and in North America increases from southern to northern latitudes and is thus inversely associated with the intensity of ultraviolet radiation (Kivelä, 2014; Virgili et al., 2007). Moreover, the incidence of

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Abbreviations

AJCC	American Joint Committee on Cancer
ALT	alanine transaminase
AP	alkaline phosphatase
AST	aspartate aminotransferase
BAP1	BRCA1-associated protein 1
BOLD	bleomycin, vincristine (Oncovin), lomustine, and dacarbazine
BRAF	B-Raf proto-oncogene
BSC	best supportive care
CHT	conventional chemotherapy
CIT	chemoimmunotherapy with interferon or interleukin
CPI	checkpoint inhibitor
CT	computed tomography
CTLA	cytotoxic T-lymphocyte associated protein
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
GT	gamma-glutamyl transferase
HIA	hepatic intra-arterial chemotherapy
HR	hazard ratio
HUH	Helsinki University Hospital
IHP	isolated hepatic perfusion
ImmTAC	immune-mobilizing monoclonal T-cell receptor against cancer
LBD	largest basal diameter
LDH	lactate dehydrogenase
LDLM	the largest diameter of the largest metastasis
LFT	liver function test
MBD4	methyl-CpG binding domain-4
MFI	distant metastasis-free interval
MRI	magnetic resonance imaging
OOG	Ophthalmic Oncology Group
OS	overall survival
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PET	positron emission tomography
PFS	progression-free survival
PHP	percutaneous hepatic perfusion
PKI	protein kinase inhibitor
SEER	Surveillance, Epidemiology, and End Results Program
SF3B1	splicing factor 3B subunit 1
SIRT	selective internal radiation therapy
TACE	transarterial chemoembolization
TNM	tumor, node, metastasis
TTP	time to progression
UNL	upper normal limit
US	ultrasonography

uveal melanoma has remained essentially stable unlike that of cutaneous and conjunctival melanoma, both of which have become increasingly more common (Aronow et al., 2018; Kivelä, 2014; Singh and Topham, 2003; Singh et al., 2011; Tuomaala et al., 2002; Tuomaala and Kivelä, 2003). The increase for conjunctival melanoma is limited to its sun exposed areas, which supports that increased exposure to ultraviolet radiation is a modifiable underlying factor (Triay et al., 2009). Although iris melanomas that amount to 8% of all uveal melanomas (Shields et al., 2012) share some of the genetic characteristics of cutaneous and conjunctival melanoma associated with exposure to ultraviolet radiation (Johansson et al., 2020; van Poppelen et al., 2018), no avoidable predisposing factor is known for uveal melanoma.

Approximately half of uveal melanomas (52%) eventually result in clinical metastases by 35 years; the 10-year mortality is about 43% (Bergman et al., 2003; Diener-West et al., 2005; Kujala et al., 2003). When patients develop clinical metastases, the liver is the first site involved in over 90% of them (Albert et al., 1996; Bedikian et al., 1995; Diener-West et al., 2004, 2005; Einhorn et al., 1974; Eskelin et al., 2003; Frenkel et al., 2009; Gragoudas et al., 1991; Kim et al., 2010; Kodjikian et al., 2005a; Lorenzo et al., 2019; Marshall et al., 2013; Nicholas et al., 2018; Piperno-Neumann et al., 2015; Rietschel et al., 2005; Rivoire et al., 2005; The Collaborative Ocular Melanoma Study Group, 2001). This propensity was described early on as the most unusual phenomenon in tumor biology (Einhorn et al., 1974; Smit et al., 2020; van der Kooij et al., 2019); other tropisms have been recognized later. Although 89% of uveal melanomas disseminate first to the liver, about 10% do not show this preference for initial hepatic dissemination, however, and metastasize to multiple diverse organs instead (Diener-West et al., 2005).

No consensus exists on surveillance for early detection of metastases or how to best treat them, although national guidelines agree that patients should be considered for surgical resection of metastases and clinical trials. Each center appears to have its preferred target population, modality of imaging, and follow-up schedule for surveillance, if any is organized. The average uveal melanoma disseminates early but grows slowly as evidenced by the rarity of clinical metastases at the time of diagnosis of the primary tumor and appearance of metastases over several decades subsequently (Eskelin et al., 2000; Kujala et al., 2003). Consequently, clinical metastases detected at the time of diagnosis of the primary tumor (i.e., synchronous metastases) are rare, 1–3%, unless the tumor already is very large (the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) stage T4) (Garg et al., 2021). It is thus more frequent to detect benign hepatic abnormalities and even synchronous second primary cancers at that time (Feinstein et al., 2010; Freton et al., 2012; Garg et al., 2021). The frequency of surveillance often depends on participation in ongoing trials and the estimated risk of dissemination as indicated by clinical stage, cell type, and genetic or gene expression profile of the primary tumor, with lower and higher risk patients most often surveilled initially every 12 months and at 3- to 6-month intervals, respectively (Choudhary et al., 2016; Davanzo et al., 2019; Diener-West et al., 2004; Gomez et al., 2014; National Comprehensive Cancer Network, 2021; Piperno-Neumann et al., 2015; Rantala et al., 2020b). In Europe, hepatic ultrasonography (US) is widely used for surveillance for metastases, and computed tomography (CT) and magnetic resonance imaging (MRI) are scheduled if a suspicious new lesion is detected (Eskelin et al., 1999; Gombos et al., 2004; Rivoire et al., 2005; Servois et al., 2010). Some large centers prefer MRI also for surveillance in high-risk patients (Gomez et al., 2014; Mariani et al., 2019). In the United States US is used less frequently (Balasubramanya et al., 2016; Choudhary et al., 2016; Gombos et al., 2004).

Because of the rarity of uveal melanoma, the number of patients with metastatic uveal melanoma is small compared with metastatic cutaneous melanoma, for which reason very few randomized controlled treatment trials have so far been conducted in the metastatic setting. These include hepatic intra-arterial against intravenous fotemustine (Leyvraz et al., 2014); selumetinib against placebo, both combined with dacarbazine (Carvajal et al., 2018); tebentafusp against investigator's choice, mostly pembrolizumab (Nathan et al., 2021; Piperno-Neumann et al., 2021); immunoembolization against bland embolization (Valsecchi et al., 2015); intrahepatic cisplatin with or without polyvinyl sponge (Agarwala et al., 2004); and a discontinuation trial with cabozantinib (Daud et al., 2017). The largest of these randomized trials enrolled 378 patients (Piperno-Neumann et al., 2021).

Retrospective cohort studies on metastatic uveal melanoma predominate and mostly lack patient-level prognostic factors and treatment

data, especially when not treated after first-line (Augsburger et al., 2008). Early on, patients who underwent surgery for metastases were suggested to have a longer overall survival (OS; for the purpose of this review, the time from either the date of diagnosis or the start of treatment for metastatic uveal melanoma to death or last follow-up) (Fournier et al., 1984; Gunduz et al., 1998), but these patients had in common early detection of relatively few metastases (Gomez et al., 2014). Immuno-oncological treatments, i.e. checkpoint inhibitors, effective in metastatic cutaneous melanoma (Schadendorf et al., 2015; Seth et al., 2020) have not been proven to prolong survival in randomized trials (Pelster et al., 2021; Piulats et al., 2021) or meta-analyses (Khoja et al., 2019; Rantala et al., 2019) of patients with metastatic uveal melanoma either as monotherapy or in combination. Choroidal melanoma carries no V600E driver mutations in B-Raf proto-oncogene (*BRAF*) (Cruz et al., 2003; Rimoldi et al., 2003; Robertson et al., 2018; Royer-Bertrand et al., 2016; Shain et al., 2019; Smit et al., 2020; van Poppelen et al., 2018) that are typical of cutaneous melanoma and make the latter responsive to BRAF inhibitors, and they have a very low tumor mutation burden (Yarchoan et al., 2017). Occasional uveal melanomas harbor either a germline or a somatic loss-of-function variant in the methyl-CpG binding domain-4 (*MBD4*) gene that may make them sensitive to checkpoint inhibitors (Johansson et al., 2019; Repo et al., 2020; Rodrigues et al., 2018, 2019).

At the time when mainly liver function tests (LFT) and chest radiograms, if any, were used for surveillance, the median OS after diagnosis of metastatic uveal melanoma was less than 6 months (Diener-West et al., 2005; Gragoudas et al., 1991; The Collaborative Ocular Melanoma Study Group, 2001). Today, a median OS is 12–13 months according to a meta-analysis of 78 articles and 2494 patients of whom 20% received first-line treatment (Rantala et al., 2019). Thirteen percent of patients survived for more than 3 years, but by 5 years, almost everyone (99%) had died. After notable progress made in diagnosing the primary uveal melanoma early, treating it effectively and preserving the eye and at least some vision in the majority of patients, and in unraveling the major genetic events related to tumor progression (Damato, 2018; Shields et al., 2000), the final frontier in managing patients with uveal melanoma lies in targeting the metastatic cascade and preventing death.

Toward that aim, we provide an evidence-based general insight into the contemporary science related especially to making the diagnosis, assessing the prognosis, assigning the stage, and choosing the treatment when faced with a patient who has metastatic uveal melanoma. We propose guidelines for surveillance and for reporting of prognostic factors and clinical trials and identify the steps most needed for future research.

2. Epidemiology

2.1. The metastatic cascade

Uveal melanoma, except in the exceedingly uncommon instance that it has infiltrated transsclerally and invaded the conjunctival lymphatics (Dithmar et al., 2000), disseminates solely hematogenously, often early in its asymptomatic phase. They have no basal membrane to breech to become invasive and to gain access to blood vessels unlike is the case with cutaneous and mucosal melanomas (Folberg, 1993). Circulating tumor cells are, consequently, common (10–88%) in patients with uveal melanoma (Anand et al., 2019; Bidard et al., 2014; Callejo et al., 2007; Suesskind et al., 2011; Ulmer et al., 2008). Unlike in most other cancers, these cells do not usually colonize the lungs first, which would be anatomically logical, because of their remarkable and so far ill understood tropism to the liver (Einhorn et al., 1974). Uveal melanomas adhere exceptionally well to the 'seed and soil' theory (Paget, 1989) that postulates specific organs to be more suitable for establishment and progression of metastases of certain cancers than other organs (Li et al., 2008).

2.1.1. Timing of micrometastasis

The small percentage of patients, typically 1–3%, who have evidence of clinical synchronous metastases at the time of diagnosis of their primary tumor (Feinstein et al., 2010; Freton et al., 2012; Garg et al., 2021; Smidt-Nielsen et al., 2021), together with the fact that metastases from uveal melanoma is the most common cause of death indicate early subclinical metastasis in patients who have acquired the genetic events necessary for dissemination (Eskelin et al., 2000; Kujala et al., 2003). Although more than one half of all metastases (62%) are diagnosed within the first five years after treating the primary tumor, the rest become clinically detectable only during the next 25 years (Kujala et al., 2003). It is thus clear that the ability of uveal melanoma cells to escape the eye is not the same as the ability of its micrometastases to grow. Although the processes that delay clinical metastasis remain unknown, a combination of progression of the micrometastases toward higher grades of anaplasia and deterioration of defenses against neoplastic growth likely are involved.

Evidence from the recent Small Fatal Choroidal Melanoma Study of the European Ophthalmic Oncology Group (OOG) suggests that 3.0 mm at the time of treatment probably represents the minimum diameter of an incipient choroidal melanoma that is capable of metastasizing (Fig. 1) (Jouhi et al., 2019). This is consistent with previous data on metastasis from the smallest uveal melanomas (Kujala et al., 2013; Malclès et al., 2015; Parrozzani et al., 2009; Robertson, 2008; Shields et al., 2002; Sobrin et al., 2005). In the OOG study, ten ocular oncology centers submitted data on all patients with a choroidal melanoma not exceeding 3 mm in thickness and 9 mm in largest basal diameter (LBD) when treated and who subsequently developed metastases. It confirmed that choroidal melanomas less than 3.0 mm in LBD at the time of treatment most likely do not metastasize (Fig. 2).

Most (65–76%) primary choroidal and ciliary body melanomas are diagnosed and initially treated when much larger than 9 mm in LBD (AJCC Ophthalmic Oncology Task Force, 2015; Kujala et al., 2013). Nevertheless, metastasis is still a relatively rare occurrence after treatment if the tumor is less than 9 mm in diameter (Jouhi et al., 2019). In another collaborative study of the OOG that the American Joint Committee on Cancer adopted for the 7th edition of its Tumor, Node, Metastasis TNM staging system for ciliary body and choroidal melanoma, among 7369 primary uveal melanomas of all sizes 12, 160, and

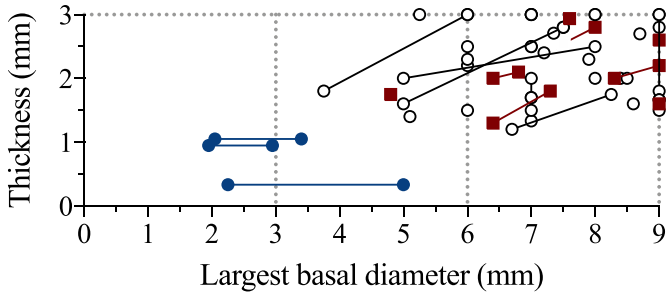


Fig. 1. Empirical evidence regarding timing of first micrometastases. The Small Fatal Choroidal Melanoma Study of the European Ophthalmic Oncology Group collected from ten participating centers data of all patients who had a choroidal melanoma 3 mm or less in thickness and 9 mm or less in largest basal diameter (LBD) when they were treated and who later developed clinical metastases. None of the 45 patients identified developed metastases if the tumor was less than 3 mm in LBD when it was treated. Note that three of the four smallest melanomas that metastasized were observed for growth and were less than 3 mm in LBD when they were detected (blue). Note that all but one of the other small fatal melanomas were at least 5 mm in diameter at the time of treatment. Melanomas that were observed for growth are identified by lines connecting their size when first seen and when treated, and tumors that recurred after treatment are indicated in red, irrespective of whether they were also first observed or not. Adapted, by adding color, from (Jouhi et al., 2019), https://doi.org/10.1016/j.ajo.2019.01.031, CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

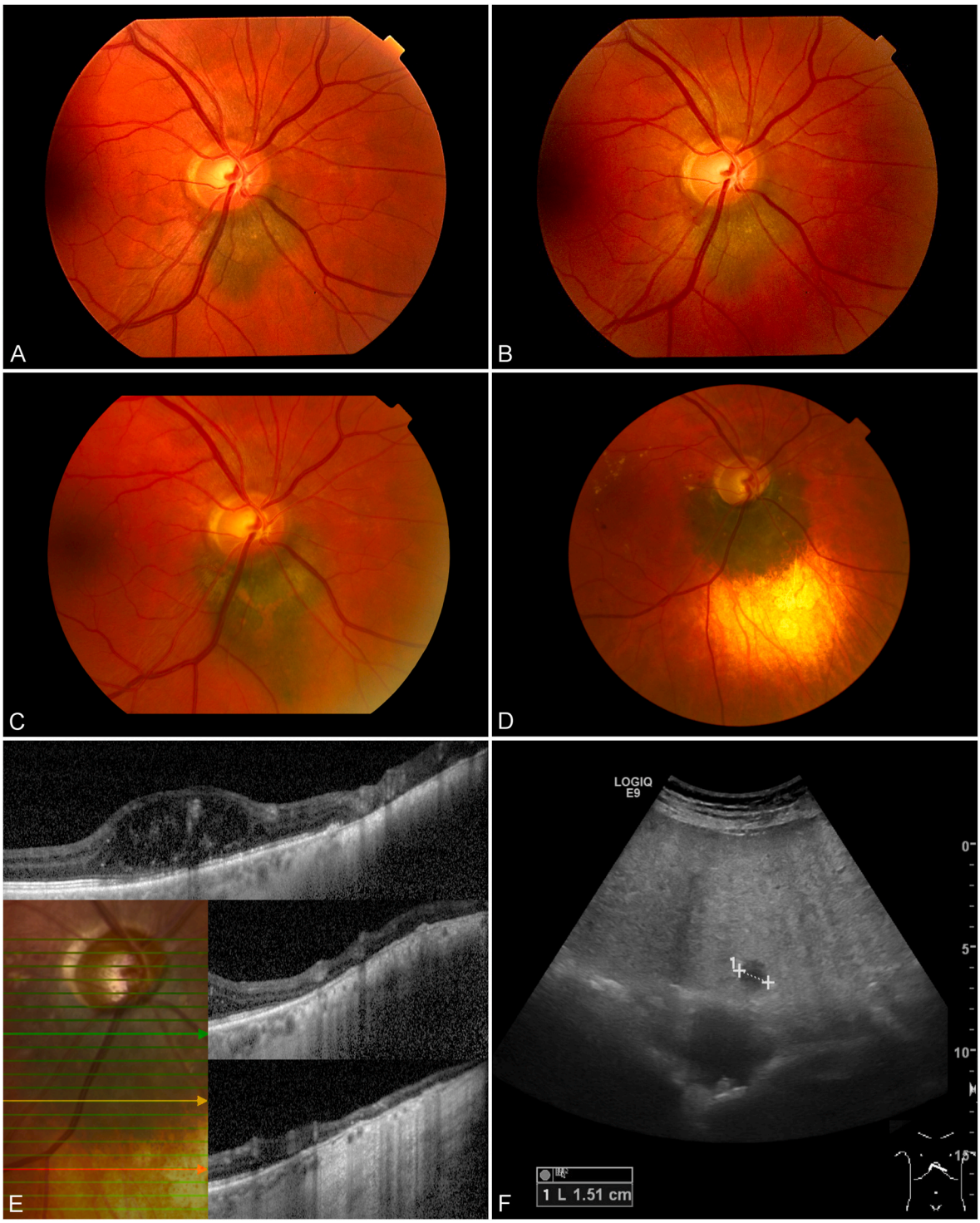


Fig. 2. A small fatal uveal melanoma. A slightly elevated choroidal tumor (T1a, stage I) with orange pigment is 2.4 mm in largest basal diameter when first seen (**A**). No growth was observed during the first year (**B**) and follow-up was continued elsewhere. The patient was referred for treatment after 5 years because the diameter had grown to 3.4 mm (**C**). The tumor was 1 mm thick and was treated with a conformal optic nerve notched iodine plaque, dose 95 Gy, shown 6 years after treatment (**D**). Optical coherence tomography at that time shows a flat scar and radiation maculopathy; the three sections correspond with the green, yellow and red arrows on the localizing grid lines (**E**). One year later, an annual surveillance upper abdominal ultrasonography showed a new solitary 15 mm lesion of low echogenicity (**F**). The radiologist interpreted it as a cyst and recommended observation. Because it did not show posterior acoustic enhancement and was not entirely anechoic magnetic resonance imaging was pursued instead. It found three lesions that did not show features typical of metastases. A core needle biopsy failed because of the localization. Multiple small pigmented subcapsular metastases were additionally seen at laparoscopic biopsy. The patient was treated with selective internal radiation therapy, went through four lines of subsequent treatment, developed also bone metastases, and died three years after diagnosis of metastases.

613 eyes were enrolled that were 3.0 mm or less in thickness and measured up to 3.0 mm, from 3.1 to 6.0 mm, and from 6.1 to 9.0 mm in LBD, respectively (Kujala et al., 2013). None (0%), 8 (5%), and 33 (5%) of these patients died of metastases, respectively. This was not only consistent with the Small Fatal Choroidal Melanoma Study in that the 10-year survival rate was 100% when the tumor was up to 3.0 mm in tdiameter, but also suggests that the vast majority (about 90%) of small (T1) uveal melanomas that are less than 3 mm in thickness and 9.0 mm in LBD when treated has not yet the capacity to seed micrometastases, at least not such that are able to progress outside the eye.

In general, 30 tumor doublings are needed that the size of the metastasis will be approximately 1 cm^3 (Collins et al., 1956; Schwartz, 1961). At least two doubling times are relevant for patients with uveal melanoma: one for the primary tumor and one for the clinical metastasis (Eskelin and Kivelä, 2001; Eskelin et al., 2000; Singh et al., 2011). In practice, both stages of the tumor are likely to have clones that have diverged and grow at different rates. The median doubling time of the primary uveal melanoma has been reported to range from 154 to 511 days (Augsburger et al., 1984; Char et al., 1997), and that of the clinical metastasis from 30 to 80 days (Eskelin et al., 2000). Mathematical modeling based on these estimates, presuming that the lowest median estimate of 154 days best applies to those primary tumors that are the most likely to metastasize, predicts that it will take about 5 years for an average micrometastasis to grow into a size that is typically diagnosed through surveillance, an event that takes place a median of 2.2 years after the diagnosis of the primary tumor (Fig. 3) (Eskelin and Kivelä, 2001). This model also predicts that at the time when the primary uveal melanoma is diagnosed, the metastasis would be on average 0.7 mm in diameter (0.5 mm^3 in volume) and, thus, not visible with current imaging methods. This fits very well with the rarity of clinical metastasis (1%–3%) at the time of diagnosis of the primary tumor (Garg et al., 2021).

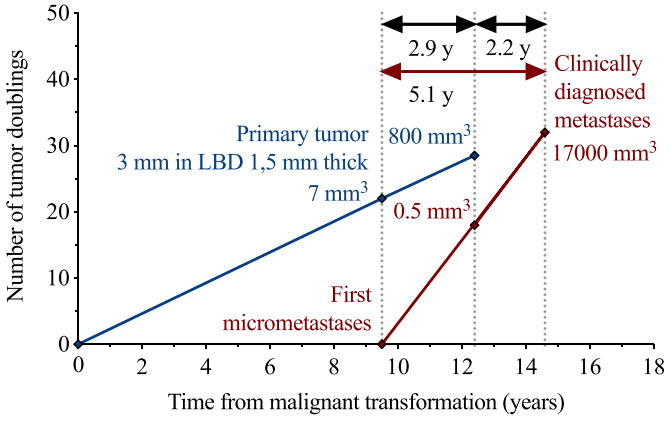


Fig. 3. Mathematical modeling of the cascade of metastases from uveal melanoma. Based on typical published tumor doubling times (154 days from Augsburger et al. (1984) for a primary uveal melanoma likely to metastasize and the median volume of a newly diagnosed primary tumor (from Eskelin et al., 2000)) it would take an average of 12.4 years from the malignant transformation of a single cell to reach the diagnosis of the primary tumor (*blue annotations*). Based on the median observed metastasis-free interval 2.2 years, the median estimated tumor doubling times of these largest metastases, and their median volume when detected (from Eskelin et al., 2000), it would take an average of 5.1 years from the first micrometastasis to reach clinical diagnosis (*red annotations*). The two curves allow making three inferences. The primary tumor would be on average 7 mm^3 in volume. This approximates a tumor that is 3 mm in diameter and 1.5 mm in thickness. The growing metastasis would be on average 0.5 mm^3 in volume and, thus, about 0.7 tmm in diameter when the primary tumor is diagnosed. This is consistent with the experience that only about 2% of patients have concurrent clinical metastases when the primary tumor is detected, although about 50% develop metastases later. Finally, micrometastasis would begin on average 2.9 years before the primary tumor is diagnosed. Data correspond to results published in (Augsburger et al., 1984; Eskelin et al., 2000; Eskelin and Kivelä, 2001).

Interestingly, this mathematical modeling suggests that when micrometastasis begins the primary tumor is about 3 mm in diameter (7 mm^3 in volume). From the clinical point of view, an incipient uveal melanoma below this size may not yet show any of their traditional clinical characteristics, suggesting that the only way to diagnose one clinically would be to observe that its growth rate is not consistent with a benign naevus (Jouhi et al., 2021).

2.1.2. *Pattern of metastasis*

Uveal melanoma metastasizes hematogenously to the liver via the hepatic artery and, possibly, in part via the splenic artery that supplies the spleen and then drains into the portal vein through the splenic vein. Once in the liver, two patterns of growth are proposed based on behavior in the liver microenvironment: an *infiltrative growth pattern* in the vast majority of cases, and a *nodular growth pattern* in the rest (Fig. 4) (Grossniklaus, 2013; Grossniklaus et al., 2016). In the infiltrative pattern, single uveal melanoma cells first form micrometastases in the sinusoidal spaces of the liver, and then expand to destroy adjacent hepatocytes and to form macrometastases that become encapsulated by collagenous matrix. In the nodular pattern, uveal melanoma cells first aggregate adjacent to portal venules, then grow to destroy adjacent hepatocytes and to form avascular nodules, and then expand to grow into larger vascularized macrometastases.

These two patterns, identified on autopsies (Barnhill et al., 2018; Borthwick et al., 2011), correlate with the findings in MRI (Liao et al., 2018; Tan et al., 2020; Xue et al., 2015). Periportal (nodular) metastases may appear by MRI to respond to chemoembolization or radioembolization while the sinusoidal (infiltrative) pattern does not (Halenda et al., 2016). This is likely due to angiogenesis or ability for the embolization to get to the vascular bed in the nodular pattern, whereas the infiltrative pattern is relatively avascular. Hepatic stellate cells produce collagen in the infiltrative pattern, thus resulting in "pseudosinusoidal spaces" and angiogenesis in the nodular pattern. In mouse models, approximately 60% of metastases are infiltrative and 40% show nodular patterns (Jones et al., 2019).

Histopathologically, hepatic metastases from uveal melanoma are divided in three patterns of growth according to the interface between the metastasis and adjacent normal liver parenchyma (Barnhill et al., 2018). The *desmoplastic growth pattern* is characterized by fibrous tissue at the periphery of the metastasis, the *pushing growth pattern* by compression of adjacent hepatocytes, and the *replacement growth pattern* by infiltrative growth among hepatocytes without architectural changes. Among 41 patients with liver metastases from uveal melanoma, 73% were categorized as showing predominantly the replacement pattern, while the remaining cases showed predominantly desmoplastic pattern (Barnhill et al., 2018). It appears that the replacement pattern is likely the same as the later infiltrative pattern. The desmoplastic and more rare pushing patterns may correspond to the nodular pattern. Some investigators hypothesize that collagenization, as occurs in the desmoplastic response, may limit penetration of drugs and immunotherapies to the liver metastases.

Emerging, unpublished evidence from mouse models suggests a limited immune response involving natural killer cells, T lymphocytes, dendritic cells, and CD11b myeloid derived suppressor cells in the liver tumor microenvironment that may be involved in maintenance of and emergence from dormancy of micrometastases from uveal melanoma. Some evidence exists that hypoxia may be a key factor for micrometastatic uveal melanoma to grow and emerge from dormancy in the liver tumor microenvironment. Preliminary evidence from mouse models also suggests that uveal melanoma may metastasize via the splenic artery, which supplies the spleen; the spleen then drains into the splenic vein, which contributes to the portal vein. The metastases then flow through the portal vein into the liver, which has a dual circulation from the portal vein and hepatic artery.

Recognizing the different growth patterns of metastatic uveal melanoma in the liver may have important clinical implications because the

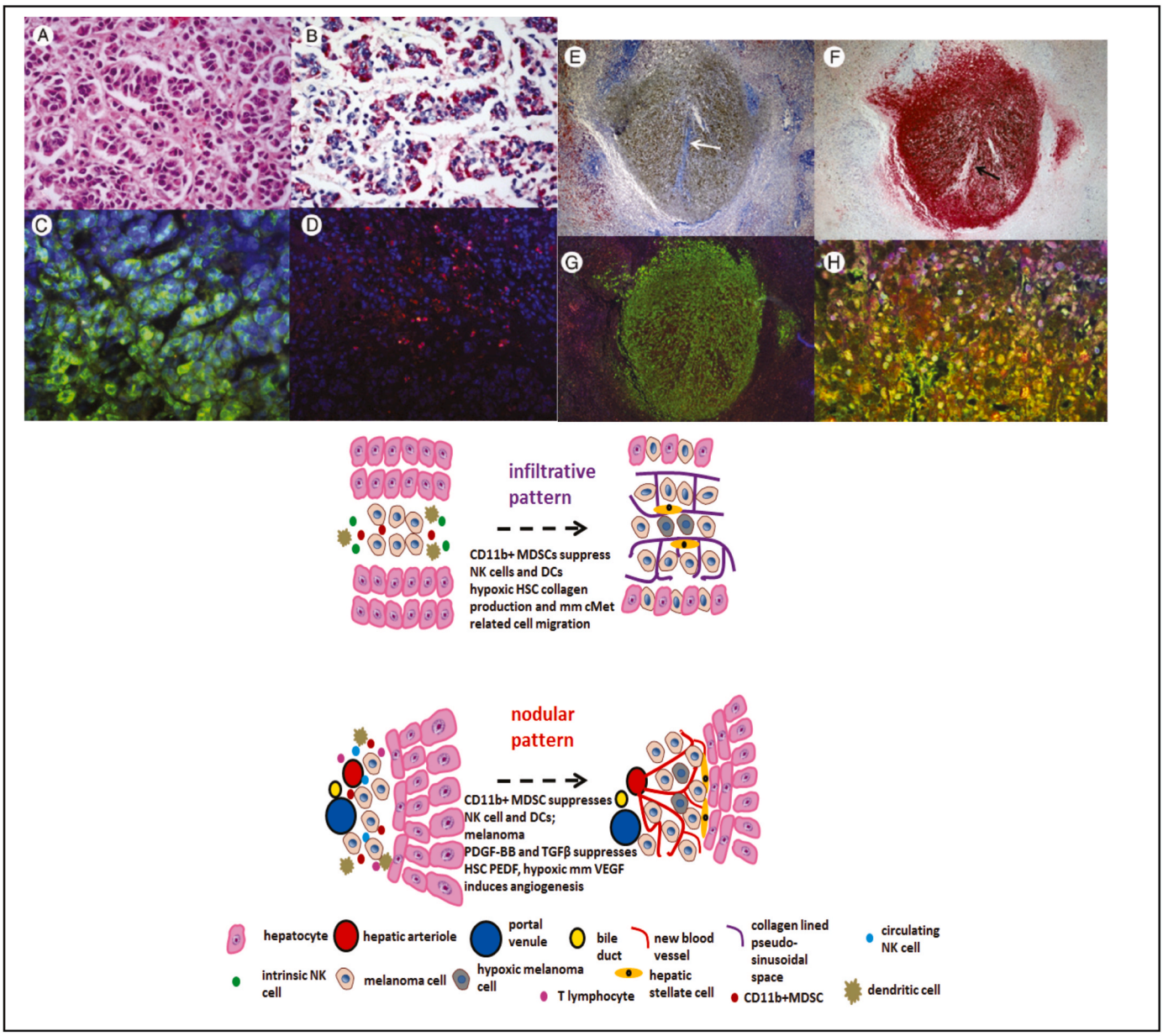


Fig. 4. Growth patterns of metastatic uveal melanoma in the human liver. Metastatic uveal melanoma in the human liver can show sinusoidal infiltrative (A–D) and periportal nodular (E–F) growth patterns. Arrow indicates portal venule with metastatic uveal melanoma forming a nodule in the periportal space; hematoxylin & eosin stain (**A**), immunostaining for HMB45 (**B, C, F, G**) and CD133 (**D**), Masson trichrome stain (**E**), and immunostaining for HMB45/VEGF (**H**). The diagram shows that in the infiltrative pattern, hepatic stellate cells and metastatic uveal melanoma cells elaborate collagen, thus creating pseudosinusoidal spaces that enable cMet-related uveal melanoma migration. In the nodular pattern, hypoxia induced vascular-endothelial growth factor is produced by the uveal melanoma cells. Published in (Grossniklaus, 2013; Grossniklaus et al., 2016), with permission from the publisher (Elsevier).

choice of treatment might be altered according to such differences in immune response, collagen production, and angiogenesis in the future (Liao et al., 2018).

2.1.3. *Frequency and timing of clinical metastases*

At the time of diagnosis of the primary tumor, only 1–3% of patients have clinical synchronous metastases (Feinstein et al., 2010; Freton et al., 2012; Garg et al., 2021; Smidt-Nielsen et al., 2021). This risk, however, is heavily dependent on the stage of the primary tumor (Table 1). According to the current TNM system (8th edition), the risk of having metastases diagnosed concurrently with the primary choroidal or ciliary body melanoma is <1% for T-category T1 (small), ≤1.5% for T2 (medium-sized), 2–3% for T3 (large), and 8–14% for T4 (very large) (Feinstein et al., 2010; Freton et al., 2012; Garg et al., 2021). Thus, although the majority of the patients with concurrent metastases have T3 and especially T4 uveal melanoma, occasionally the primary tumour can be small (Fig. 5).

When metastases are diagnosed together with the primary tumor, they are small (M1a in the TNM system, ≤3.0 cm) in about 80% of patients (Table 1) but typically multiple (most often >10). In 90% of the

Table 1
Frequency of diagnosis of metastatic uveal melanoma by screening at the time of diagnosis of the primary intraocular melanoma according to its Tumor, Node, Metastasis (TNM) T size category; metastases (M1) assign the patient to TNM stage IV.

	New York Eye Cancer Center	International registry study (10 centers from 8 countries)	Helsinki University Hospital
Time period	2003–2010	2001–2011	1999–2017
Reference	Freton et al. (2012)	Garg et al. (2021)	Finnish national referral center
No. with primary tumor	333	3610	1117
Imaging method for screening	FDG-PET/CT	Variable[c]	Mostly upper abdominal ultrasonography[d]
No. with metastases	2.1% (7/333)	1.9% (69/3610)	2.9% (32/1117)
TNM size category[a]			
T1	0% (0/104)	0.7% (8/1131)	0.6% (2/330)
T1a	0	4	1
T1b	0	3	1
T1c	0	1	0
T1d	0	0	0
T2	0% (0/162)	1.5% (20/1312)	0.3% (1/322)
T2a	0	17	0
T2b	0	2	1
T2c	0	1	0
T2d	0	0	0
T3	3% (1/37)	2.6% (23/922)	2.0% (6/296)
T3a	1	13	3
T3b	0	5	2
T3c	0	0	0
T3d	0	5	1
T4	20% (6/30)	7.9% (18/245)	13.5% (23/170)
T4a	2	9	6
T4b	1	5	9
T4c	1	0	1
T4d	0	2	1
T4e	2	2	6
TNM M category[b]			
M1a	86% (6/7)	35% (14/40)	74% (23/31)
M1b	14% (1/7)	63% (25/40)	26% (8/31)
M1c	0% (0/7)	2% (1/40)	0% (0/31)
Metastatic pattern			
Hepatic	71% (5/7)	67% (46/69)	90% (28/31)
Hepatic and extrahepatic	29% (2/7)	25% (17/69)	6% (2/31)
Extrahepatic	0% (0/7)	9% (6/69)	3% (1/31)
HUH Working formulation			
Stage IVa	86% (6/7)	N/A	81% (21/26)
Stage IVb	14% (1/7)	N/A	12% (3/26)
Stage IVc	0% (0/7)	N/A	4% (1/26)
Median survival (range)	N/A	12 (2–91)	12 (1–46)

N/A = not applicable; FDG-PET/CT = 2-deoxy-2-[18F]fluoro-D-glucose-positron emission tomography/computed tomography; HUH = Helsinki University Hospital.
[a] a = limited to choroid; b = ciliary body involvement; c = extraocular extension <5 mm; d = both b and c; e = extraocular extension >5 mm.
[b] a = ≤3.0 cm; b = 3.1–8.0 cm; c = ≥8.1 cm.
[c] 340 (9%) of the 3610 patients were screened with FDG-PET/CT.
[d] Followed by staging with magnetic resonance imaging, computed tomography, or both.

patients the synchronous metastases are found in the liver, but the percentage with extrahepatic metastases in this group can be as high as 29–34%. The median OS in this setting is 12 months. It thus does not differ from that of patients who are later diagnosed with metachronous metastases (Rantala et al., 2019).

In a Surveillance, Epidemiology, and End Results (SEER) registry study of 4070 patients, approximately 10% of patients had a history of a non-ocular primary cancer before the diagnosis of their primary uveal melanoma (Singh et al., 2011). At the time of diagnosis of primary uveal melanoma, the likelihood of diagnosing a non-ocular primary cancer can be higher than the chances of diagnosing asymptomatic metastases, especially in the more favorable TNM categories T1 and T2. When screening was performed with 2-deoxy-2-[18F]fluoro-D-glucose (FDG) -positron emission tomography (PET)/CT, 10 of 333 patients (3.3%) had a synchronous non-ocular primary cancer, all but one in patients with T1 and T2 uveal melanoma (Freton et al., 2012).

Data on very long-term follow-up of patients with primary uveal melanoma suggests that eventually 55% of them will develop metastases despite the usually successful treatment of the primary tumor – the rate of local relapse after eye conserving treatment is 5–10% and far less after primary enucleation (Kujala et al., 2003; Singh et al., 2011). Among 289 consecutive patients with uveal melanoma who underwent enucleation before brachytherapy was available and who were followed long term, 239 patients died; median follow-up of the 50 survivors was 28 years (Kujala et al., 2003). Their cause of death was audited from cancer registry data, patient charts, and immunohistochemical restaining of histologic specimens. The cumulative incidence of dying of a non-ocular primary cancer and a non-cancer related reason by 25 years was 6% and 24%, respectively. As regards these competing causes of death not related to uveal melanoma, the non-cancer related deaths increased from 14% of all deaths during the first 5 years to up to 70% after 15 years. This increase was most notable in the higher age quartiles,

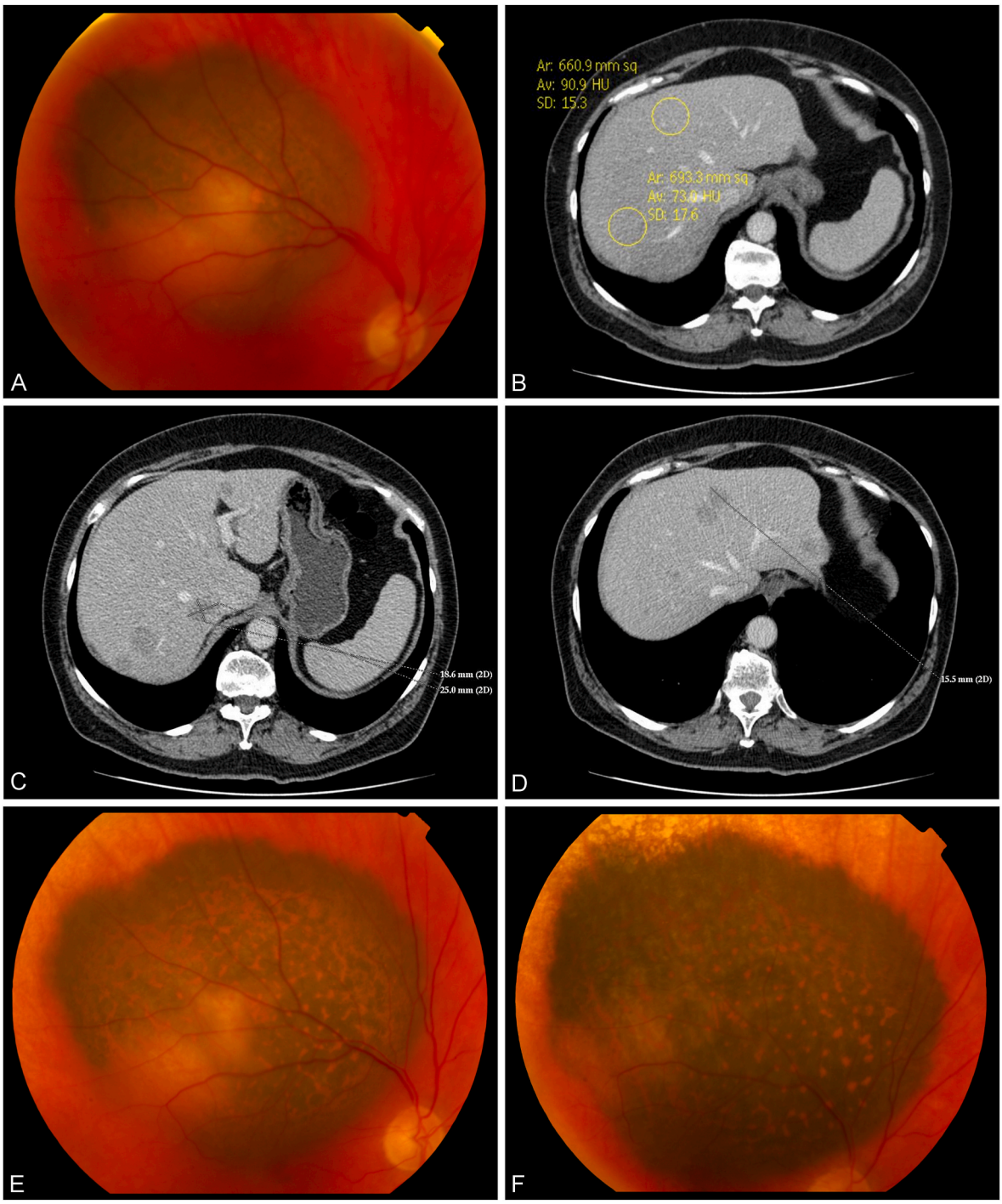


Fig. 5. Synchronous metastases (stage IV) from a small (T1a) uveal melanoma. A Choroidal tumor (largest basal diameter 8.7 mm, thickness 3.2 mm) with both a lake and many dots of orange pigment, and subretinal fluid (**A**). A computed tomography (**CT**) scan performed after a screening upper abdominal ultrasonography (US) identified a low reflective possible metastasis was equivocal; it identified only a few slightly hypodense areas (**B**). A follow-up US two months later showed multiple hypodense 10 mm lesions in both lobes of the liver that were confirmed by CT (**C, D**). The primary tumor, unusually, meanwhile continued to grow after ruthenium brachytherapy with dose 100 Gy to tumor apex and 365 Gy to the sclera (**E**). It was arrested after secondary iodine brachytherapy performed three months later, dose 80 Gy to tumor apex (**F**).

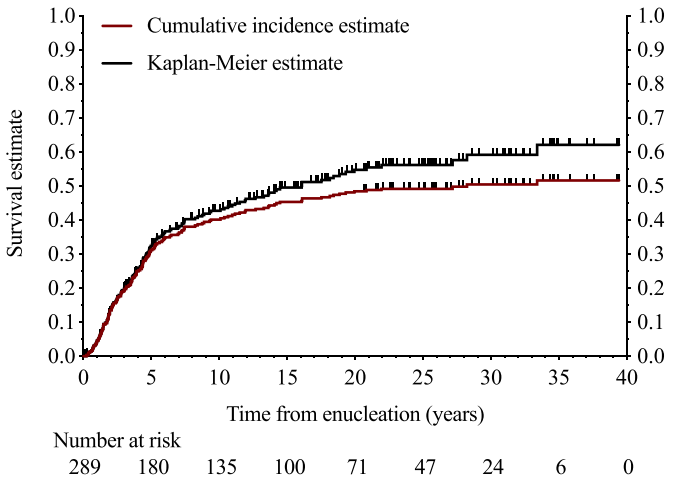


Fig. 6. Kaplan-Meier and cumulative incidence estimates of melanoma-related mortality are different. Only patients who are alive at the time of analysis or are lost to follow-up are censored in cumulative incidence analysis, because only they are still at risk to die of uveal melanoma after censoring (*ticks show censored patients*). Note that in Kaplan-Meier analysis patients who die of other causes also are censored over the entire follow-up time. Because they are no longer at risk of dying of uveal melanoma, the Kaplan-Meier estimate progressively deviates from the cumulative incidence estimate with each censoring event and thus progressively exaggerates mortality from uveal melanoma. The Kaplan-Meier estimate may be interpreted as mortality from uveal melanoma in the theoretical situation that patients would otherwise be immortal; this may be useful for research purposes if deaths from other causes can be viewed as nuisance events that prevent seeing the full effect size of a factor of interest. Estimates from cumulative incidence analysis reflect real-world experiences of patients and are better for patient counseling purposes, however. Data correspond to results published in (Kujala et al., 2003).

because with increasing age, other causes of death may intervene and prevent an otherwise forthcoming metastasis-related death (Kujala et al., 2003).

The metastatic rate of 50% is reached in 10 years in studies using the Kaplan-Meier analysis, which ignore competing causes of death, and in 25 years if competing causes of death are taken into account (Kujala et al., 2003). Therefore, the former studies exaggerate the real-life risk of metastasis-related death (Fig. 6) (Bergman et al., 2003; Eleuteri et al., 2018; Gooley et al., 2001; Kujala et al., 2003). Kaplan-Meier analysis and Cox regression are designed to presume that uveal melanoma would be the only possible cause of death, because their basic assumption is that the risk of dying of metastasis is the same before and after censoring, but obviously, a patient cannot die of metastases when they were censored for already having died of other causes (Aalen et al., 2008). Even after 30 years, metastatic melanoma is the most common single cause of death for patients treated with enucleation, an approach that minimizes risk of metastases from local recurrences, and during the first 15 years, deaths of metastasis outnumber other causes of death combined (Kujala et al., 2003).

Because the life expectancy of women is in general longer than that of men, competing risks differ not only by age but also by gender (Kujala et al., 2003). Women are more likely to live longer and will have more time to develop clinical metastases. Because of this, the real-world experience, which can be estimated by cumulative incidence analysis or relative survival, reveals that proportionally more women than men will eventually die of metastatic uveal melanoma (Fig. 7).

As mentioned, more than half of the clinical metastases are diagnosed during the first 5 years, taking other causes of death into account. Diagnosis of metastasis is most common between 2 and 5 years after the diagnosis of the primary uveal melanoma (Diener-West et al., 2005; McLean et al., 1980). Most patients will develop the first metastasis in the liver and eventually it is involved in more than 90%, followed by the lungs, bone, skin, and lymph nodes (Albert et al., 1996; Bedikian et al., 1995; Diener-West et al., 2004, 2005; Einhorn et al., 1974; Eskelin et al., 2003; Frenkel et al., 2009; Gragoudas et al., 1991; Kim et al., 2010; Kodjikian et al., 2005a; Lorenzo et al., 2019; Marshall et al., 2013; Nicholas et al., 2018; Piperno-Neumann et al., 2015; Rietschel et al., 2005; Rivoire et al., 2005; The Collaborative Ocular Melanoma Study Group, 2001).

2.2. Selection of endpoints

Oncological clinical trials can select from several frequently used endpoints: objective response rate (ORR), overall survival (OS), progression-free survival (PFS), and time to progression (TTP).

Objective response rate is defined as the proportion of patients who have complete responses (CR, complete disappearance of tumor) or partial responses (PR, a defined reduction in the sizes of measurable metastases without emergence of new lesions) for a minimum time period (US Food and Drug Administration, 2018; World Health Organization, 1979). Stable disease (SD), a lesser reduction or a minor enlargement not qualifying as progressive disease (PD), should not be included in ORR. Stable disease can reflect the natural history of disease, whereas tumor reduction is a direct effect of the treatment. When defined in this manner, ORR is a direct measure of anti-cancer activity. There are various response criteria to define partial and complete responses of which the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines are the most widely used in trials on metastatic cancer (Subbiah et al., 2017; Therasse et al., 2000). The present RECIST version 1.1 guidelines take into account advances in imaging, treatment, and understanding of tumors (Eisenhauer et al., 2009).

OS is defined as the time from randomization to death from any cause, and it is generally easily and precisely measured. However, it requires longer follow-up than PFS and TTP, and it is affected also by any subsequent therapies if a treatment that affects the prognosis exists (Brawley and Parnes, 2019a; US Food and Drug Administration, 2018). OS also includes deaths due to other reasons such as non-ocular primary cancer or unrelated medical conditions.

For measuring the effectiveness of cancer drugs, PFS is defined as the time from randomization until objective tumor progression (PD) or death from any cause, whichever occurs first (US Food and Drug Administration, 2018). PFS can be assessed earlier and from a smaller sample than OS, and it is based on well-defined assessment criteria (Therasse et al., 2000). However, especially if not masked, it is potentially subject to assessment bias. The definition of PFS also varies between studies, and frequent radiological or laboratory examinations may be needed. PFS is a frequent surrogate endpoint for assessing the activity of new anti-cancer agents in rare tumors for which no proven standard of care exists to be compared against.

TTP is defined as the time from randomization until objective tumor progression (PD). It does not include deaths, which are censored (US Food and Drug Administration, 2018).

Both the United States Food and Drug Administration and the European Medicines Agency require that the investigational product

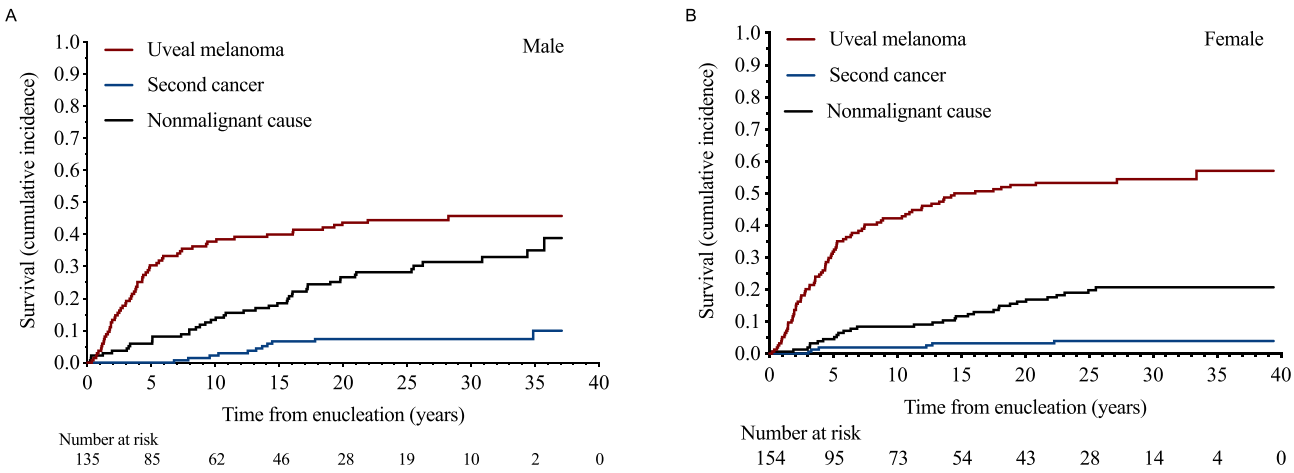


Fig. 7. Cumulative incidence estimates of melanoma-related mortality from uveal melanoma by gender. Competing causes of death are different for men and women and they thus modify real-world survival experiences of patients. Because men generally have a shorter life expectancy, fewer of them will die of metastatic uveal melanoma and, over time, nearly as many will die of nonmalignant causes (**A**). Women have a longer life expectancy and more than twice as many of them are estimated to die of metastatic uveal melanoma than of nonmalignant causes (**B**). Data correspond to results published in (Kujala et al., 2003).

provides 'clinical benefit' (European Medicines Agency, 2005; US Food and Drug Administration, 2018). The United States Food and Drug Administration considers OS as the most reliable endpoint in cancer research, and PFS and TTP may support either regular or accelerated approval (Brawley and Parnes, 2019a; US Food and Drug Administration, 2018). For the European Medicines Agency, acceptable primary endpoints are OS and PFS. If PFS is selected as the primary endpoint, then OS must be reported as a secondary one (European Medicines Agency, 2005). From the point of view of the patient, OS may be a more meaningful outcome than PFS or TTP in metastatic uveal melanoma (Kivelä et al., 2006).

3. Diagnosis of metastatic uveal melanoma

The process of diagnosing metastatic uveal melanoma is divided in 1) *screening* for synchronous metastases at the time of diagnosis of the primary tumor, 2) subsequent *surveillance* for early detection of metachronous metastases to increase chances for active treatment, 3) *confirmation* of metastases once they are suspected either because of abnormal screening or surveillance findings or after the emergence of metastasis-related signs and symptoms, and 4) *staging* to determine the extent of metastasis.

3.1. Imaging

Imaging for screening and surveillance and for staging of metastases have separate goals. The goal of the former is to raise awareness by detecting at least one metastasis if any are present. Surveillance should be sensitive, easily available, cost-efficient, and ideally without radiation hazard. The goal of staging is to chart as accurately as possible the full extent of metastases in order to guide treatment. The main requirements are then sensitivity and specificity, and higher cost and use of ionizing radiation can be accepted. For example, in the Helsinki University Hospital, if a metastasis is suspected in screening or surveillance US, confirmation with an US-guided needle biopsy and abdominal MRI is sought if active treatment is planned, and a CT to stage extrahepatic metastases is typically performed based on the evidence on the sensitivity of US and the greater ability of MRI to identify liver metastases compared to CT (Balasubramanya et al., 2016; Choudhary et al., 2016; Rantala et al., 2020b).

3.1.1. Ultrasonography

US of the liver is used for screening and surveillance. Metastases from uveal melanoma are generally hypoechoic (67%), target-like (a nodular area with a hypoechoic rim and a hyperechoic center; 6%) or present a combination of both (16%), and only rarely hyperechoic (3%) (Rantala et al., 2020b). The minimum diameter of a metastasis that is consistently detected on US is about 5 mm (Eberhardt et al., 2003). A contrast agent can be used to improve characterization of hepatic lesions (Kaur et al., 2017). Studies on upper abdominal US for screening and surveillance of hepatic metastases from uveal melanoma agree that its sensitivity is 95–100% (Table 2) (Choudhary et al., 2016; Hicks et al., 1998; Rantala et al., 2020b).

The specificity of a screening US may be as low as 14%, which is explained by the rarity of metastases (1–3% of patients) at that time (Feinstein et al., 2010; Freton et al., 2012; Garg et al., 2021; Smidt-Nielsen et al., 2021), the higher frequency (18%) of benign liver abnormalities – mostly cysts and hemangiomas (Choudhary et al., 2016) – and its dependence on the operator. During surveillance, when up to 98% of metastases from uveal melanoma appear and benign lesions have already been identified, the specificity is much higher and estimated to be 88% (Table 2). Although US has not been compared head-to-head with other imaging methods, in a nation-wide study of 215 patients, a surveillance upper abdominal US was 95% sensitive, and fully consistent with a staging CT or MRI in detecting hepatic metastases in 53% of patients; in 29% the latter showed more and in 7% fewer metastases than US (Fig. 8A and B) (Rantala et al., 2020b). In this study, 91% of the US scans preceded the CT/MRI scans. Thus, the results and conclusions do not directly apply to the opposite scenario because of the median 17 days (range, 0–56) interval between the screening and the staging imaging will to some extent favor the later examination as the metastases will grow. Use of US for surveillance is supported by its sensitivity, low cost, wide availability, and lack of radiation exposure (Choudhary et al., 2016; Eberhardt et al., 2003; Eskelin et al., 1999; Rantala et al., 2020b), even in populations in which obesity is frequent and may make US technically challenging and more time-consuming (Choudhary et al., 2016; Kaur et al., 2017). US has significant limitations close to the lung at the liver dome. US is not specific enough for use in staging hepatic metastases, and it cannot detect most extrahepatic ones (Kaur et al., 2017).

3.1.2. Magnetic resonance imaging

A metastasis from uveal melanoma is characterized on MRI by a short T1 and short T2 pattern, although a long T2 pattern is reported in 27% of patients (Balasubramanya et al., 2016; Maeda et al., 2007). The smallest

Table 2
Sensitivity and specificity of imaging modalities to detect hepatic metastases of uveal melanoma.

Imaging modality	Timing of imaging	Sensitivity %	Specificity %	Diameter of metastases range mm	No. all patients/ with metastases
Ultrasonography					
Hicks et al. (1998)	Screening at baseline	100	14	N/A	245/40
Choudhary et al. (2016)	Surveillance 6-monthly	96	88	N/A	263/30
Rantala et al. (2020b)	Surveillance 12-monthly for TNM stage I-II 6-monthly for TNM stage III	95	N/A	6–130	215/215
Magnetic resonance imaging					
Francis et al. (2019)	Screening at baseline	83	99	N/A	145/6
Piperno-Neumann et al. (2015)	Surveillance 6-monthly	100	80	1–35	100/60
Rantala et al. (2020b)	Confirmation/staging of metastases after surveillance US	100	N/A	2–160	69/69
Servois et al. (2010)	Staging after surveillance US	67	N/A	5– >10	15/12
Orcurto et al. (2012)	Biopsy-confirmed metastases	100	N/A	0.3–1.1	10/10
Computed tomography					
Rantala et al. (2020b)	Confirmation/staging of metastases after surveillance US	95	N/A	4–270	167/167
Positron emission tomography					
Kurli et al. (2005)	Variable[a]	100	100	N/A	20/8
Freton et al. (2012)	Screening at baseline	100	N/A	9–>	333/7
Francken et al. (2006)	Staging after surveillance US	100	67	N/A	22/18
Servois et al. (2010)	Staging after surveillance US	45	N/A	5– >10	15/12
Orcurto et al. (2012)	Biopsy-confirmed metastases	100	N/A	0.3–1.1	10/10
Kurli et al. (2005)	Variable[a]	100	100	N/A	20/8
Klingenstein et al. (2010)	Variable[b]	100	N/A	2.7–12	12/12[c]

N/A = not applicable; TNM = tumor, node, metastasis; US = ultrasonography.
[a] Two patients were screened at the time of diagnosis of their primary uveal melanoma and 18 patients were imaged at the time of staging of metastases.
[b] Two patients were imaged at the time of initial staging of metastases, and nine were re-staged before or after local or systemic therapy for metastatic disease.
[c] Hepatic metastases were detected in ten patients (83%) and two had bone or pulmonary metastases.

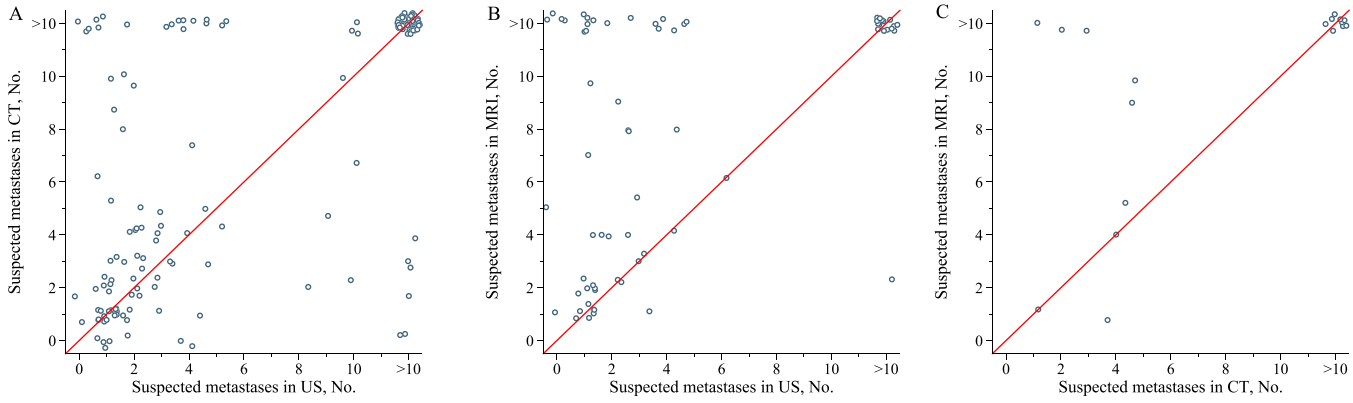


Fig. 8. Relative capabilities of surveillance imaging to detect hepatic metastases. Number of reported metastases in upper abdominal ultrasonography (US) compared to computed tomography (CT) scans (**A**) and to magnetic resonance imaging (MRI) scans (**B**), and in CT compared to MRI (**C**). Note that in one third of the patients, MRI showed more metastases than CT. Published in (Rantala et al., 2020b), https://doi.org/10.1016/j.ajo.2020.03.049, CC BY license (http://creativecommons.org/licenses/by/4.0/).

diameter of a hepatic metastasis detected in 100 patients with uveal melanoma who underwent a standard 1.5 T MRI scan was 1 mm (Piperno-Neumann et al., 2015). Diffusion-weighted sequences and delayed post-contrast sequences together with a hepatocyte-avid contrast agent that is retained by the normal liver help in the detection of the smallest liver metastases (Balasubramanya et al., 2016). Recently, a chemokine receptor 4-targeted, protein-based contrast agent was claimed to detect liver metastases from uveal melanoma as small as 0.1 mm^3 (Salarian et al., 2019; Tan et al., 2020), highlighting the future potential of MRI.

MRI with gadolinium as a contrast agent has a sensitivity of 83% in screening and up to 100% in surveillance to detect hepatic metastases from uveal melanoma (Table 2) (Francis et al., 2019; Orcurto et al., 2012; Piperno-Neumann et al., 2015; Rantala et al., 2020b; Servois et al., 2010). The specificity of MRI ranges from 80% to 99%, depending on the setting. Although head-to-head comparisons are unavailable, MRI is widely held to be the most sensitive and specific imaging method to detect hepatic metastases from uveal melanoma. In support of this, the nationwide cohort study of 215 patients with metastatic uveal melanoma, which primarily evaluated consistency of hepatic US with staging CT and MRI, compared CT with MRI in 18 patients whose hepatic metastases were staged with both methods (Rantala et al., 2020b). In one third of them MRI showed more metastases than CT (Fig. 8C). MRI as a screening and a surveillance tool is further supported by avoidance of radiation exposure. On the other hand, although a cost comparison is difficult because of differences in insurance and reimbursement policies,

MRI is typically more expensive (e.g. in the Helsinki University Hospital, five times the cost of US and less accessible than US or CT), supporting the continued use of US (Choudhary et al., 2016; Rantala et al., 2020b).

An MRI-guided needle biopsy to confirm hepatic metastases is not currently feasible. As a staging tool for hepatic metastases, the sensitivity and specificity of MRI with a contrast agent, as compared with those of US and CT, far outweigh its relative limitations. Use of MRI rather than CT for staging of hepatic metastases from uveal melanoma was recently independently promoted (Balasubramanya et al., 2016).

3.1.3. Computed tomography

The sensitivity and specificity of CT in the setting of metastatic uveal melanoma have not been evaluated to the same extent as of US and MRI (Table 2). In a single-center study, a screening CT performed within one month of the diagnosis of primary uveal melanoma found benign hepatic lesions in 55% of patients (Feinstein et al., 2010). When hepatic metastases were detected in CT, they were multiple in 90% of patients, and two of the patients with a solitary metastasis in CT had additional metastases in MRI (Patel et al., 2011). In addition to its lower sensitivity as compared to MRI, a limitation of CT as a surveillance tool is the ionizing radiation despite the fact that stochastic risks of current imaging protocols are unlikely to be of consequence to the majority of patients (Balasubramanya et al., 2016).

CT can be used as a guide for percutaneous biopsy to confirm hepatic metastases although US is usually preferred (Kaur et al., 2017). A CT with a contrast agent is also an essential staging method, especially for pulmonary and other extrahepatic metastases and when MRI is contraindicated (Feinstein et al., 2010; Patel et al., 2011).

3.1.4. Positron emission tomography

Metastases from uveal and cutaneous melanoma are FDG-avid (Finger et al., 2004; Freudenberg et al., 2004). However, because uveal melanoma typically disseminates to the liver rather than to the regional lymph nodes and because the normal, mottled hepatic uptake of FDG (Fig. 9) may obscure smaller FDG-avid metastases that show a low target-to-background ratio (Balasubramanya et al., 2016), FDG-PET is relatively less successful in imaging metastases in patients with uveal melanoma. The smallest lesions detected were 3–9 mm in diameter (Table 2). Consequently, MRI is more sensitive in detecting smallest liver metastases from uveal melanoma than FDG-PET (Orcurto et al., 2012; Servois et al., 2010). The sensitivity and specificity of FDG-PET in detecting uveal melanoma metastases larger than 12 mm is up to 100% and 67–100%, respectively, although all series are small (Balasubramanya et al., 2016; Francken et al., 2006; Freton et al., 2012; Klingenstein et al., 2010; Kurli et al., 2005; Mayerhoefer et al., 2012; Orcurto et al., 2012; Servois et al., 2010).

Usefulness of PET/CT for surveillance is limited by its lower sensitivity, exposure to ionizing radiation, higher cost, and limited availability (Kaur et al., 2017). A case can be made, however, for screening and staging patients with PET/CT because of its ability to pick up non-ocular primary cancers and extrahepatic metastases. Of 333 patients who underwent PET/CT at the time of diagnosis of uveal melanoma, synchronous second primary cancers were detected in 3% (Freton et al., 2012). In a recent multicenter registry study in which 69 of 3610 enrolled patients had metastases diagnosed concurrently with the primary melanoma (Garg et al., 2021), a screening PET/CT was performed in 340 patients; this found extrahepatic metastases in 14 (4%) of them as compared to 8 (0.2%) patients among the remaining 3270 patients imaged with other methods. This raised concerns of underestimating the frequency of multiorgan metastasis when PET/CT is not performed.

3.1.5. Chest radiogram

Metastases to the lungs from uveal melanoma are infrequent when liver imaging already shows dissemination (Diener-West et al., 2004; Eskelin and Kivelä, 2002; Eskelin et al., 1999). Only two of 46 patients newly diagnosed with metastatic uveal melanoma had pulmonary metastases which, moreover, both occurred together with hepatic metastases; 344 patients who did not develop metastases had undergone a total of 900 negative chest radiograms (Eskelin et al., 1999). The number needed to expose to radiation hazard to detect one pulmonary metastasis was thus 450 and even then, the alarm usually would be raised by liver imaging. Consequently, chest radiogram was abandoned from the surveillance protocol of the Helsinki University Hospital (Eskelin et al., 1999) and, subsequently, from other expert centers (Chadha et al., 2019; Mathis et al., 2018; Nathan et al., 2015; National Comprehensive Cancer Network, 2021; Weis et al., 2016).

3.2. Blood tests

Routine LFTs have long been used for screening and surveillance of metastases from uveal melanoma because of its propensity to metastasize to the liver. With advent of routine, sensitive liver imaging, their role has diminished. More recently, LFTs have gained new importance as prognosticators when clinical metastases have developed (*see 4.2.8.* below). Additionally, a number of other blood- and tissue-based biomarkers have been explored as indicators for metastases. Although no biomarkers have been validated either for surveillance or prognostication in patients with metastatic uveal melanoma, some evidence has emerged that biomarkers might facilitate monitoring of disease progression (Beasley et al., 2018).

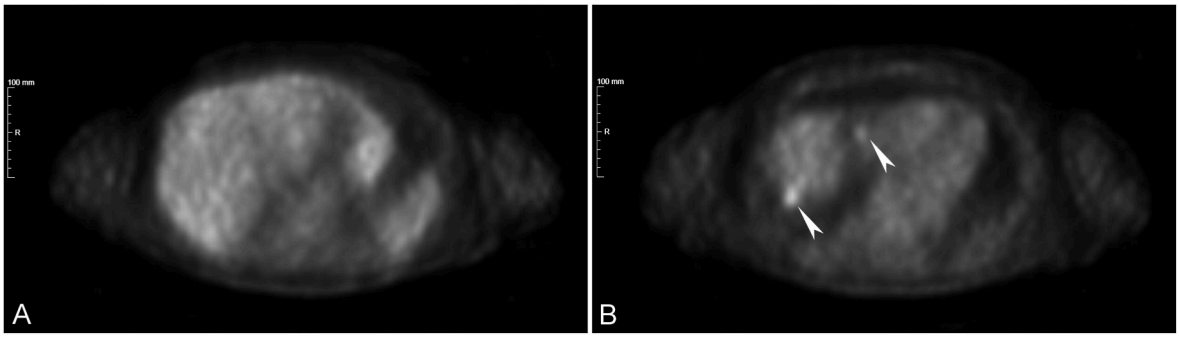


Fig. 9. Hepatic metastases on 2-deoxy-2-[18F]fluoro-D-glucose-positron emission tomography (FDG/PET). The uptake of FDG in the normal liver is randomly mottled, which complicates detection of small hepatic metastases (**A**). Two small metastases from uveal melanoma on FDG/PET, identified based on standardized uptake value (SUV, a measure of the ratio of the image-derived radioactivity concentration to the whole-body concentration of the injected radioactivity) of 3.9 in the larger one (**B**). SUV values exceeding 2.5 often suggest malignancy. Both metastases had been suspected by magnetic resonance imaging, but were not typical, leading to subsequent FDG/PET.

Table 3A
Sensitivity and specificity of liver function tests in detecting metastases of uveal melanoma.

Study	Indication	Criterion	Sensitivity %	Specificity %	No. of all patients/with metastases
Alkaline phosphatase (AP)					
Diener-West et al. (2004)	Screening at baseline, surveillance 6- or 12-monthly	>1.5 x UNL	19[a] 14[b]	99[a] 99[b]	2320/714
Eskelin et al. (1999)	Surveillance 12-monthly	>1.0 x UNL	27	93	390/46
Hicks et al. (1998)	Screening at baseline	>1.0 x UNL	25	86	245/40
Lactate dehydrogenase (LDH)					
Eskelin et al. (1999)	Surveillance 12-monthly	>1.0 x UNL	67	96	390/46
Alanine transaminase (ALT)					
Diener-West et al. (2004)	Screening at baseline, surveillance 6- or 12-monthly	>2 x UNL	13[a] 7[b]	99[a] 99[b]	2320/714
Eskelin et al. (1999)	Surveillance 12-monthly	>1.0 x UNL	38	90	390/46
Hicks et al. (1998)	Screening at baseline	>1.0 x UNL	6	98	245/40
Aspartate aminotransferase (AST)					
Diener-West et al. (2004)	Screening at baseline, surveillance 6- or 12-monthly	>2 x UNL	10[a] 7[b]	99[a] 100[b]	2320/714
Eskelin et al. (1999)	Surveillance 12-monthly	>1.0 x UNL	43	95	390/46
Hicks et al. (1998)	Screening at baseline	>1.0 x UNL	15	89	245/40
Gamma-glutamyl transferase (GT)					
Hicks et al. (1998)	Screening at baseline	>1.0 x UNL	21	92	245/40

UNL = Upper normal level.
[a] Large melanoma study arm.
[b] Medium-sized melanoma study arm.

3.2.1. *Liver function tests*

LFTs, typically a combination from alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), lactate dehydrogenase (LDH), and gamma-glutamyltransferase (GT) are widely included in screening and surveillance protocols for patients with uveal melanoma. LFTs and a chest radiogram were the mainstay of surveillance when the Collaborative Ocular Melanoma Study (COMS) was designed in the 1980's (The Collaborative Ocular Melanoma Study Group, 1993). It is important to appreciate that liver imaging in the COMS study was performed only after clinical examination, a chest radiogram or a LFT exceeding 1.5 (AP) or 2 (ALT and AST) times its upper normal limit (UNL) suggested the presence of metastases. None of them were sensitive criteria for surveillance, their sensitivity ranging from 7% to 19% (Diener-West et al., 2004; Hicks et al., 1998). Among 88 patients undergoing 6-monthly surveillance with LFTs, their sensitivity ranged from 17% to 40%, and the authors concluded that isolated or combined LFTs alone were not helpful in early detection of metastases (Mouriaux et al., 2012). Indeed, LFTs tended to become abnormal only when hepatic metastases had reached an advanced stage (Diener-West et al., 2004; Patel et al., 2011).

Like liver imaging, LFTs have a low sensitivity of 6–25% when screening for metastases at the time of diagnosis of the primary tumor because of the rarity of metastases relative to the frequency of other causes of elevated LFTs (Table 3A) (Hicks et al., 1998). Their main value at that time is, consequently, to provide a patient-level reference for later surveillance. LFTs begin to rise within their UNL in 50% of patients during the 6 months preceding detection of hepatic metastases by liver imaging (Kaiserman et al., 2004). When the UNL is used as a criterion, the sensitivity of AP as a surveillance test is 27%, and those of ALT and AST are 38% and 43%, respectively; these values are clearly inferior compared to those of liver imaging (Eskelin et al., 1999). The most sensitive LFT is LDH with a sensitivity of 67%. A panel combining ALT, AST, AP, and LDH improved the sensitivity as compared to LDH alone marginally to 70% (Eskelin et al., 1999). All LFTs are meaningfully specific tests when they exceed their UNL, ranging from 86% to 98% in specificity when used for screening or surveillance (Eskelin et al., 1999; Hicks et al., 1998).

In a nationwide cohort study of 215 patients, which primarily evaluated upper abdominal US as a surveillance tool, 90% of metastases from uveal melanoma were diagnosed on a prescheduled surveillance visit at which LFTs also were measured (Rantala et al., 2020b). US failed to suggest metastases in 10 (5%) patients. LFTs were abnormal in six of them and a new hepatic abnormality had appeared in the other four, an observation which supports both continuous use of LFTs as an adjunct to liver imaging and scheduling an MRI always when any LFT is elevated or a new hepatic abnormality emerges. Thus, upper abdominal US combined with LFTs failed to reveal hepatic metastases in only 2% of the patients (Rantala et al., 2020b), confirming earlier results (4%) (Eskelin et al., 1999).

3.2.2. *Protein biomarkers*

Search for biomarkers in patients with uveal melanoma has largely followed studies in cutaneous melanoma (Table 3B). Taken together, evidence on an association between blood levels of nine biomarkers and the presence of metastases is inconsistent (S-100β) or unconfirmed (DJ-1, GDF-15 and c-Met), in part because the series, with one exception, evaluated less than 50 patients with metastases (Barak et al., 2007; Barak et al., 2011b; Barisione et al., 2015; Chen et al., 2015; el Filali et al., 2010; Kadkol et al., 2006; Missotten et al., 2007; Missotten et al., 2003). Two exceptions are serum or plasma osteopontin and melanoma inhibitory activity, for which substantial evidence exists that elevated levels indicate metastases (Barak et al., 2007; Haritoglou et al., 2009; Klingenstein et al., 2011; Missotten et al., 2007; Reiniger et al., 2005; Schaller et al., 2002; Song et al., 2019). Melanoma inhibitory activity levels also increase with development of metastases in longitudinal analyses (Barak et al., 2011a; Klingenstein et al., 2011; Reiniger et al., 2005; Schaller et al., 2002). Notwithstanding this evidence, no serum biomarker, with the exception of LFTs, is currently in wide clinical use.

3.2.3. *Cell and nucleic acid assays*

Circulating tumor cells from uveal melanoma were first reported in the late 1960's (Horodeński, 1969). They are detected in 10%–88% of patients with metastases, largely irrespective of the stage of the tumor, applying variable procedures (Table 3C) (Anand et al., 2019; Bidard et al., 2014; Callejo et al., 2007; Suesskind et al., 2011; Ulmer et al., 2008). Circulating tumor-derived DNA (Beasley et al., 2018; Madic et al., 2012), microRNA (Achberger et al., 2014; Stark et al., 2019), and extracellular vesicles (Eldh et al., 2014) that could be associated with the presence and extent of metastases have been analyzed in pilot studies. Although none of these biomarkers is established for clinical use, they may have future potential, including as a liquid biopsy in an effort to determine the cytogenetic and molecular profile of the metastases (Bidard et al., 2014).

Table 3B
Sensitivity and specificity of proteomic biomarkers in detecting metastases of uveal melanoma; only one decimal place is used.

Study	No. of patients; level of biomarker		Type of specimen, unit	Result	Association with overall survival
	With clinical metastases	Without clinically detectable metastases			
Carcinoembryonic antigen cell adhesion molecule-1 (CEACAM-1)					
Song et al. (2019)	14; median 10[a]	9; median 12[a]	Serum, ng/ml	No significant difference	NR
Protein deglycase DJ-1					
Chen et al. (2015)	27; median 8.0 (range, 0.9–30.3); for 15 median 1.3 (range, 0.3–3.2) before and 5.5 (range, 0.7–15.5) after developing metastases	76; median 1.5 (range, 0.3–12.0)	Serum, ng/ml	Higher if metastases ($P < 0.001$)	NR
Growth differentiation factor-15 (GDF-15)					
Suesskind et al. (2011)	18; mean 10.5 (SD, 13.0)	170; 1.5 (SD, 0.7)	Serum, ng/ml	Higher if metastases ($P < 0.001$)	NR
Heat shock protein 27 (HSP-27)					
Song et al. (2019)	18; median 0.3[a]	170; median 0.4[a]	Serum, ng/ml	No significant differences	NR
Melanoma inhibitory activity (MIA)					
Barak et al. (2007)	18; mean 11[b]	38 patients; mean 4[b]	Serum, ng/ml	Higher if metastases ($P = 0.0005$)	NR
Haritoglou et al. (2009)	14; median 13.1 (IQR, 8.9–37.1)	18; 5.6 (IQR, 4.6–8.0)	Plasma, ng/ml	Higher if metastases ($P < 0.001$)	NR
Klingenstein et al. (2011)	54; median 11.7 (IQR, 9.0–27.0); for 28 patients 6.8 before and 19.6 after developing metastases	449; median 7.0 (IQR, 5.3–8.1)	Plasma, ng/ml	Higher if metastases ($P < 0.001$)	NR
Missotten et al. (2007)	30; median 8.1; 12 >UNL, 18 ≤UNL[c]	104; median 5.2	Serum, ng/l	Higher if metastases ($P < 0.001$)	NR
Reiniger et al. (2005)	20; mean 13.0; for 8 5.9 before and 12.2 after developing metastases	285; mean 6.7	Serum, ng/ml	Higher if metastases (P < 0.001)	NR
Schaller et al. (2002)	8; median 26.3; for 3 6.6 before and 29.2 after developing metastases	131; median 6.6	Serum, ng/ml	Higher if metastases ($P < 0.001$)	NR
Song et al. (2019)	14; median 0.7[a]	9; median 0.9[a]	Serum, ng/ml	Lower if metastases ($P = 0.03$)	NR
Macrophage inhibitory cytokine-1 (MIC-1)					
Song et al. (2019)	14; median 0.5[a]	9; median 0.8[a]	Serum, ng/ml	No significant difference	NR
Osteopontin (OPN)					
Barak et al. (2007)	18; mean 14[b]	38 patients; mean 8[b]	Serum, ng/ml	Higher if metastases ($P = 0.0037$)	NR
Haritoglou et al. (2009)	14; median 152.0 (IQR, 87.5–233.5)	18; 47.4 (IQR, 37.7–75.5)	Plasma, ng/ml	Higher if metastases ($P < 0.001$)	NR
Kadkol et al. (2006)	15; mean 17.6 (SD, 13.8); for 8 patients 6.2 before and 19.7 after developing metastases	37; mean 7.2 (SD, 3.0)	Serum, ng/ml	Higher if metastases ($P < 0.0001$)	NR
Song et al. (2019)	14; median 0.3[a]	9; median 75[a]	Serum, ng/ml	No significant difference	NR
Periostin (POSTN)					
Song et al. (2019)	14; median 0.3[a]	9; median 0.2[a]	Serum, ng/ml	No significant difference	NR
S100 calcium binding protein β (S-100β)					
Barak et al. (2007)	18; mean 0.3[b]	38; mean 0.03[b]	Serum, μg/l	Higher if metastases ($P = 0.0111$)	NR
Missotten et al. (2003)	20; detectable in 11	44	Serum	No significant difference	No significant difference
Missotten et al. (2007)	30; median 0.2; 16 >UNL, 14 ≤UNL[d]	104; median 0.07	Serum, μg/l	Higher if metastases ($P < 0.001$)	NR
Soluble c-Met					
Barisione et al. (2015)	17; median 590 (range, 246–12856)	40; median 296 (range, 201–469)	Serum, ng/ml	Higher if metastases ($P < 0.001$)	Survival prolonged if c-Met low ($P = 0.07$)
Spondin 1 (SPON1)					
Song et al. (2019)	14; median 8[a]	9; median 10[a]	Serum, ng/ml	No significant difference	NR
Vascular endothelial growth factor (VEGF)					
Barak et al. (2011)	39; mean 453.5 (SD, 270.2)	23; mean 407.7 (SD, 261.9)	Serum, pg/ml	No significant difference	NR
el Filali et al. (2010)	20; median 351; 6 > UNL[e]	74; median 183; 7 > UNL	Serum, pg/ml	Higher if metastases ($P < 0.001$)	NR

IQR = interquartile range; NR = not reported; SD = standard deviation; UNL = upper normal limit.
[a] Approximated from Fig. 4 in the original publication.
[b] Approximated from Fig. 2 in the original publication.
[c] UNL = 10 ng/l
[d] UNL = 0.09 ng/l
[e] UNL = maximum level of VEGF in healthy subjects.

3.3. Histopathology

Confirmation that a metastasis originates from uveal melanoma can only be obtained through biopsy. Such a confirmation is necessary if active treatment rather than best supportive care (BSC) is planned, and also to exclude origin of metastases from a known or unknown non-ocular primary cancer. The most common procedure to confirm a hepatic metastasis is a US- or a CT-guided fine-needle aspiration biopsy or, preferably, core-needle biopsy. An open biopsy or biopsy via laparoscopy or bronchoscopy remains an option especially for extrahepatic metastases. In a nationwide, real-world study of 216 consecutive patients, metastases from uveal melanoma had been confirmed with biopsy in 67% of patients whereas a biopsy was not sought in the remaining ones who were mostly offered BSC (*see 6.4.*, below) because of their advanced age or poor general health (Rantala et al., 2020b).

Analogous to the primary uveal melanoma, its metastases are of spindle cell (8–29%), epithelioid cell (55–68%) or mixed cell (6–24%) type (Fuchs et al., 1992; Griewank et al., 2014; Luyten et al., 1996; Toivonen et al., 2004), following the modified Callender system (McLean et al., 1983). Although cut-off points are arbitrary and often differ, according to the current TNM system spindle cell and epithelioid cell melanomas consist of at least 90% of the specified cell type (Kivelä et al., 2017). To confirm that metastases originate from uveal melanoma, melanin granules within tumor cells or, especially when the metastasis is amelanotic and of epithelioid cell type, an antigenic profile characteristic of melanocytes must be verified. The histopathologic diagnosis was incorrect without immunohistochemistry even in three of 45 autopsies of patients with uveal melanoma: a presumed cholangiocarcinoma was misdiagnosed as metastatic uveal melanoma and two presumed melanoma metastases actually were from a mucocellular and an anaplastic carcinoma of unknown origin upon later review (Kujala et al., 2003).

The most common immunohistochemical stains that are expected to be positive in uveal melanoma are S-100 protein, HMB-45 (human melanoma black-45) antigen, melanoma antigen recognized by T cells-1 (MART-1, also known as MelanA), and vimentin (though non-specific). Less frequent alternatives include tyrosinase, SRY-related HMG-BOX gene 10 (SOX10), and microphthalmia transcription factor (MITF) (Fernandes et al., 2007; Fuchs et al., 1992; Grossniklaus et al., 2018; Heegaard et al., 2000; Luyten et al., 1996; O'Reilly et al., 2001). In addition, Ki-67 antigen, also called MIB1, is often used to semi-quantitatively estimate proliferation index (Pe'er et al., 2001).

It is advisable to use at least two antibodies that recognize melanocytes in combination with epithelial markers, especially cytokeratin antibodies, to exclude carcinoma if an amelanotic metastasis of uveal melanoma is suspected (Grossniklaus et al., 2018). Approximately one half of breast carcinomas, the most common cancer in women, are immunopositive for S-100 protein, up to 20% for MART-1, and 2% for HMB-45 antigen (Bachmeier et al., 2008; Bonetti et al., 1989; Lee, 2013). MART-1 and HMB-45 antigen immunopositivity are rare in most other carcinomas, found e.g., in <1% and ~0% of non-small-cell lung cancer, respectively (Kriegsmann et al., 2018). Although most uveal melanomas are negative for cytokeratins, focal immunostaining for simple epithelial cytokeratins 8, 18 and 19 can be present because of an interconverted phenotype related to epithelial-mesenchymal transition (Awh and Wilson, 2020; Fuchs et al., 1992; Harbaum et al., 2012; Hendrix et al., 1998). Immunopositivity for cytokeratin 20, which is found in 94% of colon cancers, is distinctly unusual (~0%) in uveal melanoma and thus helpful in differential diagnosis.

None of the antibodies mentioned can differentiate metastatic uveal from cutaneous melanoma. In practice, when a patient has a history of uveal melanoma but not of cutaneous melanoma, metastatic melanoma to the liver is considered to be from the uveal melanoma. Also, if metastatic melanoma is found in the liver without a known primary, a dilated fundus examination is called for. If the patient has a history or suspicion of both primary tumors, an analysis of characteristic driver genes is necessary. A pathogenic variant in *GNAQ* or *GNA11* is taken to indicate uveal origin, and a variant in *BRAF* (V600E), which can be demonstrated also immunohistochemically, or in *NRAS,* indicates cutaneous origin (Everett et al., 2019; Griewank et al., 2016; Küsters-Vandevelde et al., 2008; Lee et al., 2018; Smit et al., 2020). A caveat is that 27 of 284 (10%) mucous membrane melanomas also carried a *GNAQ* or *GNA11* pathogenic variant according to one study (Sheng et al., 2016), as do melanomas from blue nevi.

3.4. Surveillance strategies

Although attempts have been made to harmonize surveillance for metastatic uveal melanoma, no consensus exists even on the necessity of surveillance (Augsburger et al., 2011; Barker and Salama, 2018; Chadha et al., 2019; Mathis et al., 2018; Nathan et al., 2015; Weis et al., 2016).

3.4.1. Justification for surveillance

Surveillance for early detection of metastatic uveal melanoma to improve survival has been recommended since the 1970's (Einhorn et al., 1974), but the utility of surveillance also has been repeatedly questioned because of lack of evidence that any treatment prolongs survival after metastases have appeared (Augsburger et al., 2011; Kim et al., 2010; Patel et al., 2011).

Early diagnosis of metastases is considered necessary to maximize the number of patients who may benefit from active treatment, especially from surgery and other liver-directed treatments (Francis et al., 2013; Gomez et al., 2014; Mariani et al., 2009, 2016; Rantala et al., 2019, 2021b; Rivoire et al., 2005; Tulokas et al., 2018; Xu et al., 2019). In practice, when an early diagnosis was attempted in high-risk patients with 6-monthly MRI-based surveillance, 25% were eligible for hepatic resection and 8% eventually received a microscopically complete (R0) resection (Piperno-Neumann et al., 2015). In two apparently overlapping studies, 14% and 11% of patients eventually were eligible for hepatic resection (Gomez et al., 2014; Marshall et al., 2013).

A more general goal is to maximize the number of patients who would be able to enroll in ongoing trials when they still have a favorable performance status and low metastatic burden. Universal surveillance guidelines would then be very beneficial because they would also contribute to the comparability of trials (Eskelin and Kivelä, 2002; Eskelin et al., 1999; Rantala et al., 2020b). In our opinion, low efficacy of current treatments for metastatic uveal melanoma is no valid reason not to offer a surveillance program, because that would limit the possibility of patients to enroll in treatment trials that might eventually benefit others with metastases.

Perceived positive psychological impact of surveillance is another benefit that some patients may appreciate (Afshar et al., 2018). On the other hand, a negative psychological impact of being repeatedly reminded of a risk of metastasis and death remains a possibility, depending in part on different cultural backgrounds between countries. In practice, patients adhere well to surveillance when one is provided. Attendance to surveillance was regular for 97% of patients in a nationwide study in Finland (Rantala et al., 2021a). Another center in the United States found, however, that adherence of high-risk patients was stronger than that of patients with a low or uncertain risk (Davanzo et al., 2019).

3.4.2. Choice of surveillance program

From the time when surveillance was first proposed to the randomized COMS trials, LFTs and a chest radiogram were the modalities recommended for surveillance of patients with uveal melanoma (Char, 1978; Einhorn et al., 1974; The Collaborative Ocular Melanoma Study Group, 1993). At the time, isotope uptake-based liver scans were not sensitive in detecting early metastases. With the advent of abdominal US, CT and, later, MRI, liver imaging became much more efficient and quickly replaced liver scanning in the 1990's (Eskelin et al., 1999, 2003; Leyvraz et al., 1997), eventually leading also to abolishment of chest

Table 3C
Sensitivity and specificity of circulating tumor cells, and tumor-derived DNA, microRNA, and extracellular vesicles in detecting metastases of uveal melanoma; survival was not reported in any of the studies.

Study	No. of patients; level of biomarker		Type of specimen, unit	Result
	With clinical metastases;	Without clinically detectable metastases		
Circulating tumor cells (CTC)				
Anand et al. (2019)	19; mean 9 (SD, 13.7); detectable in 8	20; mean 1.8 (SD, 1.0); detectable in 6	Blood, No. CTC	Higher if metastases ($P > 0.05$)
Suesskind et al. (2011)	5; range, 0–14	76; NR	Blood, No. CTC	No significant difference
Circulating tumor DNA (ctDNA)				
Beasley et al. (2018)	8; detectable in 8 (range, 2–15160)	30; detectable in 8 (range, 1.6–29)	Blood, copies/ml	Higher if metastases ($P < 0.001$)
Madic et al. (2012)	21; undetectable in 2	20 healthy subjects; NR	Blood, GE/PCR	Higher if metastases ($P < 0.05$)
microRNA (miRNA)				
Achberger et al. (2014)	6; NR	26 healthy subjects; NR	Blood	Higher if metastases ($P < 0.05$)
Stark et al. (2019)	5; NR	50; NR	Blood	Higher if metastases ($P < 0.0001$)[a]
Extracellular vesicles				
Eldh et al. (2014)	12; median 75.6 (range, 44–209)	5 healthy subjects; median 13.8 (range, 6–45)	Plasma, μg/ml	Higher if metastases ($P = 0.003$)

GE/PCR = genome equivalent present in polymerase chain reaction assay; NR = not reported; SD = standard deviation.
[a] miR-2.

radiograms from surveillance programs (*see* 3.1.5., above).

Currently, each referral center has its preferred imaging modality and frequency of surveillance. The frequency varies by center depending on availability and experience with specific treatments for metastases, especially liver surgery, and by patient, depending on their perceived individual risk for dissemination, informed by tumor stage, histology, and genetic characteristics of the primary tumor (Choudhary et al., 2016; Davanzo et al., 2019; Diener-West et al., 2004; Eskelin et al., 1999; Gomez et al., 2014; Piperno-Neumann et al., 2015; Rantala et al., 2021a, 2021b).

Calculated tumor doubling times of metastases and empirical evidence suggest that 6-monthly surveillance should catch 90% of patients with metastases when they are still asymptomatic (Eskelin et al., 1999, 2000). High-risk patients, defined as those whose risk of metastasis is estimated to be at least 50% in 5 years based on large tumor thickness >8.0 mm (Shields et al., 2009), TNM stage IIB or higher, involvement of the ciliary body, extraocular extension, high mitotic rate of ≥5 per 40 high power fields (Damato et al., 2010), epithelioid cell type (Kivelä et al., 2017; McLean et al., 1982; Shields et al., 2009), monosomy 3 especially with chromosome 8q gain, loss of BAP1 function, or class 2 gene expression profile (Damato et al., 2011; Dogrusöz and Jager, 2018; Onken et al., 2004), or because of a local tumor recurrence are consequently now initially surveilled 6- or even 3-monthly (Davanzo et al., 2019; Mathis et al., 2018; National Comprehensive Cancer Network, 2021). Patients deemed to be at low risk of metastasis are usually surveilled 12-monthly.

Less agreement exists as to which imaging modality should be used for surveillance of the liver and how long surveillance should continue. Analysis of very long-term survival after enucleation for primary uveal melanoma suggests that 90% of metastases appear within 15 years: approximately 60% are found during the first 5 years, 20% between 5 and 10 years, and another 10% between 10 and 15 years; the remaining 10% emerge during the next 15 years (Fig. 10) (Kujala et al., 2003). A recent SEER registry-based study of 10,678 patients with uveal melanoma paralleled the former one: the excess absolute risk of dying of uveal melanoma showed two waves, the first one peaking at 3 years and the second one peaking at approximately 15 years (Singh et al., 2021). The first wave was postulated to represent patients with BAP1 loss and the second those with *SF3B1* pathogenic variants.

In Europe, upper abdominal US is widely used for initial screening and surveillance which generally continues for 10–15 years, and CT and MRI are scheduled if a suspicious new lesion is detected (Eskelin and Kivelä, 2002; Eskelin et al., 1999; Gombos et al., 2004; Rantala et al., 2020b, 2021a, 2021b; Rivoire et al., 2005; Servois et al., 2010). Scottish consensus-based guidelines even propose that patients judged to be at high-risk of developing metastases should have life-long 6-monthly surveillance (Chadha et al., 2019). Large European centers with a liver surgery pipeline prefer MRI not only for staging but also for early detection of metastases (Gomez et al., 2014; Mariani et al., 2019; Marshall et al., 2013; Piperno-Neumann et al., 2015) although its superiority over US as a surveillance tool has not been documented.

In the United States, surveillance is often performed with MRI of the liver and CT of the chest, abdomen and pelvis, the frequency being based on perceived individual risk of metastases (Balasubramanya et al., 2016; Gombos et al., 2004; National Comprehensive Cancer Network, 2021). LFTs are often included in surveillance (National Comprehensive Cancer Network, 2021; Rao et al., 2020). The National Comprehensive Cancer Network (NCCN) Guidelines propose initially 3–6 monthly surveillance for 5 years, and thereafter every 6–12 months for 6–10 years and beyond 10 years as clinically indicated (National Comprehensive Cancer Network, 2021). Hepatic US is used less frequently because of its relatively higher dependence on operator skill (Kaur et al., 2017), its limitations in obese patients (Choudhary et al., 2016), reimbursement schemes that may incentivize use of CT, and even for fear of malpractice claims given absence of national practice guidelines (Lyu et al., 2017).

3.4.3. *Toward evidence-based screening and surveillance*

Although the evidence is incomplete to be firm about the recommended modality or frequency for surveillance, evidence supports use of upper abdominal US or MRI with LFTs, and a confirmation with MRI if hepatic metastases are suggested by US (Rantala et al., 2020b). To establish a universally accepted and cost-efficient surveillance strategy, a judiciously planned study comparing US and MRI head-to-head is indicated. Screening high-risk patients every 6 months for the first five years and otherwise at least every 12 months for at least 10 years (80% detected) and preferably for 15 years (90% detected) would seem rational until further evidence is available to guide the frequency and length of surveillance (Fig. 10).

For screening at the time of diagnosis of the primary tumor and for staging after metastases have been confirmed, it would be preferable to perform a CT of the chest, abdomen and pelvis or a whole body FDG-PET/CT additional to the hepatic MRI to detect all extrahepatic metastases (Garg et al., 2021), at least when the primary tumor is T4 (risk approximately 10%), as well as non-ocular primary cancers (Freton et al., 2012) so as to guide most appropriate treatment (*see* 2.1.3. and 3.1.4., above).

4. Prognostic factors

Prognostication after clinical metastases have been diagnosed serves two purposes. The first is a specific one, applies to all patients, and relates to counseling for choice of treatment. The second is a general one, applies to patients who are eligible for a prospective treatment trial or a retrospective survey and relates to staging to stratify survival analyses. For

both purposes, it is crucial to determine factors that are consistently associated with survival and which of them independently contribute to survival outcomes.

In this section, we summarize and critically evaluate the evidence available on prognostic factors that might be combined in staging systems in order to assess survival outcomes of those with metastases. We especially concentrate on OS after diagnosis of metastasis. In the next section, we discuss how prognostic factors that are independently associated with survival outcomes can be applied for staging of patients.

4.1. Pitfalls in reporting prognostic factors

In addition to the small number of patients with metastatic uveal melanoma seen in any single center, leading to low statistical power, a pervasive pitfall has been that almost every study has built their multivariable model from scratch. Additional impediments are a variable case mix as regards both the stage of metastatic disease and the choice of treatment, given that the results of any study can be directly applied only to a population that matches the one analyzed. Continuous prognostic variables such as metastatic burden and metastasis-free interval also have been variably categorized. Finally, almost universal lack of independent validation is a frequent limitation.

4.2. Clinical characteristics

4.2.1. Gender

Gender is not statistically associated with OS in 8 of 11 prognostic analyses of 24–224 patients (Eskelin et al., 2003; Gragoudas et al., 1991; Kodjikian et al., 2005b; Mariani et al., 2019; Nicholas et al., 2018; Rantala et al., 2021a, 2021b; Xu et al., 2019) (Table 4A). However, all these analyses consistently return a hazard ratio (HR) > 1.0 (Fig. 11) and suggest that male gender is associated with somewhat shorter OS (for all HRs with confidence interval, see Table 4A and forward) (Khoja et al., 2019; Kivelä et al., 2003; Rietschel et al., 2005). Otherwise, the estimates would be randomly spread around HR 1.0. The statistical power to confirm a relatively small difference likely was inadequate. A recent meta-analysis of 912 patients conducted on patient level confirms these suspicions and returns a HR of 1.41 (indicating 41% higher risk in males) by multivariable analysis that adjusted for age, Eastern Cooperative Oncology Group (ECOG) performance status, AP and ALT level, and the diameter of the largest metastasis (Khoja et al., 2019).

4.2.2. Age

Age has not been analyzed against OS in a consistent manner (Eskelin et al., 2003; Gragoudas et al., 1991; Khoja et al., 2019; Kodjikian et al., 2005a; Lorenzo et al., 2018; Nicholas et al., 2018; Pons et al., 2011; Rantala et al., 2021a, 2021b; Rietschel et al., 2005; Xu et al., 2019). In interpreting age, it is useful to know that the median age at the time of diagnosis of metastatic uveal melanoma is 61–65 years (Eskelin et al., 2003; Gragoudas et al., 1991; Khoja et al., 2019; Kodjikian et al., 2005a; Nicholas et al., 2018; Pons et al., 2011; Rantala et al., 2021b; Xu et al., 2019). It is unlikely that the risk is linearly associated with age over the full age range, affecting the use of age as a continuous variable, which in addition to low power may explain the lack of statistical significance in such analyses (Table 4B). Older age defined by a single but variable cut-off point or cut-off points has inconsistently been associated with either shorter or longer OS in several reports (Khoja et al., 2019; Lorenzo et al., 2018; Rajpal et al., 1983; Rietschel et al., 2005). The survival in the older age groups is potentially confounded by competing causes of death (*see* 2.1.3., above) that are not statistically accounted for in Kaplan-Meier and Cox regression analyses (Kujala et al., 2003). The best evidence, again, comes from the patient-level meta-analysis that returned a HR of 1.12 (12% increased risk) for age 65 years or older upon adjusting for gender, ECOG performance status, AP and ALT levels, and the diameter of the largest metastasis (Khoja et al., 2019). A recent real-world, nationwide study of 216 patients found a similar HR of 1.16 for age older than 68 years (Rantala et al., 2021b). Both studies were limited to patients who were eligible for active treatment.

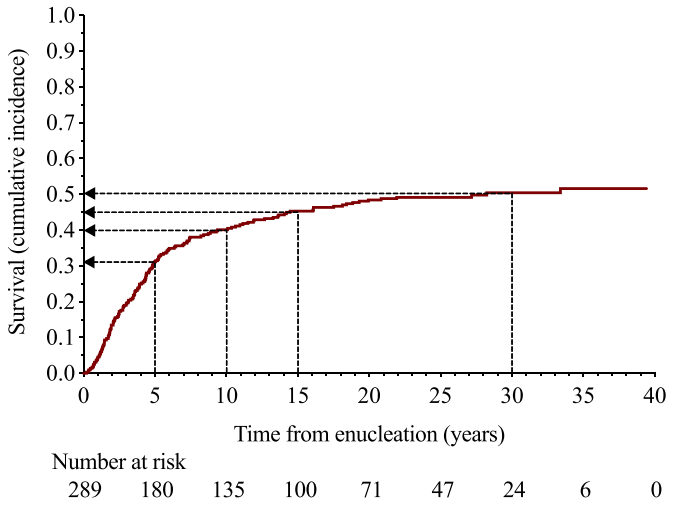


Fig. 10. Justification for continuing surveillance for early detection of metastases for 15 years after treating a primary uveal melanoma. The cumulative incidence of metastasis in a consecutive series of 289 patients who had an eye enucleated before brachytherapy was available, and who were tracked for a minimum of 20 years after treatment of the primary uveal melanoma. Fifty percent of the patients developed metastases within the first 30 years. Of these metastases, approximately 60% were diagnosed within the first 5 years from diagnosis of the primary melanoma, approximately 20% during the next 5 years, and 10% more by 15 years. Although 10% of metastases appeared even later than 15 years from diagnosis of the primary tumor, it took another 15 years to diagnose them, and the last metastasis occurred even later. Data correspond to results published in (Kujala et al., 2003).

4.2.3. Primary tumor

The characteristics of the primary uveal melanoma, recorded at the time of its diagnosis, are often left unreported in studies from oncology centers (Augsburger et al., 2009). Studies that report them, mostly from ocular oncology centers, do not document consistent associations with OS, but low power characterizes these analyses (Table 4C) (Eskelin et al., 2003; Kodjikian et al., 2005a; Mariani et al., 2019; Valpione et al., 2015b).

It is well established that larger size, ciliary body involvement and extraocular extension of primary uveal melanoma are independently associated with risk of developing metastasis and, thus, with a shorter metastasis-free interval (see *4.2.7.*, below) (Kivelä et al., 2017; Kujala et al., 2013; Shields et al., 2015). Although independent predictors, they are all interrelated because both ciliary body and extraocular extension are associated with tumor size. After diagnosis of metastases, only ciliary body involvement returned in two univariable analyses a HR of 1.42 and 1.70 with a *P*-value around 0.05 (Kodjikian et al., 2005a; Mariani et al., 2019), but a third analysis gave an opposite HR of 0.71 in a multivariable model (Valpione et al., 2015b). Thus, an association with ciliary body involvement is not verified. Orange pigment over the primary tumor was associated with survival for at least one year after metastases in a single-center study of 99 patients, but the association was lost in a multivariable logistic regression model (Lorenzo et al., 2018).

4.2.4. Performance status

Performance score is a measure to assess the general well-being and the capacity for activities of daily living of a patient with cancer. Several scoring systems exist for this purpose, the most frequent of which are the ECOG score, also called the WHO performance status, and Karnofsky index (Table 5, see page 31). Assessing performance status is essential in selecting patients who are most likely to benefit from treatment and in avoiding morbidity in patients who have little to gain from active

Table 4A
Gender as a prognostic factor for overall survival in univariable and, if available, multivariable analysis, tabulated alphabetically by author; studies were included if hazard ratio, or equivalent, and *P*-value were reported.[a]

Study	No. patients Study design	No. patients per category	Category	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Eskelin et al. (2003)	91	44	Female	Reference[b]			
	single center	47	Male	1.18 (0.78–1.79)	0.46	N/A	N/A
Gragoudas et al. (1991)	145	65	Female	Reference[b]			
	single center	79	Male	1.0 (0.67–1.38)	NS	N/A	<0.05
Khoja et al. (2019)	912	437	Female	Reference		Reference	
	multicenter	475	Male	1.38 (1.18–1.60)	<0.001	1.41 (1.16–1.72)	<0.001
Kivelä et al. (2003)	24	12	Female	Reference[b]		Reference[b]	
	multicenter	12	Male	3.03 (1.23–7.69)	0.015	4.17 (1.56–11.1)	0.005
Kodjikian et al., 2005	35	33	Female	Reference[b]			
	single center	30	Male	1.12 (0.65–1.92)	0.69	N/A	N/A
Mariani et al. (2019)	224	111	Female	Reference[b]			
	single center	113	Male	1.08 (0.79–1.12)	0.66	N/A	N/A
Nicholas et al. (2018)	132	77	Female	Reference[b]			
	single center	55	Male	1.20 (0.82–1.75)	0.35	N/A	N/A
Rantala et al. (2021a)	108	53	Female	Reference		Reference	
	single center	55	Male	1.3 (0.9–1.9)	0.16	1.3 (0.8–1.9)	0.25
Rantala et al. (2021b)	216	110	Female	Reference		Reference	
	single center	106	Male	1.21 (0.91–1.60)	0.19	1.21 (0.91–1.61)	0.20
Rietschel et al. (2005)	119	68	Female	Reference[b]		Reference[b]	
	single center	51	Male	N/A	N/A	RR 2.0 (1.20–3.33)	0.008
Xu et al. (2019)	73	36	Female	Reference[b]		Reference[b]	
	single center	38	Male	1.35 (0.82–2.22)	0.24	1.32 (0.79–2.17)	0.30

Abbreviations for Tables 4A-4P: AP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CI = confidence interval; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LDH = lactate dehydrogenase; LDLM = the largest diameter of the largest metastasis; MRI = magnetic resonance imaging; N/A = not available; NS = not significant; OR = odds ratio at one year; RR = relative risk, or risk ratio; TNM = tumor, node, metastasis; UNL = upper normal limit; US = ultrasonography.

[a] Not included in the table: did not report HR and *P*-value in a univariable analysis Buzzacco et al. (2012); Rajpal et al. (1983).

[b] For consistency, female gender was converted to reference.

treatment. As a caveat, according to a meta-analysis the concordance of performance ratings among health care professionals is variable, from poor to very good, causing bias (Chow et al., 2020).

A more favorable performance score is strongly and consistently associated with survival advantage, equally by univariable and multivariable analysis (Table 4D) (Eskelin et al., 2003; Jochems et al., 2019; Khoja et al., 2019; Lorenzo et al., 2018, 2019; Mariani et al., 2019; Nicholas et al., 2018; Pons et al., 2011; Valpione et al., 2015b).

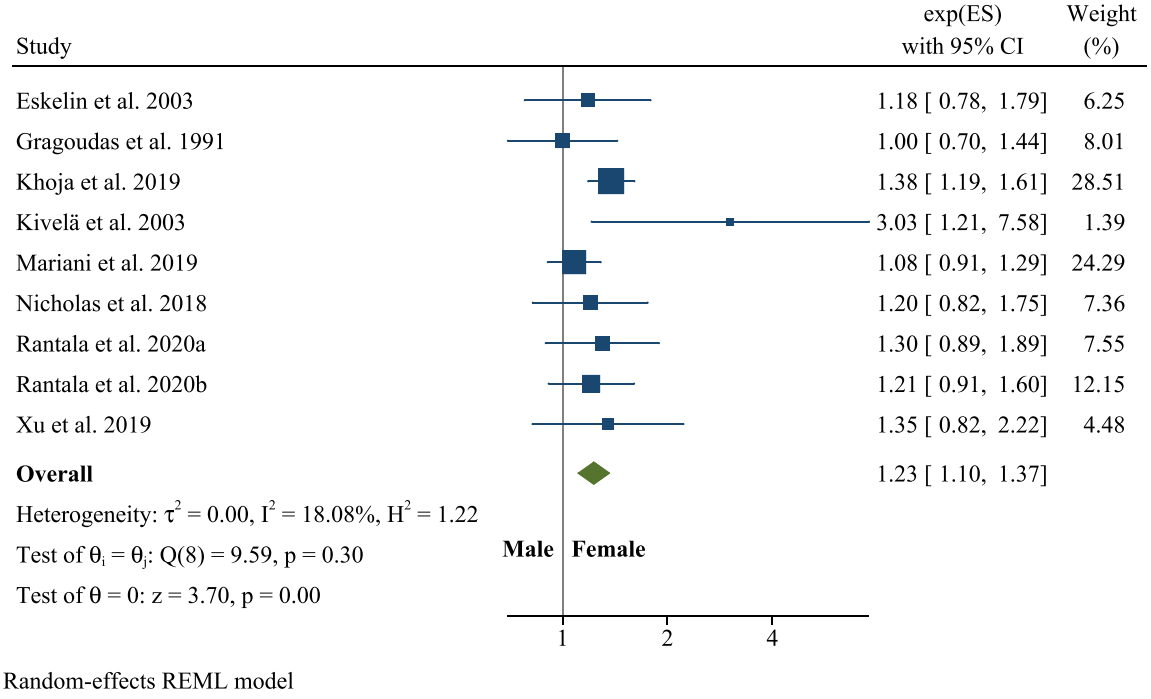


Fig. 11. Meta-analysis of univariable analyses of gender as a prognostic factor for overall survival after diagnosis of metastatic uveal melanoma. Note that the sum of the smaller studies is consistent and strengthen the results of the recent meta-analysis, supporting a small gender-related risk of metastasis. ES = effect size. Data from Table 4A.

Table 4B
Age at the time of diagnosis of metastases as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and *P*-value were reported.[a]

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Rietschel et al. (2005)	119	68	>60	Reference		Reference	
	single center	51	≤60	N/A	NA	RR 0.45 (0.27–0.76)	0.003
Khoja et al. (2019)	912	550	<65	Reference		Reference	
	multicenter	335	≥65	1.21 (1.02–1.43)	0.01	1.12 (0.97–1.31)	<0.001
Khoja et al. (2019)	912	550	<65	Reference		Reference	
	multicenter	335	≥65	1.21 (1.02–1.43)	0.01	1.12 (0.97–1.31)	<0.001
Pons et al. (2011)	58	27	≤65	Reference			
	single center	21	>65	0.92 (0.46–1.90)	>0.05	N/A	N/A
Lorenzo et al. (2018)	99	71	≤65	Reference		Reference	
	single center	28	>65	OR 3.63 (1.43–9.17)	0.005	OR 5.14 (1.44–18.31)	0.012
Kodjikian et al., 2005	35	48	≤70	Reference		Reference	
	single center	15	>70	RR 1.84 (0.99–3.39)	0.06	RR 1.01 (0.99–1.04)[b]	0.30
Pons et al. (2011)	58	33	≤70	Reference			
	single center	15	>70	0.77 (0.37–1.60)	>0.05	N/A	N/A
Rantala et al. (2021a)	108	59	<80	Reference		Reference	
	single center	49	≥80	0.7 (0.5–1.0)	0.053	0.9 (0.6–1.3)	0.47
Gragoudas et al. (1991)	145	34	<55	Reference		Reference	
	single center	72	55–69	RR 1.7 (1.1–2.7)	NS	N/A	<0.05
		38	>69	RR 1.6 (1.0–2.6)	NS	N/A	
Rantala et al. (2021b)	216	65	<59 (1st tertile)	Reference		Reference	
	single center	68	59–68 (2nd tertile)	0.77 (0.54–1.10)	0.15	0.89 (0.61–1.30)	0.21
		83	>68 (3rd tertile)	0.92 (0.66–1.30)	0.65	1.16 (0.81–1.66)	0.83
Eskelin et al. (2003)	91	N/A[c]	Age, per 5-year increase	1.03 (0.93–1.14)	0.16	N/A	N/A
	single center						
Nicholas et al. (2018)	132	N/A[d]	Age, per 1-year increase	1.01 (0.996–1.03)	0.14	1.04 (1.01–1.07)	0.006
	single center						
Pons et al. (2011)	58	N/A[e]	Age, per 1-year increase	0.99 (0.06–1.60)	>0.05	N/A	N/A
	single center						
Xu et al. (2019)	73	N/A[f]	Age, per 1-year increase	1.01 (0.98–1.03)	0.55	1.00 (0.98–1.03)	0.79
	single center						

For abbreviations, see Table 4A.
[a] Not included in the table: did not report HR and *P*-value Rajpal et al. (1983).
[b] In the multivariable analysis, age was treated as a continuous variable. The relative rates in the table were taken from the linear model. Quadratic terms were also tested and were not significant.
[c] Mean age 62 years (range, 23–86).
[d] Mean age 63 years (range, 31–92).
[e] Median age 61 years (range, 31–84).
[f] Median age at time of uveal melanoma diagnosis 63 years.

The most reliable quantitative estimates – from two separate contexts – come from multivariable analyses in a retrospective study of 249 consecutive patients who died of metastatic uveal melanoma, and patient-level meta-analysis of 912 patients enrolled in prospective systemic treatment trials (Khoja et al., 2019; Kivelä et al., 2016). They estimated the HR for ECOG >0 to be 1.55 ($P = 0.001$) and 1.26 ($P = 0.002$), respectively, adjusted for AP level and the largest diameter of the largest metastasis (LDLM) in the former and additionally for gender, age, and LDH level in the latter, explaining its lower HR. In interpreting these results, one also needs to consider that the ECOG score was unknown in 21% of patients in the meta-analysis, and that essentially none in either study had a score of 3 or 4. Thus, the HR for ECOG >0 in both studies is approximately the HR for ECOG 1–2.

4.2.5. Symptoms from metastases

The percentage of patients who have symptoms when metastases are diagnosed depends on whether, how frequently, and by which methods they have been surveilled. Different surveillance protocols contribute to lead time bias – the earlier the diagnosis of a disease, the longer the patient appears to survive (Brawley and Parnes, 2019b) – and, reciprocally, modify the metastasis-free interval (see *4.2.7.* below). Further bias results from subjectivity in reporting symptoms between patients and in recording them by physicians, and to some extent in timing surveillance tests. Symptoms also influence the performance status that can be variably judged by different observers.

Nevertheless, all univariate analyses agree that symptoms attributable to metastases are consistently and strongly associated with a shorter OS (Table 4E) (Eskelin et al., 2003; Lorenzo et al., 2018; Rantala et al., 2021a, 2021b; Xu et al., 2019). The HR varies from about 1.7 in two reports from Finland for patients who underwent surveillance for metastases mostly every 12 months using upper abdominal US and LFTs, and were actively treated, to 3.7 for patients who underwent similar surveillance but had more advanced metastases or a less favorable ECOG score and were thus managed with BSC; the corresponding multivariable estimates of 2.05 and 2.6 that adjusted for these imbalances converged (Rantala et al., 2021a, 2021b).

Although the presence of symptoms competed with a HR of 2.05 (Eskelin et al., 2003) for a place in the final multivariable model that defined the Helsinki University Hospital (HUH) working formulation for staging of patients with metastatic uveal melanoma (see 5.3.1, below) that additionally included performance score and the LDLM, it was discarded in favor of AP level because of the relative subjectivity of symptoms and the wider possibilities for categorizing AP.

Two other single institution studies (Valpione et al., 2015b; Xu et al., 2019), which analyzed symptoms that led to the diagnosis of metastases, reported a univariable HR or OR (for survival at 1 year) in the same range than the studies in Finland (Eskelin et al., 2003; Rantala et al., 2021a, 2021b). With a HR of 2.39 ($P = 0.017$) symptoms were independently associated with OS in a multivariable Cox regression model that adjusted for age, gender, presence of extrahepatic metastasis, and presence of hepatic metastases. The large meta-analysis that applied multivariable Cox regression could not consider presence of symptoms from metastases (Khoja et al., 2019).

Table 4C
Characteristics of the primary tumor as a prognostic factor for overall survival in univariable and, if available, multivariable analysis, tabulated according to characteristic; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients Study design	No patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Lorenzo et al. (2018)	99		Orange pigment over tumor				
	single center	79	No	Reference			
		20	Yes	OR 4.20 (1.48–11.9)	0.005	N/A	NS
Kodjikian et al. (2005)	35		Largest diameter				
	single center	19	≤10 mm	Reference			
		36	>10 mm	RR 1.04 (0.55–1.95)	0.91	N/A	N/A
Mariani et al. (2019)	224		Largest diameter				
	single center	128	<18 mm	Reference			
		93	≥18 mm	1.14 (N/A)	0.41	N/A	N/A
Eskelin et al. (2003)	91	N/A	Largest diameter, per 1 mm increase	0.98 (0.97–1.04)	0.54	1.17 (1.10–1.24)	<0.001
	single center						
Valpione et al. (2015)	152	N/A[a]	Larger basal diameter, per 1 mm increase	N/A	N/A	0.92 (0.80–1.05)	0.40
	multicenter						
Kodjikian et al. (2005)	35		Tumor thickness				
	single center	18	≤5 mm	Reference		Reference	
		38	>5 mm	RR 0.94 (0.50–1.78)	0.85	N/A	N/A
Valpione et al. (2015)	152	N/A[b]	Tumor thickness, per 1 mm increase	N/A	N/A	1.07 (0.91–1.27)	0.46
	multicenter						
Kodjikian et al. (2005)	35		Ciliary body involvement				
	single center	19	No	Reference		Reference	
		44	Yes	RR 1.70 (0.92–3.11)	0.09	2.20 (1.2–4.1)	0.017
Mariani et al. (2019)	224		Ciliary body involvement				
	single center	127	No	Reference			
		84	Yes	1.42 (1.03–1.96)	0.03	N/A	N/A
Valpione et al. (2015)	152		Ciliary body involvement				
	multicenter	141	No	Reference		Reference	
		11	Yes	N/A	N/A	0.71 (0.35–1.44)	0.34
Mariani et al. (2019)	224		Extrascleral extension				
	single center	191	No	Reference			
		15	Yes	0.74 (0.40–1.37)	0.34	N/A	N/A
Valpione et al. (2015)	152		TNM category[c]				
	multicenter	8	T4	Reference		Reference	
		65	T3	N/A	N/A	0.30 (0.01–3.80)	0.20
		50	T2	N/A	N/A	0.33 (0.03–3.91)	0.38
		29	T1	N/A	N/A	0.71 (0.01–3.80)	0.26
Valpione et al. (2015)	152		Cell type				
	multicenter	3	Spindle	Reference		Reference	
		146	Mixed	N/A	N/A	1.52 (0.26–1.64)	0.125
		3	Epithelioid	N/A	N/A	4.30 (0.01–100)	0.98

For abbreviations, see Table 4A.
[a] Larger basal diameter median 13 mm.
[b] Thickness median 6.1 mm.
[c] The edition of TNM was not reported.

4.2.6. *Attendance to surveillance*

Diagnosis of metastases while attending regular surveillance appointments is statistically associated with longer OS by univariable and multivariable analysis (Table 4F) (Eskelin et al., 2003; Lorenzo et al., 2018; Rietschel et al., 2005). The association is not as strong as that with presence of symptoms from metastases, a variable with which attendance to surveillance is interrelated (see *4.2.5.* above). Moreover, although patients who participated in annual surveillance to detect metastases had a longer OS than those who did not (median, 8.9 vs. 4.3 months), their survival calculated from the diagnosis of the primary tumor was comparable, suggesting that the difference largely reflected lead time bias.

4.2.7. *Metastasis-free interval*

Metastasis-free interval (MFI) is the time from the primary tumor to clinically detectable systemic metastases. Its variation is theoretically interesting and analytically complex because it is influenced by growth kinetics of the tumor, host defenses, and the surveillance strategy (Table 4G) (Bedikian et al., 1995; Buzzacco et al., 2012; Lorenzo et al., 2018, 2019; Mariani et al., 2009, 2019; Rantala et al., 2021b; Rietschel et al., 2005; Valpione et al., 2015b). The theoretical interest stems from observations on driver mutations in uveal melanomas: pathogenic variants in *BAP1* are associated with relatively frequent, rapid metastasis whereas those in *SF3B1* and, especially, *EIF1AX* lead less frequently to metastases that also appear later (Grimes et al., 2021; Piperno-Neumann et al., 2020; Robertson et al., 2018; Shain et al., 2019; Smit et al., 2020; Yavuzyigitoglu et al., 2016). This suggests that short, intermediate, and long MFI might provide a surrogate variable for these three driver genes (Szalai et al., 2018). The complexity reflects the fact that the outcome of analysis will depend, perhaps heavily, on how MFI is categorized and how much lead time bias the surveillance protocols may induce, especially when MFI is short (Kivelä et al., 2006; Szalai et al., 2018).

In practice, of several studies that divided MFI at 24 months, two small ones of 38 and 58 patients failed to verify an association with OS (though one of them suggested an effect size of HR 1.7 for MFI <24 months) (Kodjikian et al., 2005a; Xu et al., 2019). The nationwide dataset of 216 actively treated patients in Finland, was unable to confirm such an association, although a HR of approximately 1.2 would favor a weak association between short MFI and worse OS (Rantala et al., 2021b). The best evidence currently comes from two large studies of 255 and 152 patient that applied multivariable modeling. The first one found an inverse association with OS: compared to MFI >24 months the HR was 1.43 ($P = 0.09$) for MFI 12–24 months, 2.02 ($P = 0.004$) for MFI 12–6 months, and 3.39 ($P < 0.001$) for MFI <6 months (Mariani et al., 2019). The second one modeled MFI as a continuous variable and found it to be an independent predictor of OS with a HR of 0.9 ($P <$

Table 4D
Performance status as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Karnofsky index							
Kivelä et al. (2003)	24 multicenter	14[a]	Karnofsky index, per 10-unit decrease in index	1.33 (0.78–2.27)	0.30	N/A	N/A
ECOG score							
Eskelin et al. (2003)	91	55	0	Reference		Reference	
	single center	24	1–2	3.40 (2.23–5.18)	<0.001	2.36 (1.51–3.69	<0.001
Kivelä et al. (2016)	249	154	0	Reference		Reference	
	multicenter	92	1–2	N/A	N/A	1.56 (1.20–2.03)	0.001[b]
		3	3–4	N/A			
Pons et al. (2011)	58	18	0	Reference		Reference	
	single center	30	1–2	1.32 (0.65–2.70)	≥0.05	2.40 (1.06–5.80)	<0.05
Valpione et al. (2015)	152	93	0	Reference		Reference	
	multicenter	46	1	N/A	N/A	1.5	<0.001[b]
		13	2–3	N/A		4.5	
Khoja et al. (2019)	912	475	0	Reference		Reference	
	multicenter	250	≥1	1.49 (1.25–1.78)	<0.001	1.26 (1.11–1.44)	0.002
Nicholas et al. (2018)	132	65[c]	0	Reference		Reference	
	single center		≥1	1.88 (1.10–3.22)	0.022	3.44 (1.61–7.33)	0.0014
Mariani et al. (2019)	224	214	0–1	Reference		Reference	
	single center	10	2–3	1.87 (0.95–3.67)	0.07	N/A	N/A
Jochems et al. (2019)	175	131	0–1	Reference	'ECOG >1 seemed to be associated with worse survival'	Reference	
	multicenter	15	≥2	N/A		N/A	<0.05
Lorenzo et al. (2018)	99	94[d]	Lower score	Reference		N/A	N/A
	single center		Higher score	OR 2.94 (1.35–6.67)	0.007		

For abbreviations, see Table 4A.
[a] Karnofsky index was 100 for 7 patients, 90 for 11 patients, 80 for 6 patients, and never worse than 80.
[b] Only one *P*-value is given suggesting that the variable was modeled as if it would be a continuous one rather than categorical.
[c] Score was available for 65 patients, but its distribution was not reported.
[d] Score was 0, 1, 2, and 3 for 59, 25, 9, and 1 patient, respectively. For the consistency, the lower ECOG was converted to reference.

0.001) for each 1-month increase in MFI (Valpione et al., 2015b). Two other reports in which MFI was analyzed as a continuous variable have reported qualitatively similar but less strong associations (Nicholas et al., 2018; Xu et al., 2019).

The largest collaborative meta-analysis did not consider MFI as a potential predictive factor (Khoja et al., 2019). The association between MFI and OS must be explored further, along with how to best categorize this variable and how it is associated with known driver mutations.

4.2.8. *Liver function tests*

Analyses of LFTs as prognostic factors for OS in metastatic uveal melanoma have limitations. The levels of LFTs have been categorized in different ways (Table 4H–K). Their scale and the UNL vary between laboratories and over time. Each measurement is thus ideally expressed relative to its UNL to allow comparability between studies (Augsburger et al., 2009). A limitation of analyzing LFTs as continuous variables is the inherent assumption that the HR would then be consistent over the full range of values. When cut-off points are used, the larger they are relative to the UNL (e.g., 2.5 x versus 1.0 x), the larger the HR will be.

In retrospective analyses, some patients will not have all LFTs measured. In list-wise multivariable analyses this leads to loss of patients modeled. In clinical trials, the LFTs must fall in predefined ranges to fulfill the enrollment criteria. This will limit variability compared with population-based analyses.

Because metastatic uveal melanoma primarily and predominantly metastasizes to the liver, both liver damage secondary to the metastases and the metastases themselves may contribute to the elevated LFT (Kivelä et al., 2016). This is especially likely to be true of LDH, which is a strong prognostic variable in patients with metastatic cutaneous melanoma that far less frequently metastasizes to the liver (Long et al., 2016).

Table 4E
Symptoms as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Symptoms at diagnosis of metastases							
Eskelin et al. (2003)	91	31	No	Reference		Reference	
	single center	43	Yes	1.69 (1.05–2.73)	0.031	2.05 (0.94–4.47)	0.073
Lorenzo et al. (2018)	99	60	No	Reference		Reference	
	single center	31	Yes	OR 3.61 (1.36–9.55)	0.008	N/A	N/A
Symptoms at treatment initiation							
Rantala et al. (2021a)	108	44	No	Reference		Reference	
	single center	60	Yes	3.7 (2.4–5.6)	<0.001	2.6 (1.7–4.2)	<0.001
Rantala et al. (2021b)	216	164	No	Reference		Reference	
	single center	50	Yes	1.68 (1.20–2.36)	0.003	0.95 (0.65–1.39)	0.76
Diagnosis by symptoms							
Xu et al. (2019)	73	63	No	Reference		Reference	
	single center	10	Yes	2.72 (1.36–5.44)	0.005	2.39 (1.17–4.90)	0.017

For abbreviations, see Table 4A.

Table 4F
Attendance to surveillance as prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Participation in annual surveillance							
Eskelin et al. (2003)	91	14	No	Reference		Reference	
	single center	77	Yes	0.60 (0.36–1.07)	0.084	0.47 (0.26–0.85)	0.012
Metastasis diagnosis by surveillance							
Lorenzo et al. (2018)	99	31	No[a]	Reference		Reference	
	single center	68	Yes	OR 0.34 (0.12–0.96)	0.037	N/A	N/A
Rietschel et al. (2005)	119	N/A	No	Reference		Reference	
	single center		Yes	N/A[b]	N/A	N/A[b]	NS

For abbreviations, see Table 4A.
[a] The frequency of surveillance was not reported; for clarity, No was converted to reference.
[b] Relative risk was the statistic used, reference and RR are not available.

Table 4G
Distant metastasis-free interval as prognostic factor for overall survival in univariable and, if available, multivariable analyses; studies were included if hazard ratio, or equivalent, and *P*-value were reported.[a].

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Kodjikian et al. (2005)	35	26	>24[b] months	Reference		Reference	
	single center	37	≤24 months	RR 1.04 (0.60–1.82)	0.87	N/A	N/A
Mariani et al. (2009)	255	104	>24 months	Reference		Reference	
	single center	151	≤24 months	1.94 (1.47–2.63)	<0.0001	1.94 (1.47–2.63)	<0.0001
Pons et al. (2011)	58	21	>24 months	Reference		Reference	
	single center	27	≤24 months	1.71 (0.87–3.40)	>0.05	N/A	N/A
Lorenzo et al. (2018)	99	N/A	>40 months[c]	Reference		Reference	
	single center	30	≤40 months	OR 0.38 (0.16–0.93)	0.03	N/A	N/A
Mariani et al. (2019)	224	125	>24 months	Reference		Reference	
	single center	52	12–24 months	1.74 (1.19–2.53)	0.004	1.43 (0.94–2.16)	0.09
		31	6–12 months	1.54 (0.97–2.44)	0.07	2.02 (1.24–3.27)	0.004
		16	0–6 months	2.35 (1.35–4.1)	0.003	3.39 (1.90–6.05)	<0.001
Rantala et al. (2021b)	216	74	>42 months	Reference		Reference	
	single center	48	24–42 months	1.19 (0.83–1.69)	0.34	0.95 (0.66–1.39)	<0.001
		94	<24 months	1.25 (0.89–1.75)	0.19	1.14 (0.80–1.59)	<0.001
Nicholas et al. (2018)	132 single center	N/A [d]	Per 1-month increase	0.998 (0.996–1.00)	0.0542	N/A	NS
Valpione et al. (2015)	152 multicenter	N/A[e]	Per 1-month increase	N/A	N/A	0.9 (N/A)	<0.001
Xu et al. (2019)	73 single center	N/A[f]	Per 1-month increase	0.996 (0.990–1.002)	0.15	0.997 (0.991–1.004)	0.42

For abbreviations, see Table 4A.
[a] Not included in the table: did not report HR and *P*-value Bedikian et al. (1995); Buzzacco et al. (2012).
[b] For consistency, >24 months was converted to reference.
[c] For consistency, >40 months was converted to reference.
[d] Interval was known for 132 patients, but its distribution was not reported.
[e] Median interval 25.2 months (range, 0–339.2).
[f] Median interval 27 months (interquartile range, 13–46).

In fact, LDH is part of the TNM staging for cutaneous melanoma (Gershenwald et al., 2017). The prognostic value of AP in cutaneous melanoma, if any, has not received equal attention. Of note, elevated AP and LDH might also derive from multiple other causes, such as a bone disorder and muscle injury, respectively, which can be differentiated if necessary by measuring corresponding isoenzymes (Wallach, 2007).

Especially AP (Bedikian et al., 1995; Eskelin et al., 2003; Khoja et al., 2019; Nicholas et al., 2018) (Table 4H) and LDH (Eskelin et al., 2003; Jochems et al., 2019; Khoja et al., 2019; Lorenzo et al., 2018, 2019; Mariani et al., 2019; Nicholas et al., 2018; Rantala et al., 2021b; Valpione et al., 2015b) are consistently and strongly (typically $P < 0.001$) associated with shorter OS, including multivariable analyses (Table 4I). Application of the above rules help to appreciate that studies that analyzed AP and LDH relative to their UNL give consistent messages as regards the HRs associated with elevated LFTs.

Association of OS with elevated AST (Eskelin et al., 2003; Lorenzo et al., 2018) (Table 4J), ALT (Eskelin et al., 2003; Lorenzo et al., 2018) (Table 4K), and especially gamma-glutamyl transferase (GT) (odds ratio 4.38, $P = 0.018$ in multivariable analysis) (Lorenzo et al., 2019) have been analyzed less frequently than that of AP and LDH. Although they are consistently associated with shorter OS, they have not been assessed as independent predictors of OS when adjusted for AP, LDH, or both, using multivariable analysis. They also have been reported far less frequently than AP and LDH.

4.2.9. *Extent of metastases*

Metastatic burden understandably is a key prognostic factor after uveal melanoma has disseminated. Investigators have considered qualitative aspects, such as the sites of metastases, and quantitative ones, including the number, diameter, and volume of metastases focusing either on all measurable metastases or on the largest metastases. It is useful to consider both the strength of the association and the ease of using in the practice of each alternative variable that measures metastatic burden, remembering though that a certain amount of bias results from subjectivity in measuring each metastasis.

Table 4H
Alkaline phosphatase as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and P-value were reported.[a].

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Khoja et al. (2019)	912		AP, x UNL				
	multicenter	428	≤1.0	Reference		Reference	
		162	>1.0	2.76 (2.27–3.36)	<0.001	1.98 (1.61–2.42)	<0.001
Lorenzo et al. (2018)	99		AP, x UNL				
	single center	62	≤1.0	Reference		Reference	
		N/A	>1.0	OR 20.41 (2.55–166.67)	<0.001	N/A	N/A
Eskelin et al. (2003)	91		AP, x UNL				
	single center	N/A	<2.5	Reference		Reference	
			≥2.5	7.67 (2.60–22.6)	<0.001	5.00 (1.69–14.7)	0.004
Eskelin et al. (2003)	91 single center	N/A[b]	AP, per 100 IU/L increase	1.49 (1.30–1.71)	<0.001	1.43 (1.24–1.64)	<0.001
Nicholas et al. (2018)	132 single center	N/A[c]	AP, per 1 IU/L increase	1.003 (1.002–1.004)	<0.0001	N/A	N/A
Kivelä et al. (2003)	24 multicenter	N/A[d]	AP, x UNL, per 1 x increase	1.75 (0.97–3.15)	0.061	N/A	N/A
Kivelä et al. (2016)	249 multicenter	249	AP, x UNL, per 1 x increase	N/A	N/A	1.21 (1.08–1.37)	0.001

For abbreviations, see Table 4A.
[a] Not included in the table: did not report HR and *P*-value Bedikian et al. (1995).
[b] 1.0 x UNL in 23 of 76 patients at diagnosis of metastases.
[c] Known for 120 patients, distribution not reported.
[d] 1.0 x UNL in 10 of 24 patients at time of enrollment.

Table 4I
Lactate dehydrogenase as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and P-value were reported.[a].

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Khoja et al. (2019)	912		LDH, x UNL				
	multicenter	330	≤1.0	Reference		Reference	
		386	>1.0	2.64 (2.11–3.30)	<0.001	2.31 (1.87–2.87)	<0.001
Lorenzo et al. (2018)	99		LDH, x UNL				
	single center	43	≤1.0	Reference		Reference	
		N/A	>1.0	OR 4.63 (1.77–12.05)	0.001	OR 4.38 (1.29–14.88)	0.018
Mariani et al. (2019)	224		LDH, x UNL				
	single center	108	≤1.0	Reference		Reference	
		78	>1.0–1.5	1.30 (0.93–1.83)	0.13	N/A	N/A
		35	>1.5	4.15 (2.71–6.33)	<0.001	3.72 (2.30–6.00)	<0.001
Rantala et al. (2021b)	216		LDH, x UNL				
	single center	61	<1.0	Reference		Reference	
		56	1.0–2.0	1.22 (0.82–1.82)	0.32	1.87 (0.80–1.83)	0.36
		28	>2.0	5.55 (3.15–9.79)	<0.001	4.76 (1.46–5.37)	0.002
Eskelin et al. (2003)	91		LDH, x UNL				
	single center	N/A[b]	<2.5	Reference		Reference	
			≥2.5	8.42 (3.80–18.7)	<0.001	6.42 (2.88–14.3)	<0.001
Jochems et al. (2019)	175		LDH, U/L				
	multicenter	81	<250	Reference		Reference	
		34	250–500	N/A	N/A	1.8 (1.07–3.01)	
		51	>500	N/A		9.0 (5.63–14.35)	<0.001
Eskelin et al. (2003)	91 single center	N/A[b]	LDH, per 100 IU/L increase	1.06 (1.03–1.08)	<0.001	1.05 (1.02–1.08)	<0.001
Nicholas et al. (2018)	132 single center	102[c]	LDH, per 1 IU/L increase	1.00 (1.00–1.00)[d]	<0.0001	1.001 (1.000–1.001)	0.0003
Valpione et al. (2015)	152 multicenter	N/A	LDH, x UNL, per 1 x increase[e]	N/A	N/A	1.6 (N/A)	0.014

For abbreviations, see Table 4A.
[a] Not included in the table: reported HR and *P*-value for the final step of multivariable analysis already adjusted by age and sex Lorenzo et al. (2019).
[b] > 1 x UNL in 27 of 43 patients.
[c] Known for 102 patients, distribution not reported.
[d] Uninformative HR because it corresponds to a very small unit change in LDH.
[e] Median 0.8 (range, 0.3–15.6).

4.2.9.1. Metastatic pattern. Presence of hepatic metastases with or without extrahepatic ones is associated with a shorter OS than having exclusively extrahepatic metastases, which are found in 5%–15% of patients, with a HR from 2.03 to 2.81, including one multivariable analysis (Table 4L) (Jochems et al., 2019; Mariani et al., 2019; Nicholas et al., 2018; Rajpal et al., 1983; Rietschel et al., 2005; Xu et al., 2019). Comparison of studies that considered hepatic metastases separately from extrahepatic ones or allowed patients with hepatic metastases to have also extrahepatic ones shows little difference, possibly because the volume of extrahepatic metastases relative to hepatic ones may have been

Table 4J
Aspartate aminotransferase as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and P-value were reported.

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Lorenzo et al. (2018)	99		AST, x UNL				
	single center	57	≤1.0	Reference		Reference	
		N/A	>1.0	OR 9.17 (2.46–34.48)	<0.001	N/A	N/A
Eskelin et al. (2003)	91		AST, x UNL[a]				
	single center	N/A	<2.5	Reference		Reference	
			≥2.5	1.19 (1.08–1.30)	<0.001	7.84 (2.18–28.2)	0.002
Eskelin et al. (2003)	91	N/A	AST, per 10 IU/L increase[a]	11.8 (3.28–42.4)	<0.001	1.25 (1.14–1.36)	<0.001
	single center						

For abbreviations, see Table 4A.
[a] Above UNL in 21 of 58 patients.

Table 4K
Alanine transaminase as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Lorenzo et al. (2018)	99		ALT, x UNL				
	single center	61	≤1.0	Reference			
		N/A	>1.0	OR 6.90 (1.85–25.64)	0.002	N/A	N/A
Eskelin et al. (2003)	91		ALT, x UNL[a]				
	single center	N/A	<2.5	Reference		Reference	
			≥2.5	3.98 (1.42–11.2)	0.009	3.39 (1.21–9.55)	0.021
Eskelin et al. (2003)	91		ALT, per 10-IU/L increase[a]	1.19 (1.08–1.30)	<0.001	1.23 (1.13–1.33)	<0.001
	single center	N/A					

For abbreviations, see Table 4A.
[a] Above UNL in 24 of 66 patients.

Table 4L
Pattern of metastases as a prognostic factor for overall survival in univariable and, if available, multivariable analysis; studies were included if hazard ratio, or equivalent, and *P*-value were reported.[a]

Study	No. patients Study design	No. patients per category	Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Jochems et al. (2019)	175		Hepatic metastases				
	multicenter	20	No	Reference		Reference	
		154	Yes	2.09 (1.07–4.08)	0.03	N/A	N/A
Nicholas et al. (2018)	132		Hepatic metastases				
	single center	11	No	Reference		Reference	
		121	Yes	2.81 (1.30–6.89)	0.0086	N/A	N/A
Mariani et al. (2019)	224		Extrahepatic and hepatic metastases				
	single center	199	No	Reference		Reference	
		21	Yes	2.03 (1.31–3.16)	0.002	N/A	N/A
Xu et al. (2019)	73		Extrahepatic and hepatic metastases				
	single center	64	No	Reference		Reference	
		9	Yes	2.28 (1.07–4.88)	0.033	2.12 (0.88–5.14)	0.095
Pons et al. (2011)	58		Extrahepatic metastases				
	single center	30	No	Reference		Reference	
		15	Yes	1.50 (0.70–3.20)	≥0.05	N/A	N/A
Rantala et al. (2021b)	216						
	single center	17	Only other sites	Reference		Reference	
		152	Only hepatic metastases	1.13 (0.66–1.94)	0.65	1.12 (0.64–1.96)	0.69
		47	Hepatic and other sites	1.12 (0.62–2.03)	0.70	1.05 (0.57–1.94)	0.88
Nicholas et al. (2018)	132		Bone metastases				
	single center	121	No	Reference		Reference	
		11	Yes	1.32 (0.71–2.46)	0.39	N/A	N/A
Nicholas et al. (2018)	132		Brain metastases				
	single center	129	No	Reference		Reference	
		3	Yes	0.93 (0.29–2.92)	0.89	N/A	N/A

For abbreviations, see Table 4A.
[a] Not included in the table: did not report HR and *P*-value Rajpal et al. (1983).

small. Sites other than the liver are rarely involved alone, are variable, and have not been adequately studied as regards prognosis. Multiorgan metastatic pattern may reflect more advanced disease, later diagnosis, or different tumor biology. Especially extrahepatic metastases without hepatic ones might reflect a tumor that is more sensitive to immuno-oncologic treatment, as was recently proposed (Johansson et al., 2019; Pelster et al., 2021; Piulats et al., 2021; Rodrigues et al., 2018).

4.2.9.2. Metastatic burden. A larger number of liver metastases (Kodjikian et al., 2005a; Mariani et al., 2019; Pons et al., 2011), a larger number of liver segments involved (Mariani et al., 2019), a larger percentage of liver substitution (Valpione et al., 2015b), a larger total area (Mariani et al., 2019), and a larger combined volume of hepatic and extrahepatic metastases (Eskelin et al., 2003) have all been strongly and, despite that they are different measures, consistently associated with shorter OS in metastatic uveal melanoma (Table 4M).

The number of hepatic metastases has been variably dichotomized, which expectedly leads to an increasing HR with an increasing cut-off point (Mariani et al., 2019). An obvious limitation of this measure is that it is subject to the sensitivity and specificity of the imaging method used (see *3.1.* above). Additionally, the cut-off points are arbitrary, and confluent metastases are difficult to count. The other measures likewise are subject to variation in imaging methods, and additionally require an effort from the radiologist to accurately measure and grade them, leading to interobserver variation. A final limitation is that none of them can be accurately measured when a very large number of small hepatic metastases is present, i.e., the metastatic pattern is miliary.

LDLM was introduced as a surrogate for total metastatic burden – that would be quicker and easier to measure in clinical practice than the latter – because it was as strongly associated with OS as total metastatic burden among 91 patients with metastatic uveal melanoma (Eskelin et al., 2003). LDLM has later been independently confirmed to be

Table 4M
Extent metastases as a prognostic factor for overall survival in univariable and, if available, multivariable analysis, tabulated alphabetically by author; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients Study design	No. patients per category	Variable (applied imaging methods)	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Xu et al. (2019)	73		No. of hepatic metastases (N/A)				
	single center	22	1	Reference		Reference	
		51	>1	1.50 (0.87–2.58)	0.14	1.29 (0.73–2.28)	0.39
Mariani et al. (2019)	224		No. of hepatic metastases (MRI)				
	single center	109	1 to 4	Reference		Reference	
		57	5 to 10	1.27 (0.87–1.83)	0.22	1.58 (1.07–2.33)	<0.001
		58	>10	2.89 (2.0–4.18)	<0.001	2.95 (1.97–4.43)	<0.001
Pons et al. (2011)	58		No. of hepatic metastases (N/A)				
	single center	15	<5	Reference		Reference	
		30	≥5	3.06 (1.36–6.87)	<0.05	5.65 (2.2–14.50)	<0.05
Kodjikian et al. (2005)	63		No. of hepatic metastases (CT)				
	single center	17	≤10	Reference		Reference	
		46	>10	RR 4.02 (1.85–8.73)	<0.001	RR 4.98 (2.1–11.6)	<0.0001
Mariani et al. (2019)	224		No. of hepatic segments involved (MRI)				
	single center	119	1 to 3	Reference		Reference	
		66	4 to 6	1.32 (0.94–1.86)	0.11	N/A	N/A
		39	7 to 8	3.57 (2.34–5.44)	<0.001	N/A	N/A
Valpione et al. (2015)	152		Hepatic substitution by metastases (CT/MRI)				
	multicenter	63	<20%	N/A	N/A	1.6 (N/A)[b]	<0.001
		48	20–50%				
		19	>50%				
Eskelin et al. (2003)	91 single center	N/A	Total metastatic burden, per 1000 cm^3 increase (US/CT/MRI)	1.51 (1.18–1.92)	<0.001	1.52 (1.19–1.94)	<0.001
Barnhill et al. (2018)	41		LDLM (N/A)[c]				
	single center	N/A[c]	≤17 mm (median)	Reference		Reference	
			>17 mm	2.86 (1.16–7.05)	0.02	2.58 (0.86–7.73)	0.091
Khoja et al. (2019)	912		LDLM (N/A)				
	multicenter	232	<30 mm	Reference		Reference	
		365	>30 mm	1.65 (1.41–1.93)	<0.001	1.26 (1.10–1.45)	0.002
Eskelin et al. (2003)	91 single center	N/A	LDLM, per 10 mm increase (US/CT/MRI)	1.16 (1.10–1.24)	<0.001	1.17 (1.10–1.24)	<0.001
Kivelä et al. (2003)	24 multicenter	N/A[d]	LDLM, per 10 mm increase (N/A)	1.13 (1.01–1.26)	0.032	N/A	N/A
Kivelä et al. (2016)	249 multicenter	249	LDLM, per 10 mm increase (N/A)	N/A	N/A	1.09 (1.04–1.14)	<0.001
Nicholas et al. (2018)	132 single center	114[e]	LDLM, hepatic metastases, per 1 mm increase (N/A)	1.07 (1.03–1.12)	0.001	N/A	N/A
Lorenzo et al. (2018)	99		LDLM, hepatic metastases (N/A)				
	single center	N/A[f]	Smaller	Reference		Reference	
			Larger	OR 1.03 (1.01–1.06)	0.034	OR 1.04 (1.00–1.09)	0.063
Mariani et al. (2019)	224		Area of the largest hepatic metastasis (MRI)				
	single center	143	1–500 mm^2	Reference		Reference	
		27	501–800 mm^2	1.17 (0.74–1.86)	0.51	N/A	N/A
		20	801–1200 $mm^{2>}$	2.56 (1.56–4.19)	<0.001	1.74 (1.00–3.05)	<0.001
		34	1201–mm^2	3.28 (2.14–5.02)	<0.001	2.47 (1.53–3.98)	<0.001

For abbreviations, see Table 4A.
[b] No reference provided; apparently the variable was modeled as a continuous and not a categorical one.
[c] Mean diameter 16.6 mm (standard deviation, 2.9) and median 17 mm (range, 10–23).
[d] Median diameter 42.5 mm (range, 10–141).
[e] Known for 114 patients, distribution not reported.
[f] Median diameter 22 mm; for consistency, the category smaller LDLM was converted to reference.

strongly and consistently associated with shorter OS (Table 4M) (Barnhill et al., 2018; Eskelin et al., 2003; Khoja et al., 2019; Kivelä et al., 2003; Lorenzo et al., 2018; Nicholas et al., 2018). In two large studies, this association held true also in multivariable analysis both when modeled as a continuous variable (Kivelä et al., 2016) and when dichotomized at 30 mm (Khoja et al., 2019). A similar association is documented in one study for the largest area of the largest hepatic metastasis (Mariani et al., 2019).

4.2.10. Histopathology

Histopathological characteristics of metastases from uveal melanoma are likely associated with the course of the disseminated disease, but their contribution to OS has been addressed neither systematically nor comprehensively. Only small selected series of 11–41 patients have so far been explored (Table 4N). The vast majority of metastases from uveal melanoma (92%) contain epithelioid cells, the more so than matched primary tumors, which limits possibilities of confirming a statistical association with OS (Griewank et al., 2014; Toivonen et al., 2004).

A potential, but not confirmed, histopathological association with shorter OS is the replacement rather than the desmoplastic growth pattern of hepatic metastases (Barnhill et al., 2018). This might result from the ability to detect easier a desmoplastic (nodular) versus replacement (infiltrative) type of metastasis (Halenda et al., 2016). Other histopathologic variables potentially associated with shorter OS are the presence of ≥5% of inflammatory cells in the tumor based on 11 patients (Abdel-Rahman et al., 2012), microvascular density exceeding 57 vessels/mm^2 in 13 and 21 patients (Al-Jamal et al., 2010; Toivonen et al., 2004) with a median OS of 1.5 months versus 6.5 months (P = 0.096), and pleomorphic as compared to uniform nuclear morphology in 25 patients (Griewank et al., 2014). Because of inadequate power in these analyses, further confirmation is needed.

4.2.11. Genetics

The cytogenetic and molecular genetic features of metastases most likely are not only associated with but may also directly influence the course of metastatic uveal melanoma. However, their contribution to OS has been addressed in a very preliminary manner. Cytogenetic abnormalities – especially partial or complete monosomy 3 – and pathogenic variants in *BAP1* – that can also be alternatively demonstrated though loss of nuclear immunoreactivity for BAP1 protein – are found in 70–100% and 60–80% of metastases from uveal melanoma, respectively (Table 4O) (Aalto et al., 2001; Abdel-Rahman et al., 2012; Griewank et al., 2014; Hoefsmit et al., 2020; Luscan et al., 2015; McCarthy et al., 2016; Singh et al., 2009; Trolet et al., 2009). The importance of BAP1 loss for OS of patients with metastasis remains to be shown (Table 4 P) (Abdel-Rahman et al., 2012; Griewank et al., 2014; Valpione et al., 2015b). Targeting BAP1 may be ineffective as a therapy for metastatic uveal melanoma because 20–40% of hepatic metastases seem to have retained functional BAP1 (Dong et al., 2019; Kaluz et al., 2021). Molecular characterization of metastasis could thus help to identify patients who might benefit from BAP1 targeting.

A mutually exclusive pathogenic variant in *GNAQ* or *GNA11* is found in more than 90% of uveal melanomas (Van Raamsdonk et al., 2009, 2010), and a mutually exclusive one in *PLCB4* or *CYSLTR2* in nearly all

Table 4N
Histopathological features as prognostic factor for overall survival in univariable analysis, tabulated alphabetically by author; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients in the study	No. patients per category	Variable	HR (95% CI)	*P*-value
Barnhill et al. (2018)	41		Growth pattern		
		30	Desmoplastic	Reference	
		11	Replacement	3.09 (1.02–9.36)	0.05
Abdel-Rahman et al. (2012)	11		Tumor vasculature		
		3	Not strong	N/A	
		8	Strong		0.24
Abdel-Rahman et al. (2012)	11		Prominent tumor necrosis		
		7	Absent	N/A	
		4	Present		>0.99
Abdel-Rahman et al. (2012)	11		Epithelioid cells		
		5	Absent (spindle)	N/A	
		6	Present (epithelioid/mixed)		0.06
Griewank et al. (2014)	30		Epithelioid cells		
		2	Absent (spindle)	N/A	
		23	Present (epithelioid/mixed)		0.11
Griewank et al. (2014)	30		Nuclear morphology		
		15	Uniform	N/A	
		10	Pleomorphic		0.11
Abdel-Rahman et al. (2012)	11		Ki-67 index		
		3	<10%	N/A	
		8	≥10%		0.24
Abdel-Rahman et al. (2012)	11		Inflammatory infiltrate		
		4	<5%	N/A	
		7	≥5%		0.008
Abdel-Rahman et al. (2012)	11		Prominent tumor fibrosis		
		7	Absent	N/A	
		4	Present		>0.99
Griewank et al. (2014)	30		Tumor-infiltrating lymphocytes		
		15	Absent	N/A	
		7	Mild		
		3	Moderate		0.81[a]
Griewank et al. (2014)	30		Lymphatic invasion		
		21	Absent	N/A	
		4	Present		0.98
Griewank et al. (2014)	30		Perineural invasion		
		23	Absent	N/A	
		2	Present		0.90

For abbreviations, see Table 4A.
[a] Globally accross all categories.

remaining primary tumors (Johansson et al., 2016; Moore et al., 2016; Nell et al., 2021); the genetics of primary uveal melanoma were recently reviewed in this journal (Smit et al., 2020). In the largest cohort of metastases from uveal melanoma, mainly to the liver, *GNAQ* and *GNA11* mutations likewise were mutually exclusive and detected in 51 (57%) and 32 (36%) of 89 specimens, respectively (Piperno-Neumann et al., 2020).

BAP1 pathogenic variants were detected in 54% and *SF3B1* pathogenic variants in 23% of 89 metastatic uveal melanomas; *EIF1AX* was not included in the panel (Piperno-Neumann et al., 2020). *GNAQ* and *SF3B1* pathogenic variants in that study were associated with a longer PFS and a smaller change in tumor burden from baseline, and *BAP1* variants with shorter PFS; OS was not analyzed. *SF3B1* and *EIF1AX* pathogenic variants are somewhat underrepresented in metastases, consistent with the observation that primary tumors that carry *SF3B1* and *EIF1AX* metastasize less frequently and later than those with *BAP1* (Harbour et al., 2013; Martin et al., 2013; Shain et al., 2019). Among 58 patients with metastases carrying *SF3B1* mutation, the median OS was 3.9 years (95% CI 2.3–6.2) (Grimes et al., 2021). The OS rate at 12 months was 94% (95% CI 86–99). Twenty-nine percent of patients had only extrahepatic metastases with a median OS of 6.2 years vs. 3.2 years for the remaining patients. A pooled analysis of two large data sets (Shields et al., 2009; Yavuzyigitoglu et al., 2016) showed a higher mutation rate in smaller primary tumors; moreover, the type of mutation correlated with early versus late metastasis: *BAP1* was associated with small peak at 1 year and a large one at 3.5 years, whereas the *SF3B1* peaks occurred between 2 and 3 years and at 7 years (Grimes et al., 2021; Grossniklaus, 2013; Singh et al., 2004; Szalai et al., 2018; Zimmerman et al., 1978). A recent SEER registry-based study of 10,678 patients with uveal melanoma paralleled the former one: the excess absolute risk of dying of uveal melanoma showed two waves, the first one peaking at 3 years and the second one peaking at approximately 15 years (Singh et al., 2021). The first wave was postulated to represent patients with BAP1 loss and the second one those with *SF3B1* pathogenic variants.

5. Staging

Staging of cancer is universally recommended for prognostication. It provides several advantages to the clinician (Greene and Sobin, 2008), the ocular and medical oncologist alike, as well as to their patients. Staging allows patients to be assigned into groups that are prognostically relatively homogenous but differ meaningfully from one another. In clinical practice, this contributes to the decision to treat and to the selection of treatment if any will be recommended. Second, staging enables exchange of comparable data as regards the extent of metastases, both from the anatomic and the patient perspective. Staging facilitates exchange of research data for descriptive purposes and for comparisons between centers and countries, and over time. When the stage-specific OS exceeds the stage-specific historical OS available from the staging model used, it is indirect evidence of treatment benefit. The stage-specific OS of this new treatment might then become the new yardstick to compare with. Stratification of patients by staging metastases is crucial to controlled clinical trials and even more so for informed interpretation of non-randomized prospective trials and retrospective analyses. Finally, the stage distribution provides a measure against which to judge the efficacy of imaging, other diagnostic methods, surveillance protocols, and treatment outcomes.

5.1. Evolution of systems for staging metastatic uveal melanoma

Systematic staging of cancer began in 1968 with the TNM system of the International Union Against Cancer and later the American Joint Committee on Cancer (Greene and Sobin, 2008). TNM staging for uveal melanoma was introduced in the 2nd edition in 1974. It categorized metastases only as being absent (M0) or present (M1).

The first proposal for a staging system for metastatic uveal melanoma in 2003 was the Helsinki University Hospital (HUH) working formulation (Eskelin et al., 2003) that was later validated by the OOG (Kivelä et al., 2016). Additionally, two prognostic nomograms for metastatic uveal melanoma have been developed by the Veneto Oncology Institute and the Mayo Clinic in 2015, and the Institut Curie in 2019 (Mariani et al., 2019; Valpione et al., 2015b).

The three dedicated systems available for staging metastatic uveal melanoma were built based on multivariable modeling, and two of them have been validated externally, but none have yet been widely applied to be developed further.

5.2. Tumor, node, metastasis M staging

The current TNM classification for ciliary body and choroidal melanoma is based on assessing the anatomical extent of the primary tumor

Table 4O
The frequency of cytogenetic alterations in uveal melanoma metastases, tabulated alphabetically by author; studies were included if they included ≥5 patients.

Study	No. samples of metastases	Chromosome 3 status	Chromosome 8 status	*GN/A11* mutation	*GN/AQ* mutation	*BAP1* loss	*SF3B1* mutation	*EIF1AX* mutation
Aalto et al. (2001)	6	Monosomy 5/6	Aneusomy 6/6	N/A	N/A	N/A	N/A	N/A
Abdel-Rahman et al. (2012)	12 from 11 patients	Monosomy 3/11 Disomy or partial alterations 7/11	Loss of heterozygosity 4/12 Allelic imbalance 6/12 Retention of heterozygosity 2/12	8/11	N/A	9/11	N/A	N/A
Griewank et al. (2014)	30	N/A	N/A	6/30	18/30	13/16	1/26	N/A
Hoefsmit et al. (2020)	15	N/A	N/A	10/15	4/15	12/15	1/15	0/15
Luscan et al. (2015)	5	N/A	N/A	3/5	2/5	3/5	N/A	N/A
McCarthy et al. (2016)	12	Monosomy 3/12 Isodisomy 3/12 Disomy 1/12	Amplification 11/12 Partial amplification 1/12	N/A	N/A	N/A	N/A	N/A
Piperno-Neumann et al. (2020)	89	N/A	N/A	32/89	51/89	Amplification 0/48 Loss 2/48 Short variant 46/48	20/89	N/A
Shain et al. (2019)	36	N/A	N/A	N/A	N/A	25/36	4/36	3/36
Singh et al. (2009)	10	Monosomy 5/8 Aneusomy 2/8	N/A	N/A	N/A	N/A	N/A	N/A
Trolet et al. (2009)	63	Partial or complete monosomy 48/66	Gains of 8q 59/88	N/A	N/A	N/A	N/A	N/A

For abbreviations, see Table 4A.

Table 4P
Cytogenetic alterations as a prognostic factor for overall survival in univariable analysis, tabulated alphabetically by author; studies were included if hazard ratio, or equivalent, and *P*-value were reported.

Study	No. patients in the study	No. patients per category	Variable	HR (95% CI)	*P*-value
Abdel-Rahman et al. (2012)	11		Chromosome 3		
		4	Monosomy	N/A	
		7	Disomy or partial alteration		0.003[a]
Valpione et al. (2015)	152		Chromosome 3		
		16	No aberration	Reference	
		75	Loss	0.87 (0.57–1.13)	0.517
Griewank et al. (2014)	30		*GNA11* or *GNAQ*		
		6	Both wildtype	N/A	
		24	Either one mutated		0.34
Griewank et al. (2014)	30		*GNA11* mutation		
		22	Wildtype	N/A	
		18	Mutation		0.16
Griewank et al. (2014)	26		*GNAQ* mutation		
		24	Wildtype	N/A	
		6	Mutation		0.39
Griewank et al. (2014)	16		BAP1 nuclear staining		
		13	Absent	N/A	
		3	Present		0.73
Bidard et al. (2014)	40		Circulating tumor cells, per 7.5 mL		
		32	<1	Reference	
		8	≥1	N/A	0.0009
Bidard et al. (2014)	40		ctDNA, copies per mL		
		8	<5	Reference	
		8	5–46	N/A	
		10	145–11421	N/A	<0.0001[b]
Mariani et al. (2019)	224		Genomic analysis[c]		
		78	High	Reference	
		19	Intermediate/Low	1.06 (0.54–2.08)	0.87

For abbreviations, see Table 4A.
[a] Fischer's exact test.
[b] Globally accross all categories.
[c] No further information on the genomic analysis.

(T), regional lymph node metastases (N), and systemic metastases (M). Beginning with the 7th edition, which was a major overhaul of TNM to make the system in general evidence-based, primary ciliary body and choroidal melanomas are classified in subcategories T1a–T4d according to tumor size (T1–T4) and involvement of the ciliary body and extrascleral tissues (a–d), with a separate subcategory (T4e) for extrascleral extensions larger than 5 mm in diameter (Kivelä et al., 2017; Kujala et al., 2013). T-subcategories associated with similar survival are combined to form prognostic stages I, IIA–B, IIIA–C, and IV, each of which is as homogenous in survival as possible but as different from each other than feasible (Kivelä et al., 2017). The classification of primary tumors was empirically derived and internally validated using a collaborative dataset of 7359 patients, compiled by the OOG (Kujala et al., 2013). It was later externally and independently validated with 3217 additional patients (AJCC Ophthalmic Oncology Task Force, 2015) and is supported by large single-center studies (Shields et al., 2013, 2015). The current 8th edition (Kivelä et al., 2017) is for practical purposes identical to the 7th one. In particular, no changes were made to staging of metastatic uveal melanoma, known as stage IV disease in the TNM system. Of ciliary body and choroidal melanomas, 21–32% are classified as stage I, 32–34% stage IIA, 22–23% stage IIB, 9–17% stage IIIA, 3–7% stage IIIB, 1% stage IIIC, and 2% as stage IV (AJCC Ophthalmic Oncology Task Force, 2015; Kujala et al., 2013).

Although TNM stage IV for uveal melanoma includes patients who have involvement of regional lymph nodes or discrete tumor deposits in the orbit that are not contiguous to the eye (N1) and patients with distant systemic metastases (M1), the former group of patients is very small (0.2%) (Dithmar et al., 2000; Garg et al., 2021; Kivelä et al., 2017). Regional lymph node involvement from uveal melanoma is extremely rare because of lack of a traditional lymphatic drainage system from the eye and the orbit (Clarijs et al., 2001).

Patients with metastases (M1, or rM1 when metastases are detected after treatment of the primary uveal melanoma) are categorized into M1a, M1b and M1c by LDLM (M1a denotes LDLM ≤3 cm, M1b 3.1–8.0 cm, and M1c ≥ 8 cm). These subcategories were devised to provide a simple staging system and are based on the fact that the LDLM was the strongest prognostic factor of those three that formed the previously developed HUH working formulation (Kivelä et al., 2017). They were constructed empirically using the at the time unpublished and still accumulating validation dataset being compiled by the OOG, so that the three subcategories would be strongly associated with OS. When applied to the final OOG data set of 249 patients who died of metastases, 47%, 45% and 8% of patients fell into rM1a, rM1b, and rM1c, respectively, and the corresponding median survival times were 17.5, 9.6, and 5.0 months (Kivelä et al., 2017).

5.3. *Dedicated staging systems*

5.3.1. *The Helsinki University Hospital working formulation*

The working formulation was the first dedicated staging system developed to predict survival after metastatic uveal melanoma to inform design, analysis, and reporting of trials and retrospective reports (Eskelin et al., 2003; Kivelä et al., 2016). It is based on a single-center multivariable model built with data from 91 patients from Helsinki, Finland, who all died of metastases so that their eventual OS was known (Eskelin et al., 2003); upon our review of the patient charts of that study, for 51 (57%) of the 66 patients who received chemoimmunotherapy or conventional chemotherapy this was their only active treatment, 15 (17%) also received 2nd or higher line of systemic treatment, and 24 (27%) patients received only BSC that included palliative radiotherapy in two of them. Additionally, 9 of the 90 patients underwent one or more surgical resections of metastases primarily for diagnostic purposes, and 10 actively treated patients later received palliative irradiation. Cox proportional hazards regression identified Karnofsky index (3 categories), serum or plasma AP level (continuous), and LDLM (continuous) as independent predictors of survival (Eskelin et al., 2003). Additionally,

the model adjusted for time on chemotherapy as a confounding factor, based on the assumption that a long time on chemotherapy might indicate not only effect from treatment but also less aggressive metastases that would progress more slowly and allow the patient to receive treatment longer, even if the treatment was largely ineffective. Because the eventual time on chemotherapy is not known at the time of diagnosis, the working formulation is calculated by using for all predictions a constant of 5 months, which was the median time in the building dataset (Eskelin et al., 2003; Kivelä et al., 2016).

For a new patient, the multivariable model is used to calculate the median predicted OS of patients who share the three characteristics with the newly diagnosed patient with metastatic uveal melanoma. The predicted OS is used to so assign them to stage IVa, IVb, or IVc that correspond to a predicted median OS of ≥12 months, <12 to 6 months, and <6 months after diagnosis of metastases, respectively.

The working formulation was validated in 2016 by seven ocular and medical oncology services of the European OOG who provided data of 249 consecutive patients who died of metastatic uveal melanoma based on autopsy, biopsy, or presence of progressive hepatic metastases in the absence of non-ocular primary cancer (Kivelä et al., 2016). Use of the ECOG performance status instead of Karnofsky index was promoted, and serum or plasma AP level was scaled relative to its UNL. The 12- and 24-month survival rates were 53% and 22%, respectively. Of all 249 patients in this validation study, 44%, 44%, and 12% were staged to IVa, IVb, and IVc, respectively. The corresponding median OS was 19, 11, and 4.6 months, respectively ($P < 0.001$) (Kivelä et al., 2019). The observed median OS by stage of 201 patients who did not undergo surgery in the same study was 17, 10, and 4.6 months ($P < 0.001$), respectively. Recently, the working formulation was shown to differentiate by OS also patients managed with BSC (Rantala et al., 2021a). Of 105 patients, 24% represented stage IVa, 19% IVb, and 55% IVc. Their median OS from the diagnosis of metastasis was 14, 8.6, and 1.1 months, respectively ($P < 0.001$) (Fig. 12). The weighted kappa for agreement between observed and predicted OS category from diagnosis of metastases and treatment decision was 0.364 (75% agreement) and 0.549 in the OOG validation dataset and in a nationwide, real-world analysis of 216 actively treated patients in Finland, respectively (Kivelä et al., 2016; Rantala et al., 2021b). In stage IVa, 74% of patients survived >12 months; in stage IVb, 76% survived >6 months and 44% > 12 months; and in stage IVc, 63% and 90% of patients died within <6 and < 12 months, respectively.

The median OS of the 47 patients who had been managed with surgical resection was 28 months for stage IVa and 26 months for stage IVb; only one patient had received surgical treatment for stage IVc and survived for 17 months. Thus, the working formulation did not similarly differentiate patients by OS if metastases were resected ($P = 0.69$). This important observation is likely explained by the fact that resection usually removes the largest metastases and, in effect, will migrate the working formulation stage of the patient to a lower category, typically IVa. It is useful to note that the working formulation will still predict what the median survival of a corresponding group of patients would have been had they been managed with systemic therapy, providing a comparison base for the OS outcome.

The working formulation has been used to compare active treatment in two clinical trials from Finland (Pyrhönen et al., 2002; Vihinen et al., 2010), one nationwide study (Rantala et al., 2021b), and one phase II multicenter trial by the European Organisation for Research and Treatment of Cancer (EORTC) (Kivelä et al., 2003). An online calculator is now available to facilitate the use of the HUH working formulation in clinical and research practice (Fig. 13) (http://www.prognomics.org/huhwf.aspx). In some instances, not all data are available to calculate the stage, but it can often be assigned also on the basis of incomplete information by using the schematic lookup table that accompanied the original description (Eskelin et al., 2003) and that recently was updated to show AP relative to its UNL in the supplemental Table S1 in (Rantala et al., 2021b).

5.3.2. *The Veneto-Mayo nomogram*

The first prognostic nomogram for predicting the prognosis of a patient with uveal melanoma was built with data of 152 patients from

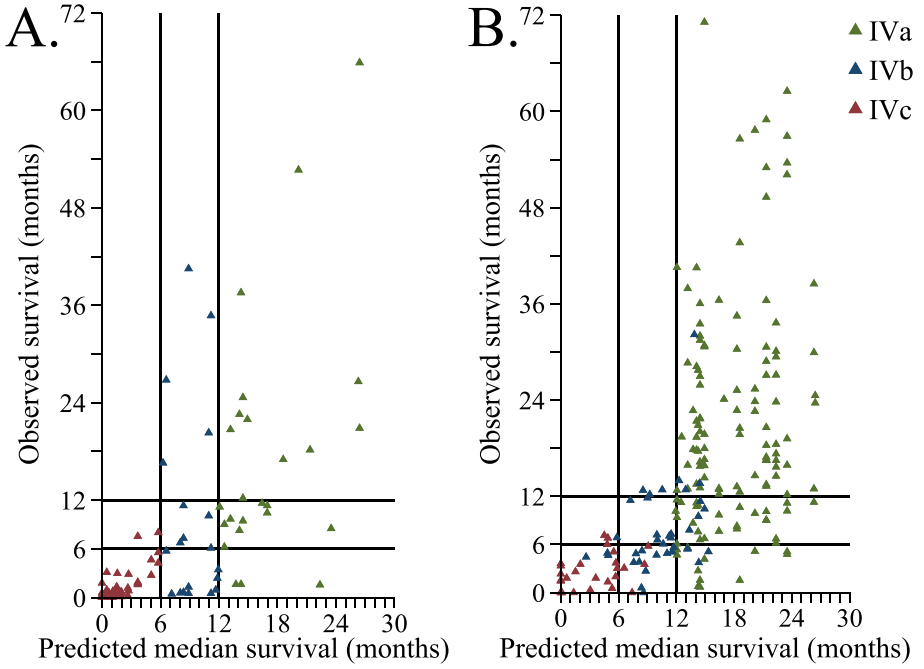


Fig. 12. Scatterplot of predicted median overall survival against observed individual overall survival for patients staged by the Helsinki University Hospital working formulation. Patients who received only best supportive care (**A**) and active treatment (**B**) are plotted, divided between formulation stages IVa (predicted median survival ≥12 months), IVb (<12–6 months), and IVc (<6 months). Compare (**A**) with Fig. 21. Data correspond to results published in (Rantala et al., 2021a, 2021b).

the prospective melanoma database at the Melanoma Oncology Unit of the Veneto Oncology Institute, Padova, Italy (Valpione et al., 2015b). Of the 152 patients, 131 were actively treated and 108 had died by the time of analysis whereas 44 were still alive with metastases or lost to follow-up. The nomogram was built on the basis of a multivariable analysis and includes ECOG performance status (3 categories), serum or plasma level of LDH relative to its UNL (continuous), percentage of liver involvement (4 categories), and MFI (continuous). Liver substitution was graded retrospectively from three-dimensional reconstruction of a helical CT scan or, in a minority of patients, from an MRI scan. The 12- and 24-month survival proportion in the building dataset was 63% and 35%, respectively. The nomogram is used to predict 6-, 12-, and 24-month survival.

At the time of its description, the model had been externally validated using a dataset from Mayo Clinic, Rochester, Minnesota, that included 102 actively treated patients of whom 32 had died and 70 were still alive or lost to follow-up (Valpione et al., 2015b). The 12- and 24-month survival proportions in the validation dataset, 62% and 36%, respectively, were almost identical to those in the building dataset. Harrell's C-index was 0.75 in the building dataset as compared to 0.80 in the validation dataset, indicating that the model predicted the OS well for 75% and 80% of the patients. A comparison of predicted to observed survival times has not been published.

5.3.3. The Institut Curie nomogram

The second prognostic nomogram, which predicts the prognosis after diagnosis of hepatic metastases, was built at the Institut Curie, Paris, France, with data from 224 of 725 patients with metastatic uveal melanoma, 60 of whom were managed with liver resection (Mariani et al., 2019). Inclusion criteria were that both a liver MRI at the time of diagnosis of metastases was available and the entire treatment was performed in Institut Curie, and that the MRI had been stored in a format that allowed retrospective analysis. The imaging protocol included axial 2D fat suppressed fast-spin echo T2-weighted and dual gradient-recalled echo T1-weighted scans and 3D axial dynamic contrast-enhanced gradient-recalled echo T1-weighted scans before and after injection of gadolinium. In 2002–2009, the slice thickness for 2D and 3D sequences was 8 mm and 5 mm, respectively, as compared to 6 mm and 3.5 mm, respectively, in 2009–2013. The four variables selected for the nomogram by multivariable regression are serum or plasma LDH relative to its UNL (3 categories), the number of metastases (3 categories), the area of the largest metastasis (4 categories), and MFI (4 categories). The 6-, 12-, and 24-month OS proportions in the building dataset were 88%, 68%, and 26%, respectively. The nomogram predicts 6-, 12-, and 24-month survival.

The nomogram was internally validated using bootstrapping. Harrell's C-index was 0.71, indicating that the nomogram predicted OS well for 71% of patients. At 6 months, the nomogram tended to overestimate the OS. At 12 months, it was well calibrated when the probability of OS was 0.5 or better, otherwise it increasingly underestimated survival. The nomogram was best calibrated at 24 months (Mariani et al., 2019). Comparison of predicted to observed survival times has not been published.

5.4. Similarities and differences between staging systems

The HUH working formulation (Eskelin et al., 2003; Kivelä et al., 2016), and the Veneto-Mayo (Valpione et al., 2015b) and the Institut Curie (Mariani et al., 2019) nomograms all share two basic components – the size of metastases (Kivelä et al., 2016; Mariani et al., 2019; Valpione et al., 2015b) and a LFT (Kivelä et al., 2016; Mariani et al., 2019; Valpione et al., 2015b) – but these components are assessed differently (Table 6). The working formulation and the Veneto-Mayo nomogram additionally share performance status (Kivelä et al., 2016; Valpione et al., 2015b). MFI is part of both the Veneto-Mayo and the Institut Curie nomograms.

The HUH working formulation and the Veneto-Mayo nomogram are modeled and applicable regardless of metastatic site, whereas the Institut Curie nomogram applies only to patients with hepatic metastases, although it allows concomitant extrahepatic dissemination. The latter also requires that a liver MRI at the time of diagnosis of metastases is available. The Veneto-Mayo nomogram requires either a CT or an MRI scan, whereas the HUH working formulation makes no assumptions regarding the method with which LDLM is measured.

In building the HUH working formulation, the percentage of liver involvement was not evaluated, but LDLM was found to be at least as good as metastatic burden evaluated as the sum of the product of the

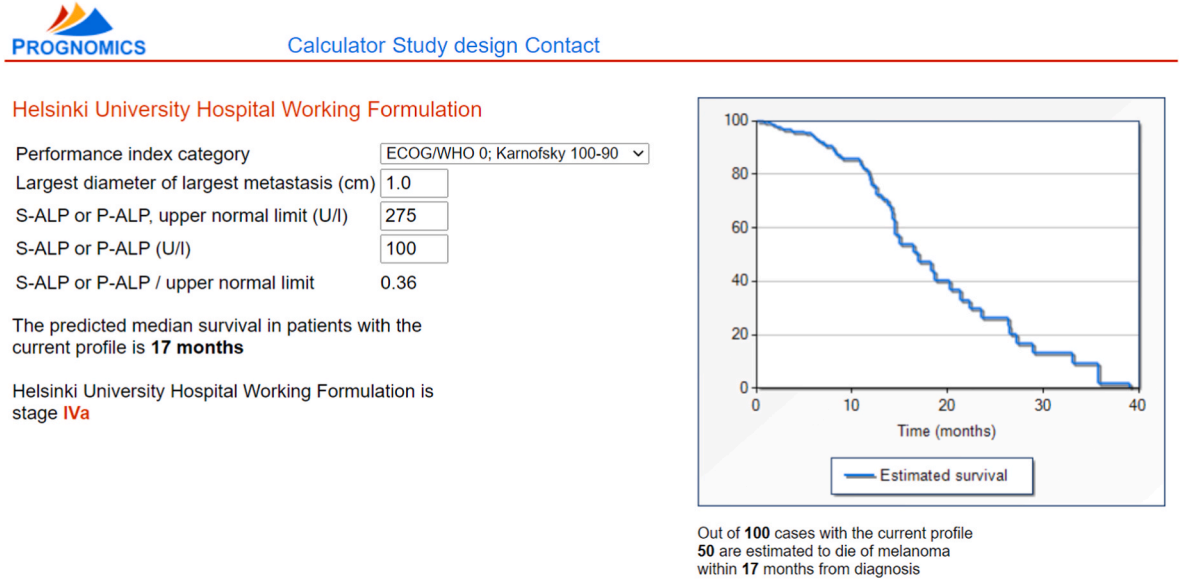


Fig. 13. A screenshot of the Helsinki University Hospital working formulation calculator. The calculator assigns stage IVa, IVb, or IVc, based on predicted median overall survivals of ≥12 months, <12–6 months, or <6 months, respectively, after entering Eastern Cooperative Oncology Group performance status (ECOG) or Karnofsky index, the largest diameter of the largest metastasis, and serum or plasma alkaline phosphatase level (ALP) with its upper normal limit to the calculator. The survival curve corresponding to the prediction is also plotted. Available at http://www.prognomics.org/huhwf.aspx and based on results in (Eskelin et al., 2003).

Table 5
Comparison of Eastern Cooperative Oncology Group (ECOG) performance score and Karnofsky index.

ECOG score	Karnofsky index	Status
0	90–100	Fully active, able to carry on all predisease activities without restriction.
1	70–80	Restricted in physically strenuous activity but ambulatory and able to carry on light work.
2	50–60	Ambulatory and capable of all self-care but unable to carry out any work activities.
3	30–40	Capable of only limited self-care, confined to bed or chair ≥50% of waking hours
4	10–20	Completely disabled. Cannot carry on self-care.

largest perpendicular dimensions of measurable metastases, multiplied by their mean, to obtain total volume (Eskelin et al., 2003). Liver involvement was measured as percentage of the liver in the Veneto-Mayo nomogram, based on the hypothesis that it is the 'best indicator of the effective volume of hepatic disease' (Valpione et al., 2015b). LDLM was not reported. The Institut Curie nomogram analyzed the surface area of the largest metastasis, assuming that the total number of hepatic metastases is associated with the surface of the largest metastasis (Mariani et al., 2019). LDLM was tested but arbitrarily dichotomized at 18 mm, and this categorization turned out not to be a good predictor. The percentage of hepatic substitution was not reported because it would 'be a time-consuming task' to analyze.

The HUH working formulation adopted AP levels because they had a stronger association with survival than LDH in the building dataset (Eskelin et al., 2003). Of note, the LDH level was known for less than 50% of patients, which reduced the statistical power of this variable (Rantala et al., 2021b). In the Veneto-Mayo and the Institut Curie nomograms, LDH was preferred (Mariani et al., 2019; Valpione et al., 2015b). AP was considered for the Veneto nomogram, but the results were not reported. For the Curie nomogram, AP was not analyzed (Mariani et al., 2019). LDH is known to be elevated in metastatic cutaneous melanoma even without hepatic metastases and it is included in the TNM staging of cutaneous melanoma. It is likely to reflect metastatic burden both directly and indirectly in patients with uveal melanoma (Kivelä et al., 2016). It is possible that the HUH working formulation would benefit from considering also LDH, given that in a national dataset it was associated with shorter OS in stage IVa when its level was >2.0 x UNL (Rantala et al., 2021b).

In the dataset that was used to develop the Institute Curie nomogram, only 10 of the 224 patients had an ECOG performance status worse than 1 (Mariani et al., 2019), likely explaining why the performance status did not qualify for this nomogram. MFI was analyzed when the HUH working formulation was built (Eskelin et al., 2003). It proved not to be an independent prognostic factor in that model, which was based on a smaller dataset than the two nomograms. However, MFI did not improve the model in a large nationwide dataset from Finland either (Rantala et al., 2021b).

All three staging systems are suggested to provide a good prediction of OS in 75%–80% of patients (Kivelä et al., 2016; Mariani et al., 2019; Valpione et al., 2015b). A head-to-head comparison has not been made yet. In principle, if the predicted probability of surviving 12 months is 0.5 or better (i.e., >50% likeihood to survive at least 12 months) by either nomogram, the survival could be viewed as being roughly equivalent with HUH working formulation stage IVa (i.e., predicted OS > 12 months), and if the predicted probability of surviving 6 months is worse than 0.5, the survival could be considered similar to working formulation stage IVc. Patients whose prediction falls between these categories would then correspond to working formulation stage IVb. The predictions of the two nomograms could in this way be compared directly with the working formulation.

In summary, all three dedicated staging systems can be considered valid. Before they are compared against each other, none of them can be said to be superior to the others. From the practical point of view, the HUH working formulation currently is the one most extensively documented, it does not discriminate between imaging modalities and metastatic sites, and staging can be obtained from a website. According to a Scopus search in December 2021, the Veneto-Mayo and the Institut Curie nomograms had not yet been applied in published articles after their description. The HUH working formulation had been used in six publications that reported different populations of patients from different sources, including an EORTC multicenter trial, an OOG multicenter study, papers from two different Finnish universities, and one North American center (Freton et al., 2012; Kivelä et al., 2003; Pyrhönen et al., 2002; Rantala et al., 2020b, 2021a, 2021b; Vihinen et al., 2010).

6. Treatment

Treatment for metastatic uveal melanoma has been evaluated mainly in many small, typically non-controlled, mainly phase II trials. Because of the small number of patients, few randomized trials have been initiated. Recently, two large meta-analyses have attempted to aggregate studies in meaningful ways.

The first one evaluated OS outcomes by extracting patient-level OS data from peer-reviewed articles either directly or by digitizing Kaplan–Meier curves and by pooling data for comparison (Rantala et al., 2019). It included data from 78 articles and 2494 patients published from 1980 to 2017. It presumed that collating data from many publications would effectively lead to averaging of unreported patient-level prognostic factors. The median OS was 13 months (95% Cl 12–14) and 1 year OS rate was 52% (95% CI 50–54). The OS with chemoimmunotherapy, hepatic intra-arterial chemotherapy, transarterial chemoembolization, protein kinase inhibitors, and selective internal radation therapy (SIRT) were comparable with that of conventional chemotherapy (median 10–14 vs. 11 months; $P = 0.13–0.80$). Surgery, isolated hepatic perfusion, and immunoembolization were associated with longer OS: median 17 months (95% CI 16–20), 16 months (95% CI 14–20), and 20 months (95% CI 15–22), respectively ($P < 0.001$, $P = 0.004$, and $P = 0.008$, respectively). However, patients selected for surgical treatment typically form a specific subset, immunoembolization data might not be generalizable because they were solely derived from a single-centre phase I and a subsequent phase II trial with a total of 59 patients (Sato et al., 2008; Valsecchi et al., 2015), and the OS benefit of isolated hepatic perfusion depended entirely on one study with an exceptionally long OS (Ben-Shabat et al., 2016). Checkpoint inhibitors were associated with a shorter OS, median 7.1 months (95% CI 6.4–8.5), than conventional chemotherapy ($P < 0.001$). However, only approximately 8% of treatments with checkpoint inhibitors were first-line treatments.

The second one evaluated PFS and OS outcomes and collected patient-level data from original investigators of 29 prospective trials with 914 patients, initially published from 2000 to 2016 (Khoja et al., 2019). The median OS was 10.2 months (95% CI 9.5–11.0) and 1 year OS rate was 43% (95% CI 40–47). The main prognostic factors as regards OS, by univariable and multivariable analysis, were elevated LDH and AP. Patients treated with liver directed treatments had significantly longer PFS and OS (Fiorentini et al., 2009; Huppert et al., 2010; Leyvraz et al., 2014; Patel et al., 2005; Sato et al., 2008; Valsecchi et al., 2015; van Iersel et al., 2008; Vogl et al., 2007). The median OS was 8.9 months (95% CI 7.0–11.6) for immunotherapy, 9.1 months (95% CI 7.0–10.4) for mitogen-activated protein kinase kinase inhibitor, 11.0 months (95% CI 8.2–15.2) for anti-angiogenic therapy, 9.2 months (95% CI 8.4–10.4) for chemotherapy, and 14.6 months (95% CI 12.6–17.5) for liver directed therapy. However, the metastases were not staged, and more favorable stage mix might have contributed to the longer OS with liver directed therapy.

Table 6
Comparison of three dedicated staging systems designed to be used when metastatic uveal melanoma is diagnosed and considered for treatment.

	Helsinki University Hospital (HUH) Working Formulation		Veneto-Mayo Nomogram		Institut Curie Nomogram	
	Building dataset	Validation dataset	Building dataset	Validation dataset	Building dataset	Validation dataset
Study	Eskelin et al. (2003)	Kivelä et al. (2016)	Valpione et al. (2015b)		Mariani et al. (2019)	
Institute	Helsinki University Hospital, Finland	Externally validated by the Ophthalmic Oncology Group	Melanoma Oncology Unit of the Veneto Oncology Institute, Padova, Italy	Externally validated by Mayo Clinic, Rochester, Minnesota	Institut Curie, Paris, France	Internally validated by Institut Curie, Paris, France
Study design	Single center	Multicenter	Single center	Single center	Single center	Single center
No. patients	91	249	152	102	224	Bootstrapping[a]
No. patients dead/ alive or lost to follow-up	91/0	249/0	108/44	32/70	N/A	N/A
Treatment	75 actively treated (13 chemotherapy, 53 chemoimmunotherapy, 9 surgical resection); 11 BSC; 5 missing data	238 actively treated (168 chemotherapy; 4 chemoembolization; 6 interferon usually with tamoxifen; 9 tumor vaccine; 47 surgical resection w/o systemic therapy; 4 other therapies); 11 BSC	131 actively treated (56 with systemic therapy, 17 with locoregional therapy, and 68 with locoregional and systemic therapy); 21 not treated	102 actively treated (74 systemic therapy; 17 locoregional therapy; 5 locoregional and systemic therapy); 0 not treated; 9 missing data	183 actively treated (60 surgery, 123 systemic); 14 BSC; 27 missing data	N/A
Method	Cox proportional hazards regression		Cox proportional hazards regression, bootstrapping		Cox proportional hazards regression, bootstrapping	
Variables	Karnofsky index (or ECOG performance status) LDLM Serum or plasma AP level relative to UNL (additionally, the model was adjusted for time on chemotherapy as a confounding factor; 5 months is used in the predictions)		ECOG performance status Percentage of liver involvement Serum or plasma level of LDH relative to UNL Metastasis-free interval		Number of metastases Area of the largest metastasis Serum or plasma LDH relative to UNL Metastasis-free interval	
Applicability regarding the metastatic sites	Hepatic and extrahepatic metastases; measured as LDLM (cm)		Hepatic and extrahepatic metastases; measured as percentage of the liver involvement		Liver involvement required; measured as the area of the largest metastasis[b,c]	
Measurements of liver involvement considered in the building dataset; argument for final selection	The percentage of liver involvement was not evaluated; LDLM was found to be at least as good as metastatic burden evaluated as the sum of the product of the largest perpendicular dimensions of measurable metastases, multiplied by their mean, to obtain total volume.		Liver substitution was analyzed retrospectively from 3D reconstruction of helical CT or, in a minority of patients, from MRI of the liver, and registered as percentage of the liver. 'best indicator of the effective volume of hepatic disease', LDLM was measured but no reported.		It was assumed that the total number of hepatic metastases together with the surface of the largest metastasis would be 'quite comparable' to calculation of the percentage of hepatic invasion, leaving LDLM and the percentage of hepatic substitution unreported because the latter would 'be a time-consuming task'.	
OS categories	IVa median survival ≥12 months, IVb <12 to 6 months, IVc <6 months.		Nomogram predicts 6-, 12-, and 24-month survival, no stage categories defined.		Nomogram predicts the 6-, 12-, and 24-month survival, no stage categories defined.	
Median OS, months (range)	8.4 (0.25–73)	19, 11, and 4.6 for stage IVa, IVb, and IVc, respectively ($P < 0.001$)	17.2 (1.2–86.4)	19.7 (12.4–23.4)	16.1 (0–71)	N/A
Survival proportion	12-, 24-, and ≥36-month survival proportions 40%, 13%, and 4%, respectively.	12- and 24-month survival rates 53% and 22%, respectively.	12- and 24-month survival proportions 63% and 35%, respectively.	12- and 24-month survival proportions 62% and 36%, respectively.	6-, 12-, and 24-month survival proportions 88%, 68%, and 26%, respectively.	N/A
Publications where it has later been applied	Pyrhönen et al. (2002); Vihinen et al. (2010); Rantala et al. (2021a, 2021b); Kivelä et al. (2003)		None so far		None so far	

BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LDLM = the largest diameter of the largest metastasis; MRI = magnetic resonance imaging; N/A = not available; OS = overall survival; UNL = upper normal limit.

[a] The total number of patients is equivocal.

[b] A liver MRI at the time of diagnosis of metastases stored in a format that allowed analysis was required.

[c] Protocol included axial 2D fat suppressed fast-spin echo T2-weighted and dual gradient-recalled echo T1-weighted images and 3D axial dynamic contrast-enhanced gradient-recalled echo T1-weighted images before and after injection of gadolinium; the slice thickness for 2D and 3D sequences was 8 mm and 5 mm, respectively, in 2002–2009, and 6 mm and 3.5 mm in 2009–2013, respectively.

6.1. *Adjuvant therapy*

Because of the assumption that dormant micrometastases may reside in the liver (Borthwick et al., 2011) or, perhaps, in the bone marrow (Eide et al., 2015, 2019) years before the clinical diagnosis of metastasis can be made, adjuvant therapy at the time of treatment of the primary uveal melanoma would be a logical strategy (Nichols et al., 2017). Interferon (Lane et al., 2009), combined dacarbazine and interferon (Binkley et al., 2020), intra-arterial fotemustine (Voelter et al., 2008), sunitinib (Valsecchi et al., 2018), ipilimumab (Fountain et al., 2019), dendritic cell vaccine (Bol et al., 2016), and methanol-extracted residue of bacille Calmette-Guerin (McLean et al., 1990) have been tested for this purpose (Table S1A). All these trials either failed to show longer OS (Binkley et al., 2020; Lane et al., 2009; McLean et al., 1990; Voelter et al., 2008) or they were very small with ≤25 patients and thus had low power (Bol et al., 2016; Fountain et al., 2019). A larger multicenter

randomized phase III trial with adjuvant fotemustine versus surveillance only showed no difference in OS between these groups, was stopped as futile after 244 patients had been enrolled, and was published as a congress paper without patient-level OS data (Piperno-Neumann et al., 2017). A single-arm phase 2 study of adjuvant nivolumab combined with ipilimumab in 50 high-risk uveal melanoma patients who had a 3-year risk of relapse of >50% is nearing completion (NCT03528408) (Rapisuwon et al., 2019). The OS will be compared to that of matched contemporaneous controls treated in other centers.

High-risk patients for adjuvant trials may be selected by the same criteria that are used to assign closer surveillance (see *3.4.2.*, above). They also might be selected by using available online tools such as the Liverpool Uveal Melanoma Prognosticator Online (LUMPO) (Eleuteri et al., 2012) or PRIMeUM (Vaquero-Garcia et al., 2017) which use a combination of clinical factors and cytogenetic features to predict melanoma-related death. Another approach are gene panels and prognostic assays such as the DecisionDx-UM gene expression profile test (Harbour and Chen, 2013; Onken et al., 2012; Plasseraud et al., 2016; Schefler et al., 2020). In the adjuvant setting it would be important to have a treatment that also has a high response rate, and adjuvant treatment is still an option for the future with regard to uveal melanoma.

6.2. Local therapy

6.2.1. Surgical resection

When metastases are restricted to the liver or another single organ and limited enough so that resecting them is technically possible, attempted radical surgical resection (R0, microscopically complete) is considered to be the preferred treatment option (Frenkel et al., 2009; Gomez et al., 2014; Kodjikian et al., 2005b; Mariani et al., 2009; Nathan et al., 2015; Salmon et al., 1998; Weis et al., 2016). Regrettably, the percentage of patients eligible for liver resection is limited, approximately 25%, because of diffuse or widely distributed hepatic metastases or unfavorable performance status (Aoyama et al., 2000; Gomez et al., 2014; Mariani et al., 2009). The eventual resection quite often falls short of being microscopically complete because more metastases are seen during surgery than preoperatively (Salmon et al., 1998).

On the other hand, in our experience a small subset of patients that presents with focal sequential oligometastatic disease can survive for years with repeated local resections. In addition, a MFI >2 years was an independent favorable predictor in a large study of 255 surgically treated patients (Mariani et al., 2009), and in a small series 4 of 8 patients whose MFI was >5 years were recurrence free or developed a systemic recurrence after 4 years as opposed to 4 patients whose MFI was shorter and who experienced a systemic recurrence within 2 years (Aoyama et al., 2000) (*see* 4.2.7. above). The longer MFI may be a surrogate for *SF3B1* or *EIF1AX* pathogenic variants (Grimes et al., 2021; Piperno-Neumann et al., 2020; Shain et al., 2019; Yavuzyigitoglu et al., 2016) (*see* 4.2.11., above).

Twelve studies, 11 of them retrospective case series, report on surgical resection of hepatic or extrahepatic (lung, stomach, bone, adrenal, and lymph node) metastases for a total of 528 patients, 5 to 157 per study (Table S1B) (Aoyama et al., 2000; Frenkel et al., 2009; Gomez et al., 2014; Hsueh et al., 2004; Kodjikian et al., 2005b; Mariani et al., 2009, 2016; Nicholas et al., 2018; Rantala et al., 2021b; Rivoire et al., 2005; Salmon et al., 1998; Servois et al., 2019; Yang et al., 2013). Although a complete resection is naturally preferred, in practice only 25–50% of the patients underwent a microscopically complete (R0) resection (Frenkel et al., 2009; Kodjikian et al., 2005b; Mariani et al., 2009; Rantala et al., 2021b; Rivoire et al., 2005; Salmon et al., 1998). Of patients with liver metastases, 6–44% underwent metastatic debulking (R2 resection) instead (Frenkel et al., 2009; Gomez et al., 2014; Hsueh et al., 2004; Kodjikian et al., 2005b; Mariani et al., 2009; Rantala et al., 2021b) and the remaining attempted radical resections were found to be incomplete by histopathologic examination (R1 resection).

The median OS ranged from 11 to 90 months and was longer when the resection was microscopically complete (R0). According to a meta-analysis of patient level-data from 500 of these patients (Rantala et al., 2019), their median OS was 17 months. A nationwide, real-world study that staged 216 patients according to the HUH Working Formulation (*see* 5.3.1., above) included 19 patients who had metastases resected, and 17 of them represented the most favorable stage IVa (Rantala et al., 2021b). Their median OS, 27 months for all patients and 34 months for those with hepatic metastases, was longer than with BSC ($P = 0.010$), unlike with any other active treatment (Fig. 14A). The collaborative OOG study that validated the working formulation also included patients who underwent surgery of whom 27 (57%) patients had stage IVa metastases and 19 (40%) patients represented stage IVb (Kivelä et al., 2016). The median OS for both stages was similar, 26.7 months and 26.0 months, respectively, and far exceeded the median OS of 10.0 months for patients who underwent any other active treatment for stage IVb disease. A larger subset of patients who have undergone resection of metastases rather than other treatments are also long-term survivors (over 5 years) (Frenkel et al., 2009; Rantala et al., 2021b).

6.2.2. Regional chemotherapy

6.2.2.1. Hepatic intra-arterial chemotherapy. The vasculature of the liver provides a unique opportunity for chemotherapy: hepatic metastases receive their blood supply primarily via the hepatic artery whereas the liver parenchyma is supplied by the portal vein, allowing intra-arterial delivery of chemotherapeutic or other agents quite selectively to hepatic metastases.

Eleven studies evaluate hepatic intra-arterial chemotherapy in 370 patients, ranging from 7 to 101 per study (Table S1C) (Boone et al., 2018; Cantore et al., 1994; Egerer et al., 2001; Farolfi et al., 2011; Heusner et al., 2011; Leyvraz et al., 1997, 2014; Melichar et al., 2009; Peters et al., 2006; Salmon et al., 1998; Siegel et al., 2007). The chemotherapeutic agents that have been administered are predominantly fotemustine (a nitrosourea that concentrates in the liver) in 7 studies, although melphalan (an alkylating agent), carboplatin, cisplatin (both of which cross-link DNA in several ways leading to apoptosis), vinblastine (a vinca alkaloid that inhibits formation of the mitotic spindle), and dacarbazine (an imidazole derivative which is bioactivated to an alkylating agent in the liver) in various combinations have also been infused. Five of the studies were prospective, one being a randomized controlled EORTC trial with intra-arterial fotemustine in which the control arm was systemic intravenous delivery. The median OS ranged from 2.9 to 22 months. The meta-analysis combined data from 335 patients, and estimated a median OS of 13.9 months, which was comparable with that of 272 patients with conventional chemotherapy (CHT) ($P = 0.17$) (Fig. 15A) (Rantala et al., 2019). In line with the meta-analysis, the EORTC randomized trial that enrolled 171 patients (86 in the hepatic intra-arterial chemotherapy arm, and 85 in the intravenous arm) found no difference in OS despite a significant benefit in the objective response rate and PFS in favor of hepatic intra-arterial chemotherapy (Leyvraz et al., 2014).

6.2.2.2. Transarterial chemoembolization. Transarterial chemoembolization augments intra-arterial chemotherapy by completely or partially cutting off the blood supply from the hepatic artery to the tumor to make the tumor more susceptible to the chemotherapy by starving it of oxygen and nutrients. It additionally helps the chemotherapeutic agent to remain longer in the metastases. The most common devise used to accomplish the block is gelatin sponge, but polyvinyl alcohol particles, or starch microspheres can also be used (Table S1D). In a modification, drug-eluting beads are used to block the circulation.

Sixteen studies report a total of 522 patients, 10 to 125 per study, none of whom were staged (Agarwala et al., 2004; Carling et al., 2015; Dayani et al., 2009; Edelhauser et al., 2012; Fiorentini et al., 2009; Gonsalves et al., 2015; Gupta et al., 2010; Huppert et al., 2010; Itchins

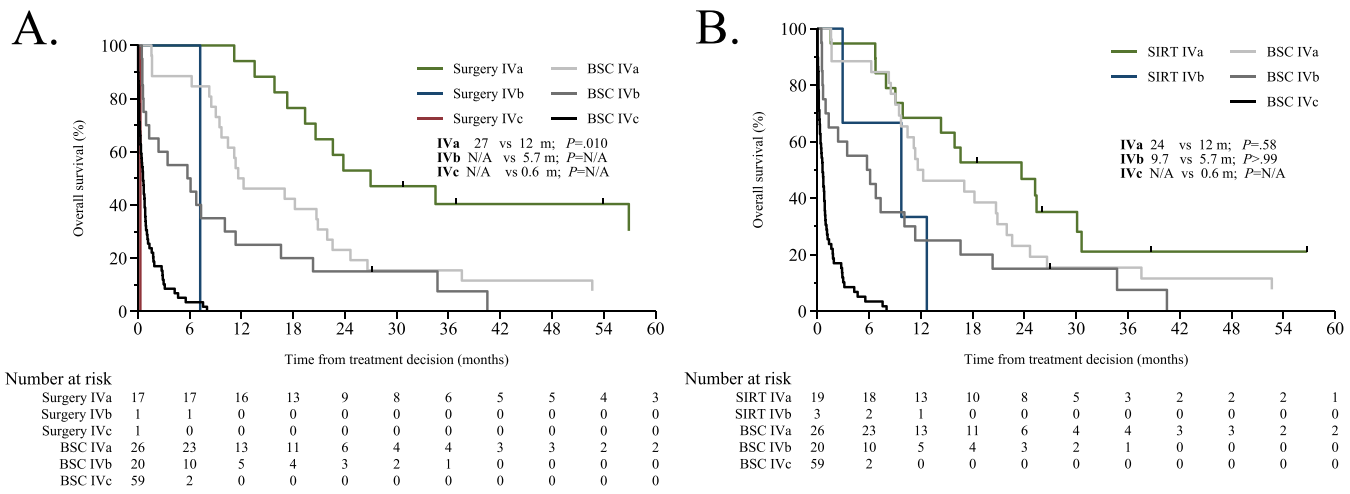


Fig. 14. Two local treatments for metastatic uveal melanoma compared retrospectively with best supportive care using staging in a nationwide dataset. Kaplan-Meier graph of overall survival (OS) from treatment decision to manage the patient first-line with surgery (**A**) and selective internal radiation therapy (SIRT) (**B**), plotted against best supportive care (BSC) and divided by Helsinki University Hospital working formulation stage (*see* 5.3.1.). Median OS and *P* value are calculated by log-rank test, with Bonferroni correction. Note survival difference in stage IVa, only in (**A**). Reproduced from (Rantala et al., 2021b), doi:10.1097/CMR.0000000000000728, CC BY license (http://creativecommons.org/licenses/by/4.0/), adapted layout.

et al., 2017; Mavligit et al., 1988; Patel et al., 2005; Schuster et al., 2010; Shibayama et al., 2017; Valpione et al., 2015a; Valsecchi et al., 2015; Vogl et al., 2007). Six studies were prospective with a maximum of 30 patients, and two of them were randomized. The most frequently used chemotherapeutic agents were cisplatin and fotemustine. The median OS ranged from 5.1 to 28.8 months, and was 10 months according to the meta-analysis (Fig. 15B) (Rantala et al., 2019).

6.2.2.3. Isolated hepatic perfusion. Isolated hepatic perfusion is a more complex type of intra-arterial chemotherapy. The liver is temporarily isolated from the systemic blood circulation and perfused with high doses of a chemotherapeutic agent. The liver is by-passed by placing a catheter in the hepatic artery and another in the hepatic vein. Although isolated hepatic perfusion has been available for six decades, its clinical application has been limited because of its relatively high morbidity and mortality (Alexander et al., 2000; Ausman, 1961). Most reports on metastatic uveal melanoma come from one Swedish center in which the earlier 1-month mortality of 7% has over time decreased to 2% through refined technique and patient selection (Ben-Shabat et al., 2016, 2017). Percutaneous isolated hepatic perfusion is a minimally invasive repeatable alternative to isolated hepatic perfusion that enables vascular isolation and perfusion of the liver using endovascular techniques (Burgmans et al., 2016).

Five studies on isolated hepatic perfusion and four on percutaneous isolated hepatic perfusion from eight groups include 176 and 91 patients, respectively, who were not staged, 3 to 61 per study (Table S1E) (Alexander et al., 2003; Artzner et al., 2019; Ben-Shabat et al., 2016, 2017; Brüning et al., 2020; de Leede et al., 2016; Forster et al., 2014; Karydis et al., 2018; van Iersel et al., 2014; Vogl et al., 2017). Two percutaneous isolated hepatic perfusion trials were prospective but not randomized. The patients received melphalan with or without tumor necrosis factor-α or oxaliplatin (an inhibitor of DNA synthesis). The median OS ranged from 10 to 26 months for isolated hepatic perfusion and was 14–27 months for percutaneous isolated hepatic perfusion. The meta-analysis combined data from 147 patients, and estimated a median OS of 16.1 months, which was longer than that with CHT ($P = 0.037$) (Fig. 15C) (Rantala et al., 2019). This advantage was solely based on the data from the most dedicated Swedish center (Ben-Shabat et al., 2016, 2017).

A multicenter phase III trial (FOCUS 301) was originally planned to enroll 240 patients with hepatic metastases and ECOG 0–1 in a randomized trial to compare chemosaturation therapy with melphalan against best alternative care chosen by the investigator, either transarterial chemoembolization, pembrolizumab, ipilimumab, or dacarbazine (EudraCT Number, 2015-000417-44, NCT02678572). In 2019, its design was amended to a nonrandomized single arm study of 80 patients (FOCUS 301A). The trial eventually enrolled 144 patients (FOCUS 301 and 301A) of whom 102 were assigned to percutaneous isolated hepatic perfusion (59 of whom were not randomized) and 91 received the treatment (Zager et al., 2021). According to a preliminary analysis of 79 evaluable patients who received percutaneous isolated hepatic perfusion, the median PFS was 9.0 months (95% CI 6.2–11.8) and 40% of patients experienced a transient serious treatment-related adverse event, the majority of which were hematological. This is longer than the median benchmark PFS of 3.3 months (95% CI 2.9–3.6) for 873 patients from the recent meta-analysis of 29 phase 2 trials (Khoja et al., 2019), and 3.1 months (95% CI 2.7–5.7) for 29 evaluable patients in the randomized control arm (FOCUS 301), but the patients were not staged and OS has not been reported yet.

6.2.3. Other regional therapies

Other regional therapies have been tested, usually in highly selected patients enrolled in small non-randomized trials.

6.2.3.1. Immunoembolization. Two prospective studies provide patient-level OS data on immunoembolization, a transarterial chemoembolization -like procedure in which granulocyte-macrophage colony stimulating factor instead of a cytotoxic agent is infused to the hepatic artery. This factor stimulates monocytes and macrophages to produce pro-inflammatory cytokines, thought to enhance cancer-directed immunologic responses. A phase I and a phase II study included 34 and 25 patients who reached a median OS of 14 and 22 months, respectively (Table S1F) (Sato et al., 2008; Valsecchi et al., 2015). A retrospective comparison of outcomes in two previously published studies from the same institution (Yamamoto et al., 2009) – 34 patients treated with immunoembolization (Sato et al., 2008) and 19 patients who received chemoembolization (Patel et al., 2005) – reported median OS of 20.4 months and 9.8 months, respectively. The data do not allow any firm conclusions (Fig. 15D) (Rantala et al., 2019).

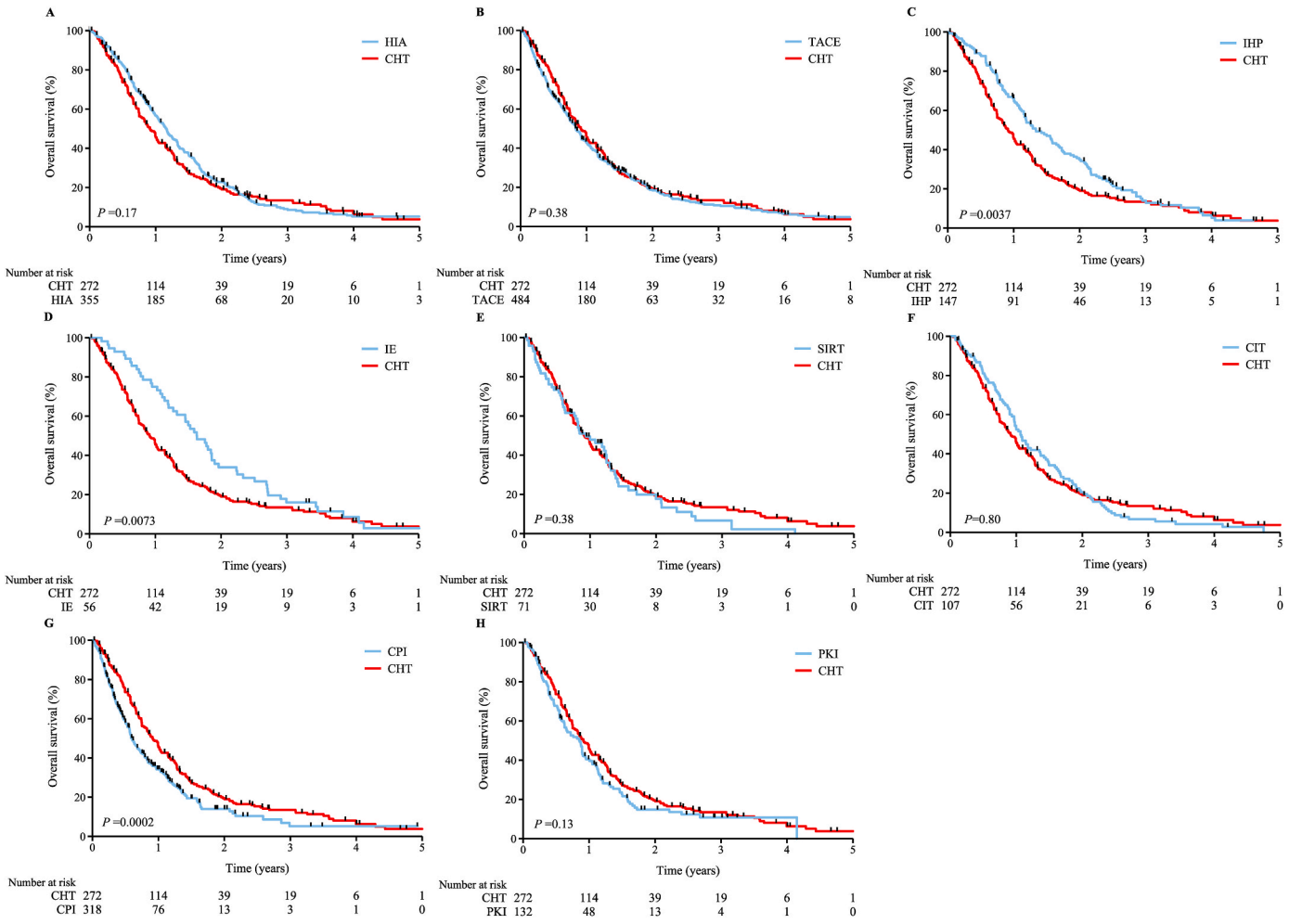


Fig. 15. Kaplan-Meier plots based on pooled data from a meta-analysis of overall survival after metastatic uveal melanoma for eight treatment modalities that were administered to a total of more than 50 patients. Kaplan-Meier graphs compare survival with conventional chemotherapy (CHT) against hepatic intra-arterial chemotherapy (**A**; HIA), transarterial chemoembolization (**B**; TACE), isolated hepatic perfusion (**C**; IHP), immunoembolisation (**D**; IE), selective internal radiation therapy (**E**; SIRT), chemoimmunotherapy (**F**; CIT), checkpoint inhibitor (**G**; CPI), and protein kinase inhibitor (**H**; PKI). *P*-values were calculated by log-rank test. Reproduced from (Rantala et al., 2019), doi: 10.1097/CMR.0000000000000575, an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/), adapted layout and colors.

6.2.3.2. Selective internal radiation therapy. In SIRT, resin microspheres or glass particles coupled with yttrium-90, a high-energy beta-emitting radionuclide, are injected into the hepatic arterial circulation. The microspheres are tiny enough to enter into tumor blood vessels but not further in significant numbers. They emit radiation within the liver to destroy metastases. Although the spheres are too large to enter capillaries and theoretically do not spread to the pulmonary circulation, a mapping angiogram is required to identify which hepatic arteries supply the metastases and to exclude presence of arteries that would carry microspheres to other abdominal organs. If such arteries are found, they need to be blocked. Substantial flow of microspheres from the liver to the lungs also needs to be excluded. In recent years, SIRT has become the primary local treatment modality of liver metastases not eligible for surgical resection in some centers, superseding systemic therapy as first line therapy (Tulokas et al., 2018).

Eight small non-controlled studies evaluate SIRT in a total of 169 patients, 8 to 50 per study (Table S1G) (Eldredge-Hindy et al., 2016; Gonsalves et al., 2019; Klingenstein et al., 2013; Levey et al., 2020; Ponti et al., 2020; Schelhorn et al., 2015; Tulokas et al., 2018; Zheng et al., 2018). A single prospective phase II study in 23 treatment-naïve patients and 24 patients who progressed after immunoembolization reported a median OS of 18.5 months and 5.2 months, respectively (Gonsalves et al., 2019). In a nationwide Finnish study, 18 patients without extrahepatic metastases who were ineligible for resection received SIRT as first-line (14 patients) and as second-line or salvage therapy (4 patients), and the median OS after SIRT was 13.5 months, 2 months longer than for a historical chemotherapy control group ($P = 0.047$) (Tulokas et al., 2018). In a later study, median OS of 19 patients representing the HUH Working Formulation stage IVa was 24 months after SIRT as compared to 12 months with BSC (Fig. 14B). The difference in this small series was inconclusive. The median OS ranges from 2.8 to 19 months across other studies. A meta-analysis combined data from 71 patients, and the estimated median OS was 11.3 months, comparable to that with CHT ($P = 0.38$) (Fig. 15E) (Rantala et al., 2019). Current evidence thus does not allow concluding that SIRT would be superior to CHT or, indeed, BSC (Rantala et al., 2021b).

6.2.3.3. Thermotherapy. Thermal destruction of liver metastases can be induced by stereotactic radiofrequency ablation or laser-based thermotherapy. Two small retrospective case series evaluated the use of liver-directed thermotherapy for hepatic metastases of uveal melanoma (Table S1H) (Bale et al., 2016; Eichler et al., 2014). The reported median OS was 29 months for 6 patients and 38 months for 18 selected patients, respectively.

6.3. Systemic therapy

Systemic treatment regimens used for metastatic uveal melanoma have typically been adopted from protocols developed for cutaneous melanoma, which is genetically and in other respects a profoundly different type of melanocytic tumor.

6.3.1. Conventional chemotherapy

Sixteen studies of 5–85 patients report individual-level OS data on CHT to treat metastatic uveal melanoma in 454 patients (Table S1I) (Bol et al., 2019; Carling et al., 2015; Carvajal et al., 2018; Corrie et al., 2005; Homsi et al., 2010; Leyvraz et al., 2014; Luke et al., 2020; Nicholas et al., 2018; Pföhler et al., 2003; Piperno-Neumann et al., 2016; Pons et al., 2011; Rantala et al., 2021b; Schinzari et al., 2017; Schmittel et al., 2005a, 2005b; Terheyden et al., 2004). Of note, CHT was used as a control (in lieu of BSC) for the investigational regimen in 5 (31%) of these studies, three of which were prospective randomized trials, including a multicenter randomized trial by EORTC (Bol et al., 2019; Carling et al., 2015; Carvajal et al., 2018; Leyvraz et al., 2014; Luke et al., 2020). Seven other reports were prospective, non-controlled phase I or II trials (Corrie et al., 2005; Homsi et al., 2010).

The chemotherapy agents investigated include the alkylating agents dacarbazine, temozolomide (a prodrug of MTIC, demethylated form of dacarbazine), fotemustine, docosahexaenoic acid–paclitaxel (a prodrug of a naturally occurring taxane that inhibits mitosis through disruption of microtubule function), gemcitabine (a pyrimidine nucleoside prodrug that acts as a faulty base and inhibits further DNA synthesis) with the alkylating agent treosulfan, and with or without cisplatin, temozolomide with bevacizumab (an anti-vascular endothelial growth factor antibody), and dacarbazine with cisplatin and vinblastine. Combined data on CHT were utilized as the comparison base in a meta-analysis of individual-level OS, extracted from tables or Kaplan-Meier plots of the original publications (Rantala et al., 2019).

The reported median OS with CHT ranged from 4.6 to 17.0 months, but the individual results cannot be legitimately compared in the absence of staging that was performed in only one of the 16 studies (Rantala et al., 2021b), though one additional prospective trial tabulated the components necessary to assigning the working formulation stage (Terheyden et al., 2004). In the nationwide real-world cohort study that used HUH working formulation staging, conventional CHT provided for 43 patients an OS of 10, 6.9, and 2.4 months for stage IVa, IVb, and IVc, respectively, which was not different from that of 108 patients managed with BSC ($P = 0.17$). In fact, 26 patients who represented the best stage IVa appeared to survive slightly, though not significantly, longer with BSC (median, 12 months) than 19 patients with CHT (Fig. 16A). Conversely, those 15 patients who were staged to IVc survived two months longer with CHT (median OS, 2.4 months; 95% CI 1.0–3.3) as compared to 59 patients who received BSC (median OS, 0.6 months; 95% CI 0.3–0.9; $P = 0.026$, corrected for multiple comparisons). Their ECOG performance status was, however, better than that of patients managed with BSC, which instead of treatment may explain this difference.

The evidence thus suggests that CHT does not provide an OS benefit to patients with metastatic uveal melanoma as a group, and that variable unreported stage distributions likely explain the diverse median OS estimates reported in previous reports.

6.3.2. Chemoimmunotherapy

Seven studies that included 3 to 104 patients report individual-level OS data on chemoimmunotherapy (CIT) with interferon or interleukin-2 administered to 211 patients in combination with various chemotherapy regimens (Table S1J) (Fig. 15F) (Becker et al., 2002; Kivelä et al., 2003; Pyrhönen et al., 2002; Rantala et al., 2021b; Solti et al., 2007; Terheyden et al., 1998; Vihinen et al., 2010). Of note, one of them was a multicenter EORTC phase II study with bleomycin (which induces DNA strand breaks), vincristine, lomustine (an alkylating nitrosourea), and dacarbazine (BOLD combination) with recombinant interferon-alpha that was conducted to confirm an objective response rate (see *2.2.* for definition) of 15–20% that had independently been reported from the United States and Finland (Kivelä et al., 2003; Nathan et al., 1997; Pyrhönen et al., 2002). However, no objective responses were observed, and the EORTC trial did not suggest an OS benefit either (Kivelä et al., 2003).

In general, the median OS with CIT ranged from 3.7 to 41 months. Three of the studies were conducted in Finland and together with the EORTC trial applied the HUH Working Formulation staging of metastases (Kivelä et al., 2003; Pyrhönen et al., 2002; Rantala et al., 2021b; Vihinen et al., 2010). Of these four studies, the nationwide, real-world survey included 104 patients of whom 47 received BOLD-interferon and the remaining ones other combinations (Rantala et al., 2021b). The median OS with CIT, 13 months, was overall longer than with conventional CHT, 5 months ($P < 0.001$), a difference that resulted from a longer median OS in stage IVa (18 versus 10 months) whereas the

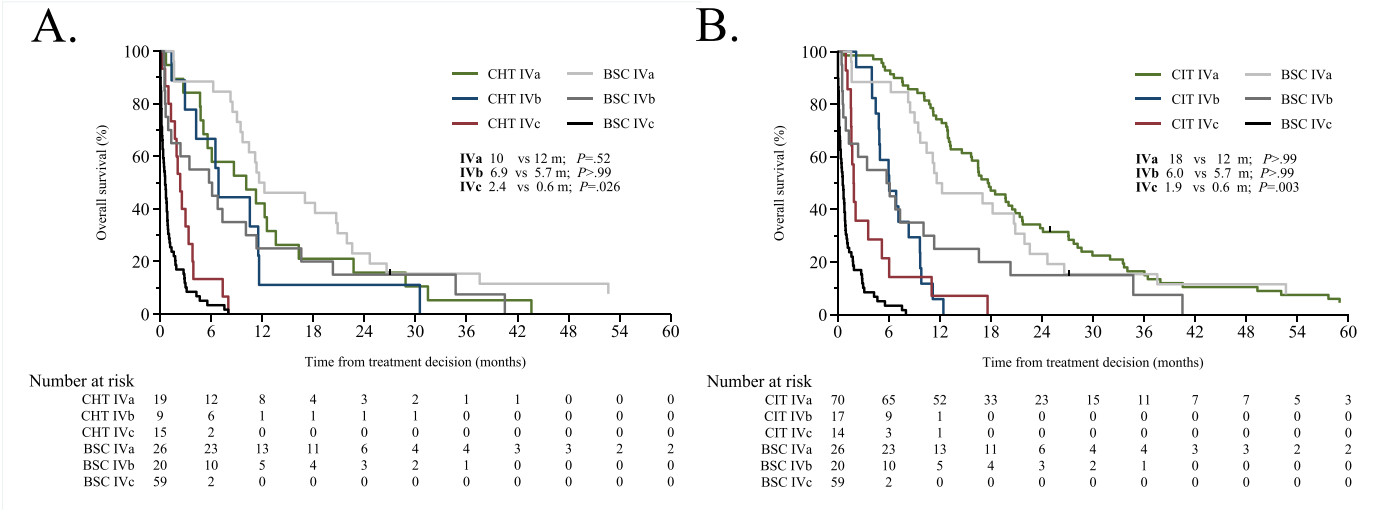


Fig. 16. Two systemic treatments for metastatic uveal melanoma compared retrospectively with best supportive care using staging in a nationwide dataset. Kaplan-Meier graph of overall survival (OS) from treatment decision to manage the patient first-line with conventional chemotherapy (CHT) (**A**) and chemoimmunotherapy with interferon or interleukin (CIT) (**B**), plotted against best supportive care (BSC) and divided by Helsinki University Hospital working formulation stage (see 5.3.1.). Median OS and *P* value are calculated by log-rank test, with Bonferroni correction. Note survival difference in stage IVa only in (**A**). Reproduced from (Rantala et al., 2021b), doi:10.1097/CMR.0000000000000728, CC BY license (http://creativecommons.org/licenses/by/4.0/), adapted layout.

median OS in stage IVb (6.0 months) and IVc (1.9 months) were comparable with those for CHT. The OS with CIT also was not appreciably longer than that of 70 patients managed with BSC who represented HUH working formulation stage IVa (Fig. 16B). Again, patients in stage IVc survived longer than with BSC, but the ECOG performance status of the latter was worse.

Retrospective and non-controlled evidence suggests that, irrespective of the combination, CIT might perhaps provide a slightly longer OS than CHT for patients with metastatic uveal melanoma who represent stage IVa, but it is at best uncertain whether the OS would markedly differ from what can be obtained with BSC (Rantala et al., 2021b).

6.3.3. Immunotherapy

6.3.3.1. Checkpoint inhibitors. Immune checkpoint inhibitors are a new type of anticancer drug, typically antibodies that block proteins that are expressed on specific immune system cells, especially T cells, and on tumor cells. They provide checkpoints that help to keep the immune responses from being unduly strong. Blocking a checkpoint allows T cells to kill cancer cells more vigorously.

Twenty-two publications that report a total of 804 patients, 5 to 89 patients per study and drug or a combination of drugs, have evaluated three checkpoint inhibitors: anti-cytotoxic T-lymphocyte associated protein (CTLA)-4, anti-programmed cell death (PD)-1 receptor and its ligand (PD-L1). Anti-CTLA-4 antibody ipilimumab, the first checkpoint inhibitor to be approved for treatment of cancer, was given to 275 patients with metastatic uveal melanoma, and tremelimumab was administered to 11 patients (Table S1K) (Algazi et al., 2016; Bol et al., 2019; Danielli et al., 2012; Heppt et al., 2017, 2019; Johnson et al., 2019; Joshua et al., 2015; Karivedu et al., 2019; Karydis et al., 2016; Keilholz et al., 2019; Kelderman et al., 2013; Kirchberger et al., 2018; Klemen et al., 2020; Luke et al., 2013; Maio et al., 2013; Najjar et al., 2020; Namikawa et al., 2020; Nicholas et al., 2018; Rossi et al., 2019; Rozeman et al., 2020; van der Kooij et al., 2017; Zimmer et al., 2015). Anti-PD-1 antibodies nivolumab and pembrolizumab alone were given to 64 and 196 patients, respectively, whereas anti-PD-L1 antibodies atezolizumab and avelumab alone were given to 2 and 16 patients, respectively. Various combinations of an anti-CTLA-4 and an anti-PD-1 antibody have been given to 234 patients. Eight studies were prospective, but none were randomized or staged the patients. Forty-two percent of patients were treated first-line.

The median OS ranged from 4.6 to 20 months, and with a combination of ipilimumab and anti-PD-1 or anti-PD-L1 the median OS ranged from 12 to 19 months (Bol et al., 2019; Heppt et al., 2017, 2019; Karivedu et al., 2019; Kirchberger et al., 2018; Klemen et al., 2020; Najjar et al., 2020). Only one of the latter studies reported on first-line treatment (Bol et al., 2019) and all were retrospective. Very recently, two single-arm prospective phase II trials with 52 (Piulats et al., 2021) and 33 (Pelster et al., 2021) patients who received nivolumab combined with ipilimumab had a 1-year OS of 52% and 56% and a median OS of 13 and 19 months, respectively. The fact that no prospective study used a published staging system for metastatic uveal melanoma complicates assessment of the results. The nationwide, real-world survey was not informative because only five patients or less were included in all stages (Rantala et al., 2021b). The recent meta-analysis found a significantly shorter median OS, 7 months, with checkpoint inhibitors than with CHT ($P = 0.0002$) (Fig. 15G) (Rantala et al., 2019). A very small proportion (8%) of first-line treatments in the studies on checkpoint inhibitor in the meta-analysis may explain the worse survival. More data are needed on first-line treatment with checkpoint inhibitors to draw any firm conclusion (Rantala et al., 2019).

Uveal melanoma is characterized by an unusually low mutational burden for an adult cancer (Rodrigues et al., 2019), and this likely accounts for the limited value of checkpoint inhibitors as compared to their efficacy in cutaneous melanoma that are known for their very high mutation load, mostly because the skin is exposed to ultraviolet radiation. While results on checkpoint inhibition do not suggest an OS better than with BSC in metastatic uveal melanoma in general, preliminary evidence raises hopes that they might benefit a small subset of patients who carry a germline or a somatic pathogenic variant in *MBD4* on chromosome 3 and who have lost the other copy of this chromosome. In these selected tumors mutations quickly accumulate, and an objective response or at least stable disease with a checkpoint inhibitor is possible (Johnson et al., 2019; Rodrigues et al., 2018).

6.3.3.2. ImmTACS. Recently, immune-mobilizing monoclonal T-cell receptors against cancer (ImmTACs) have been tested against metastatic uveal melanoma (Middleton et al., 2020; Piperno-Neumann et al., 2021; Sacco et al., 2020; Sato et al., 2018). They are artificial fusion proteins constructed by combining a T cell receptor, which has been stabilized and affinity-enhanced to create a targeting function, with an antibody fragment that will recognize a T cell co-receptor. The targeting part can recognize a peptide of cancer cell origin that is presented on its surface by the human leukocyte antigen system. Any cytotoxic T cell can thereafter bind to the co-receptor part and will be redirected to kill the cancer cell.

Tebentafusp (an ImmTAC also known as IMCgp100) is designed to target melanoma-associated antigen gp100 via an affinity-enhanced, HLA-A*02:01–restricted T-cell receptor binding domain fused with an anti-CD3 T-cell engaging domain which redirects T cells to kill gp100-expressing melanoma cells. It showed a 1-year OS of 74% and 64%, respectively, in a 19 patient phase I trial (Sato et al., 2018) and a multicenter phase I/II trial of metastatic cutaneous (65 patients) or uveal melanoma (19 patients) unresponsive to more conventional treatment (Middleton et al., 2020). Most recently, tebentafusp as monotherapy showed in a preplanned interim analysis of an international randomized phase III trial a 1-year OS of 73% as first-line treatment versus 58% obtained with investigator's choice of pembrolizumab, ipilimumab or dacarbazine (Nathan et al., 2021; Piperno-Neumann et al., 2021). In that study, 252 of 378 patients were randomized to tebentafusp and the rest to investigator's choice. At a median follow-up of 14.1 months, the median OS was 21.7 months (95% CI, 18.6–23.6) with tebentafusp and 16.0 months (95% CI, 9.7–19.4) in the control arm. Early skin rash at first week of treatment was strongly associated with OS benefit (Hassel et al., 2021). However, the benefit was observed across all categories of responses, including patients whose best response was progressive disease (Joshua et al., 2021).

Tebentafusp has now been granted fast track and orphan drug designations from the US Food and Drug Administration for uveal melanoma, promising innovative medicine designation under the United Kingdom's Early Access to Medicines Scheme, and both the US Food and Drug Administration and the European Medicines Agency have accepted applications that seek the approval of tebentafusp for use in the treatment of adult patients with HLA-A*02:01–positive metastatic uveal melanoma.[1]

Moreover, other immune-based cell therapies have been tested in non-controlled studies that omitted staging. Adoptive transfer of tumor-infiltrating lymphocytes showed in a single-center, single-arm, phase II study tumor regression in 7 of 20 evaluable patients (Chandran et al., 2017). Six of them had achieved partial response. One response was complete and maintained at 21 months. No OS was reported. Cell based vaccines have been investigated in a small cohort of 14 patients with a median OS of 19.2 months (Bol et al., 2014).

6.3.4. Targeted therapy

Targeted therapy is an emerging type of anti-cancer treatment

[1] Note added at proof: The U.S. Food and Drug Administration approved tebentafusp (Kimmtrak) for treatment of adult patients with HLA-A*02:01–positive, unresectable or metastatic uveal melanoma, on January 26, 2022.

directed against cancer cells, used either alone or in combination with other types of treatment. The drugs either inhibit signals that promote growth of cancer cells or tumor blood vessels or enhance signals that directly or indirectly lead to cancer cell death. Such targets can be either cancer type specific or cancer agnostic, and the drugs can be either small or large molecules.

Eleven studies with 294 patients with metastatic uveal melanoma, 8 to 97 patients per study, report on targeted therapy (Table S1L) (Bhatia et al., 2012; Carvajal et al., 2018; Daud et al., 2017; Hofmann et al., 2009; Luke et al., 2020; Mahipal et al., 2012; Mouriaux et al., 2016; Nicholas et al., 2018; Niederkorn et al., 2014; Penel et al., 2008; Shah et al., 2018). The drugs include receptor tyrosine kinase inhibitors imatinib, sorafenib, sunitinib, and cabozantinib; a mitogen-activated protein kinase kinase inhibitor selumetinib; and a heat shock protein 90 inhibitor ganetespib; three of these studies combined the agent with CHT (Bhatia et al., 2012; Carvajal et al., 2018; Niederkorn et al., 2014). Nine trials were prospective, and three of them were randomized. In addition, trametinib and protein kinase C inhibitor AEB071 have been tested; however, without OS data (Falchook et al., 2012; Piperno-Neumann et al., 2020). Targeted therapy has significantly improved the prognosis of metastatic cutaneous melanoma, but its usefulness in metastatic uveal melanoma is limited because of different driver mutations (Croce et al., 2019; Piperno-Neumann et al., 2020; Spagnolo et al., 2016; van der Kooij et al., 2019).

The median OS of patients with metastatic uveal melanoma treated with targeted therapy ranges from 6.3 to 16 months. Of note, the first clinical double-blind multicenter trial designed to eventually register with a regulatory body a drug to be used for metastatic uveal melanoma, the SUMIT trial, tested selumetinib versus placebo in combination with dacarbazine but failed to document improved outcomes (Carvajal et al., 2017, 2018). Despite the fact that KIT, the target of imatinib, is strongly expressed (>90%) in 76% of metastases from uveal melanoma, this has not translated to clinical efficacy of drugs targeting it (Hofmann et al., 2009). Although no trial has staged the patients, and targeted therapy was first-line in only 28% of the patients, we are inclined to accept the median OS estimate of 10 months in the recent meta-analysis of 132 patients treated with protein kinase inhibitors, which was comparable to that with conventional CHT ($P = 0.13$) (Fig. 15H) (Rantala et al., 2019). Later, a phase I, multicenter, single-arm study using protein kinase C inhibitor AEB071 was published, again with modest results (Piperno--Neumann et al., 2020).

6.3.5. *Other systemic treatments*

Fourteen patients treated with everolimus, an immunosuppressant, combined with pasireotide, a somatostatin analog, in a prospective, non-randomized phase II trial reached a median OS of 11 months from treatment decision (Shoushtari et al., 2016), comparable both with conventional CHT and BSC. None of the patients received it as first-line treatment.

6.4. *Best supportive care*

BSC refers to care that is given to manage disease-related symptoms and that is judged by the managing physician to be the most appropriate for each patient without any other anticancer therapy, according to the standards of their center (Lester et al., 2013). It can be either the first and only option to manage metastatic disease or an end-of-life type final option after active treatment. BSC can and should additionally be administered concurrently with active treatment (Cherny et al., 2003; Ferris et al., 2009; WHO Expert Committee, 1990). In general, patients with advanced cancer who receive BSC report improved quality of life and mood compared to placebo and, possibly, may survive longer, highlighting the importance of prompt integrated palliative care (Temel et al., 2010).

Definitions and descriptions of BSC in trials and retrospective studies typically have been minimal or absent (Hui et al., 2013; Zafar et al., 2008). Despite proposed consensus definitions for clinical trials (Zafar et al., 2012), lack of standardization of BSC is a persistent obstacle in comparing results between reports (Lee et al., 2015; Lester et al., 2013; Nipp et al., 2015).

What BSC administered to patients with metastatic uveal melanoma includes has not been specifically described but, in general, some of the most frequent modalities of BSC are non-narcotic and narcotic analgesics, corticosteroids, and gastrointestinal medication, and BSC also can include palliative radiotherapy to relieve pain, blood transfusions, and social and psychological support (Lester et al., 2013). Typically, 30%–40% of patients with metastatic uveal melanoma in current practice receive only BSC to manage metastasis-related symptoms (Table S1M). Of note, the percentages of patients who received only BSC in two nationwide studies, 32% and 39% (Jochems et al., 2019; Rantala et al., 2021a), are comparable to those in recent reports from single tertiary referral centers, 31% and 33% (Lane et al., 2018; Nicholas et al., 2018).

Eight studies report individual-level survival data on 11 to 191 patients who received only BSC for metastatic uveal melanoma (Table S1M) (Gomez et al., 2014; Gragoudas et al., 1991; Jochems et al., 2019; Lane et al., 2018; Nicholas et al., 2018; Pons et al., 2011; Rantala et al., 2021a; Xu et al., 2019). Taken together they comprise 626 patients. One study included prognostic factors on patient-level (Rantala et al., 2021a).

Only one study specifically focused on BSC (Rantala et al., 2021a). Overall, the 1-, 2-, 3-, and 5-year survival rate with BSC in 108 patients was 17%, 8%, 5%, and 2% respectively (Rantala et al., 2021a). Patients who received only BSC were typically older and had more advanced disease (Rantala et al., 2021a, 2021b), making comparisons against active treatment impossible without staging. Using the HUH Working Formulation that study found the median OS to be 12 (range, 1.6–83), 5.7 (range, 0.5–40), and 0.6 (range, 0–8.0) months for stage IVa, IVb, and IVc, respectively ($P < 0.001$) (Rantala et al., 2021a). In stage IVa, 50% of the patients survived ≥12 months. In stage IVb, 50% survived ≥6 months and 25% ≥ 12 months. In stage IVc, 97% of patients died within 6 months. As expected, the stage distribution was skewed toward worse stages as compared to active treatment (Fig. 17). Of the 108 patients, 24%, 19%, and 55% were assigned to stage IVa, IVb, and IVc, respectively, as opposed to 66%, 17%, and 15% of the actively treated patients from the same national cohort (Rantala et al., 2021a) and 44%, 44%, and 15% of 201 patients who had received active treatment in the earlier OOG validation dataset (Kivelä et al., 2016). Migration towards stage IVc in the BSC dataset resulted mostly from a worse ECOG score; 56% of the patients as opposed to 1% of those treated actively represented score >2, reflecting the fact that most treatment trials require score 0–1 (Lee et al., 2015): in the three clinical trials that have reported the working formulation stage, it was IVa in 46% (Kivelä et al., 2003), 50% (Pyrhönen et al., 2002), and 100% (Vihinen et al., 2010) of the patients.

The control arm in clinical trials of metastatic uveal melanoma has been variable. One goal of the nationwide study that focused on BSC was to provide an open access historical reference to allow investigators to compare OS between experimental active treatment and the reference BSC, both overall and according to HUH Working Formulation (Rantala et al., 2021a). The BSC data are available at Zenodo, an open-access repository developed under the European Union OpenAIRE program, https://doi.org/10.5281/zenodo.3369090 (Rantala et al., 2020a). Moreover, the early integration of supportive care for patients with metastatic UM is currently investigated in a multicenter phase III trial (NCT04728113).

6.5. *Predictive factors*

Predictive factors differ from prognostic ones in that they predict whether a metastasis will respond to a specific treatment rather than what the survival of the patient will be. At present, one such factor has been proposed.

Loss of function variants in *MBD4*, located on chromosome 3, appear

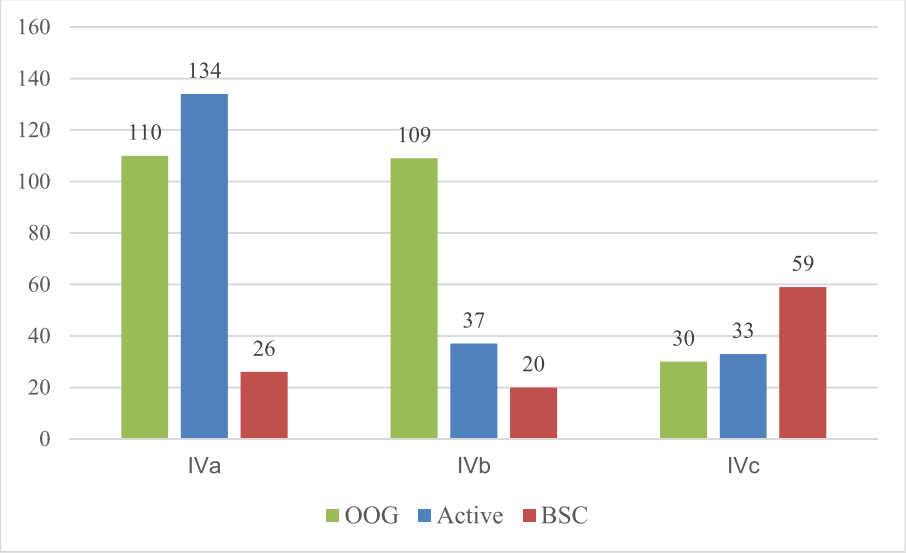


Fig. 17. Stage migration suggested by the Helsinki University Hospital working formulation (*see* 5.3.1. for definition of stages). Comparison of stage distribution in a nationwide study of actively treated patients to that of patients who received only best supportive care (BSC) for metastatic uveal melanoma, and to that of an earlier multicenter validation data set of the Ophthalmic Oncology Group (OOG). The stage distribution of patients managed with BSC is skewed toward worse stages as compared to active treatment, and that of actively treated patients toward more favorable stages as compared to the earlier multicenter data from patients who had not been surveilled as consistently. Note that this suggests stage migration from attending a standard surveillance program, which creates lead time bias. Because of this, survival between studies should be compared by working formulation stage or another staging system, such one based on either of the two available nomograms, rather than for all patients combined. Data correspond to results published in (Rantala et al., 2021a, 2021b; Kivelä et al., 2016).

to lead to an unusual, high mutational burden in uveal melanoma that may render metastases responsive to a checkpoint inhibitor, according to published case reports (Johansson et al., 2019; Rodrigues et al., 2018). The frequency of germline loss-of-function variants in *MBD4*, which may become uncovered when the other copy of chromosome 3 is lost, was 0.7% (95% CI 0.3–1.4) in 1093 patients with a primary uveal melanoma in France (Derrien et al., 2020). The frequency of likely pathogenic germline variants, though none were loss-of-function in type, was 0.2% (95% CI 0.01-1.3) in 432 patients in Finland (Repo et al., 2020). Because of their rarity, no screening for *MBD4* germline variants was recommended. It might be worthwhile to look for somatic pathogenic variants in *MBD4* (Derrien et al., 2020; Repo et al., 2020) when a metastasis is biopsied for confirmation to inform choice of treatment, however. Detection of a favorable variant in *MBD4* might predict therapeutic response to a checkpoint inhibitor.

6.6. National guidelines

No international consensus statement on treatment of metastatic uveal melanoma is available. A few national guidelines exist in Canada (Weis et al., 2016), France (Mathis et al., 2018), United Kingdom (Nathan et al., 2015) (currently being updated), Scotland (Chadha et al., 2019), and the United States (Barker and Salama, 2018; Rao et al., 2020; Seth et al., 2020). Moreover, European guidelines that will be supported by the European Society for Medical Oncology (ESMO) and European Rare Adult Solid Cancer Network (EURACAN), a virtual network connecting patients and healthcare providers across Europe, are being drafted. All of them were evidence-based at least in part and none was developed based on expert consensus only. However, a recent systematic analysis of some of the guidelines (Barker and Salama, 2018; Nathan et al., 2015; Weis et al., 2016) assigned consistently poor values to the usability of the recommendations in clinical practice (Steeb et al., 2020). The national guidelines have in common that the patients with metastatic uveal melanoma should be considered for clinical trials whenever possible, should be informed of available trial options at expert centers, and should be considered for surgical resection, radiofrequency ablation or equivalent local therapy of metastases potentially amenable to such treatments (Barker and Salama, 2018; Mathis et al., 2018; Nathan et al., 2015; Rao et al., 2020; Seth et al., 2020; Weis et al., 2016). NCCN additionally recommends local therapies including isolated hepatic perfusion, embolization, and ablative procedures (National Comprehensive Cancer Network, 2021).

6.7. Evidence of impact from active treatment on overall survival

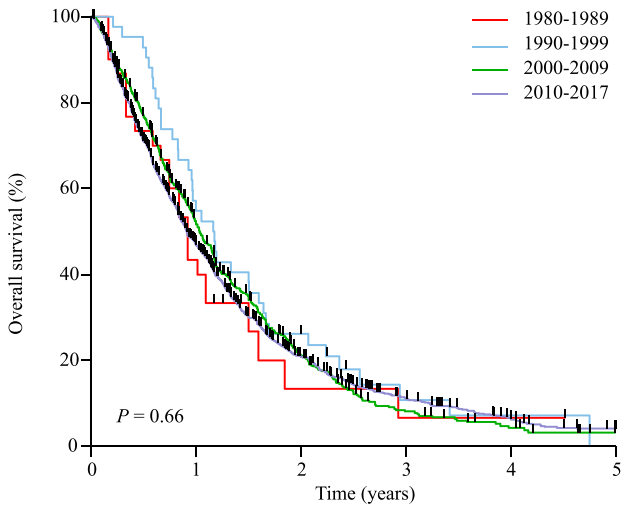
It is widely considered that prognosis of patients with metastatic uveal melanoma has not changed over the last few decades. Yet, the median survival in older studies has consistently been 6 months or less (Gragoudas et al., 1991) in contrast to many reports and meta-analyses of more recently treated patients among whom it was 10–13 months so that 43%–52% of patients have survived at least for one year (Khoja et al., 2019; Rantala et al., 2019).

Survival rates in different time periods have been formally compared in two retrospective single-center studies and one meta-analysis. The first single center survey included 661 consecutive patients of whom 344 were treated for metastatic uveal melanoma of any metastatic pattern, and reported no consistent improvement in survival rate between the periods 1982–1991, 1992–2001, and 2002–2009 (Lane et al., 2018). A study of 73 patients with liver metastases reported the same for periods 2004–2011 and 2012–2016 (Xu et al., 2019). A meta-analysis of 78 studies, which included 1994 patients after exclusion of surgical treatment, likewise showed no improvement in OS from the 1980s to the 2010s by decade of publication ($P = 0.66$) despite progressive increase in other liver-directed therapies (Fig. 18) (Rantala et al., 2019).

Despite evidence to the contrary, OS of patients with uveal melanoma also has been claimed, or at least assumed, to be longer with active treatment as compared to BSC (Gomez et al., 2014; Gragoudas et al., 1991; Lane et al., 2018; Nicholas et al., 2018; Xu et al., 2019). Only rarely has the perceived difference been suggested to be related to different patient characteristics rather than to treatment effect (Augsburger et al., 2009; Pons et al., 2011).

When a historical or concurrent control group has been included it has typically been conventional CHT, most often dacarbazine (Carling et al., 2015; Carvajal et al., 2018; Leyvraz et al., 2014; Luke et al., 2020; Tulokas et al., 2018). Regarding comparison with BSC (see 6.4., above), the OS of patients who received systemic, non-surgical treatment in the OOG multicenter study for HUH working formulation stage IVa and IVb disease (described in 5.3.1., above) was comparable to that with BSC ($P = 0.41$ and $P = 0.75$, respectively) (Fig. 19) (Kivelä et al., 2016; Rantala et al., 2021a, 2021b). Only in stage IVc, the OS was shorter with BSC than with treatment ($P < 0.001$). For the latter stage, a survival benefit can not be confirmed because of probable bias: 85% of the patients who received BSC had an ECOG score 3–4 and, therefore, were not eligible to receive any active treatment.

Regarding evidence of survival benefit from specific treatment modalities, the OS with CIT, hepatic intra-arterial chemotherapy,



Number at risk

1980-1989	30	13	2	1	1	0
1990-1999	42	24	10	3	1	0
2000-2009	519	236	84	25	10	1
2010-2017	1403	582	214	87	38	14

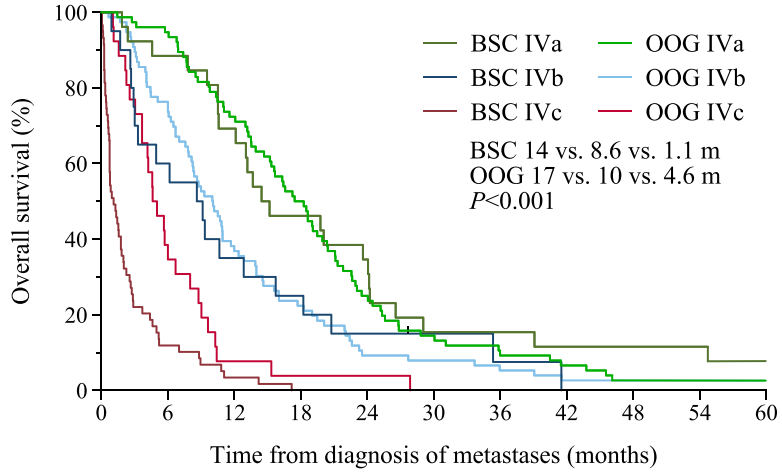
Fig. 18. Lack of improvement in overall survival of patients with metastatic uveal melanoma. Kaplan-Meier graph of overall survival after metastatic uveal melanoma, pooled data by decade of publication. All treatment modalities are included except for surgery. *P*-value was calculated by log-rank test for trend. Published in (Rantala et al., 2019), doi: 10.1097/CMR.0000000000000575, an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

transarterial chemoembolization, protein kinase inhibitor, and SIRT were comparable with that after CHT in a meta-analysis of 2494 patients ($P = 0.13–0.80$) (Fig. 15) (Rantala et al., 2019). Surgery, isolated hepatic perfusion, and IE were associated with longer OS ($P < 0.001$, $P = 0.004$, and $P = 0.008$, respectively) and checkpoint inhibitor was associated with shorter OS than CHT ($P < 0.001$). However, in closer analysis, only approximately 8% of patients were treated with checkpoint inhibitor first-line. For IE the difference solely derived from a single-center phase I and a subsequent phase II trial with a total of 59 patients. The OS benefit of isolated hepatic perfusion depended entirely on one study with an exceptionally long OS (Ben-Shabat et al., 2016). The analysis could not be limited to first-line treatments because such patient-level data were available only for CHT, CIT, hepatic intra-arterial chemotherapy, and transarterial chemoembolization. Furthermore, any method of staging was applied in only 4% of the studies and for 2% of the patients. The interval from the diagnosis of metastases to the initiation of study treatment varied widely, and no more than 18% of the studies diligently reported the components of OS from diagnosis of metastases to death or censoring. The meta-analysis supports assumptions that no clinically significant improvement in OS regardless of the mode of treatment so far is confirmed. In the meta-analysis most of the difference in OS between individual studies likely was attributable to surveillance, selection, reporting, and publication bias and not to treatment-related prolongation of survival (Rantala et al., 2019).

The International Rare Cancers Initiative conducted another meta-analysis in which patient-level prognostic variables and also PFS outcomes were available from 29 phase Ib/III trials in metastatic uveal melanoma from 2000 to 2016 (Khoja et al., 2019). They collected the original study data of all treated patients from trial investigators. OS data were available for 912 patients for whom the median PFS was 3.3 months and OS 10 months. The analysis suggested that liver-directed therapy might provide longer PFS and OS than CHT, immunotherapy, anti-angiogenic agents, and protein kinase inhibitors, but neither the line of therapy nor staging (to reduce lead-time bias) were considered.

In general, the median OS of actively treated patients is 10–13 months according to the two meta-analyses of 2494 and 912 patients, and the most detailed nation-wide study of 216 patients (Fig. 20) (Khoja et al., 2019; Rantala et al., 2019, 2021b). In the meta-analyses the cumulative proportion that survived declined rapidly from 43% to 52% at 1 year to 25% at 2 years, 13% at 3 years, and to 2% at 5 years (Khoja et al., 2019; Rantala et al., 2019).

The first OS results from the randomized phase III study IMCgp100-202 on tebentafusp in HLA-A*02:01–positive patients with metastatic uveal melanoma that reported an OS of 21.7 months as compared to 16.0 months in the control arm as first-line treatment (Nathan et al.,



Number at risk

BSC IVa	26	23	18	12	9	4	4	3	3	3	2
BSC IVb	20	12	7	5	3	2	1	0			
BSC IVc	59	7	2	0							
OOG IVa	76	72	55	38	19	11	7	5	2	2	2
OOG IVb	76	58	28	17	7	6	4	2	2	2	2
OOG IVc	26	10	2	1	1	0					

Fig. 19. Comparison of overall survival (OS) from the date of diagnosis of metastasis to death. Data are for patients who received best supportive care (BSC) in a nationwide dataset from Finland and patients who received systemic, non-surgical treatment in the Ophthalmic Oncology Group (OOG) validation dataset. Kaplan-Meier graph divides patients by the Helsinki University Hospital working formulation stage (*see* 5.3.1.). Median OS and P-value from log-rank test for trend are shown. Note that the graph suggests a treatment benefit only in stage IVc, but the stage IVc patients who do not receive active treatment generally tend to show less favorable characteristics. Data available at the open-access repository Zenodo (Kivelä et al., 2019; Rantala et al., 2020a), doi:10.5281/zenodo.3533543, doi:10.5281/zenodo.3369090.

2021; Piperno-Neumann et al., 2021) might change the current treatment approach and prognosis in this group of patients.

6.8. Challenges in clinical trial analysis

Because of the typically small number of patients, few randomized trials have been conducted in the metastatic setting, the largest two of which included 378 patients (Nathan et al., 2021; Piperno-Neumann et al., 2021) and 171 patients (Leyvraz et al., 2014). Five larger studies on the real-world outcomes of metastatic uveal melanoma in tertiary care centers have been published with 89–730 actively treated patients (Jochems et al., 2019; Lane et al., 2018; Nicholas et al., 2018; Rantala et al., 2021a, 2021b; Seedor et al., 2020), including two nationwide studies from the Netherlands and Finland with 175 and 324 patients, respectively (Jochems et al., 2019; Rantala et al., 2021a, 2021b). Such studies often have gaps in reporting patient-level prognostic factors and the treatments administered, or they lack a comparison group (Abraira et al., 2013; Altman et al., 1995; Augsburger et al., 2009). Additionally, lead time bias typically poses a problem in interpreting results (Augsburger et al., 2011; Seedor et al., 2020). Unless surveillance for metastases is similar, patients are staged, or both, comparing results by treatment modality is impossible even in otherwise controlled trials. Attention to a few key issues would help to move the field forward.

6.8.1. Staging of patients

To reduce bias, staging of patients is extremely important. Despite availability of the TNM system and, especially, three dedicated staging systems for metastatic uveal melanoma (Table 6), two of which are externally validated, only six studies have reported any staging or used it for analysis (Freton et al., 2012; Kivelä et al., 2003; Pyrhönen et al., 2002; Rantala et al., 2021a, 2021b; Vihinen et al., 2010). One additional study provided the necessary information to calculate the HUH working formulation stages (Terheyden et al., 2004).

6.8.2. Including a comparison group

It is not uncommon that therapies for rare cancers are based on inadequate or incomplete evidence from studies that did not include any control group, or on randomized controlled phase II trials with a small number of patients who were not staged (Blay et al., 2016). As a solution, collaboration between existing reference and research networks is proposed first to define the standard treatment and then to ensure adequate accrual of patients. Examples of international collaboration in the field of uveal melanoma are the EURACAN (Piperno-Neumann et al., 2019), the European OOG (Al-Jamal et al., 2016; Jouhi et al., 2019; Kivelä et al., 2016; Kujala et al., 2013), the International Rare Cancers Initiative (Khoja et al., 2019), and the Ophthalmic Oncology Task Force of the AJCC (AJCC Ophthalmic Oncology Task Force, 2015; Garg et al., 2021).

BSC has been proposed as the ideal comparison base for trials in metastatic uveal melanoma, but it is also widely considered an option that patients likely would not accept. Historical reference data to compare trial results against BSC are now available at the open-access repository Zenodo on 175 patients consecutively staged according to the HUH working formulation and managed only with BSC in a nationwide retrospective survey (Fig. 21) (Rantala et al., 2021a), doi:10.5281/zenodo.3369090 (Rantala et al., 2020a).

An additional historical benchmark is also available through Zenodo, based on meta-analysis of 2494 actively treated patients in the literature, which allow comparison of OS by main treatment category (Rantala et al., 2019) https://doi.org/10.5281/zenodo.1490563 (Rantala et al., 2018). The International Rare Cancers Initiative provides benchmarks of PFS and OS from 912 patients enrolled in 29 trials published from 2000 to 2016, using individual patient level trial data (Khoja et al., 2019). It even provides separate benchmarks for systemic therapy and liver directed therapy.

7. Future directions

The final frontier in managing patients with uveal melanoma—conquering the metastatic cascade and preventing death—still appears as a shimmer far on the horizon. However, it is not too difficult to see many steps that would take one much nearer to that highly desirable target.

7.1. Maintaining tumor dormancy

Although it has been said that one should aim to eradicate a cancer rather than try to control it, maintenance of dormancy of micrometastatic uveal melanoma is emerging as a potential alternative therapeutic endpoint to prolong life (Blanco et al., 2012; Grossniklaus, 2019). Common mechanisms, such as hypoxia, seem to contribute to waking micrometastatic uveal melanoma from dormancy in hepatic microenvironment (Grossniklaus, 2019). One factor appears to be a pigment epithelium derived factor (Lattier et al., 2013) that is produced by hepatic stellate cells and suppresses angiogenesis and tumor growth. It is possible that degradation of this factor by metastatic uveal melanoma (Nwani et al., 2016) is related to emergence from dormancy. It will be useful to apply what has been learned about mechanisms of metastatic tumor emergence from dormancy in other types of cancers (Aguirre-Ghiso, 2018) to inform therapeutic options for prevention of emergence from dormancy of micrometastases from uveal melanoma.

These goals speak for coordinated collection of specimens from a

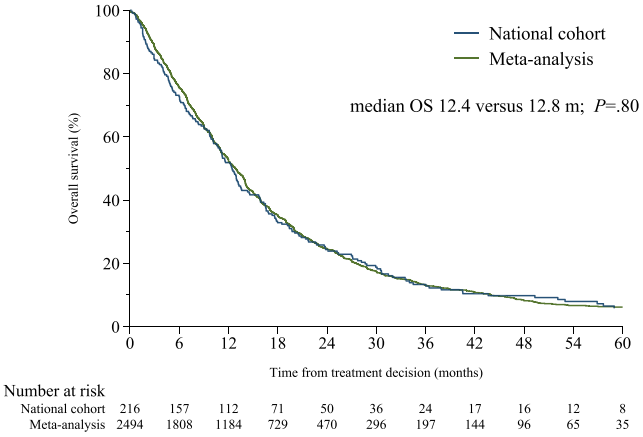


Fig. 20. Kaplan-Meier graph of overall survival after metastatic uveal melanoma for actively treated patients from the nationwide cohort in a real-life setting compared against meta-analysis of treatment trials. Note that the overall survival experience is highly similar. Data from (Rantala et al., 2021b), doi:10.1097/CMR.0000000000000728, CC BY 4.0 adapted colors. *P*-value is calculated using the log-rank test.

large number of patients with metastases for systematic and detailed translational research. This project should include patients who die of unrelated causes after treatment of their primary uveal melanoma. A pilot autopsy study of six such patients found that the likely explanation for dormancy of micrometastases that were found in two of them was the inability of uveal melanoma cells to grow in the liver, but the investigators were unable to identify any reason for this (Borthwick et al., 2011). Current understanding on risk factors for metastasis is still very incomplete as to which variables relate to the ability of uveal melanoma cells to intravasate and escape from the eye, and which relate to their ability not only to survive but also to eventually proliferate in the liver and other organs.

7.2. Harmonizing surveillance protocols

To improve comparability of treatment outcomes by reducing lead time bias, both universal staging and establishment of a widely applicable follow-up strategy will be important. Although the imaging methods used for surveillance ideally are chosen based on sensitivity, specificity, and lack of radiation exposure, in practice, availability, expense, and population characteristics such as obesity will influence the choice. A study comparing US and MRI head-to-head as a surveillance tool in high-risk patients with a cost-benefit analysis based on stage-specific OS outcomes would be a logical step toward international guidelines (see *3.4.3.* above*)*. Probably more influential than choice of the specific method is timing and frequency of imaging, which should also be easier to agree upon. The frequency of surveillance can increasingly precisely be guided by the true risk of metastasis, ideally based on a molecular genetic characterization of the primary tumor (Aaberg et al., 2020) in combination with the anatomical TNM stage at the time of diagnosis (Bagger et al., 2014; Berry et al., 2020; Dogrusöz et al., 2017; Mazloumi et al., 2020).

Novel imaging methods such as chemokine targeted protein-based contrast agent that potentially detects hepatic metastases soon after ending their dormancy can be explored and developed to be applicable in clinical practice (see *3.1.2*, above) (Tan et al., 2020). Mathematical modeling suggests that at the time of diagnosis of the primary tumor, a typical asymptomatic metastasis would be on average 0.5 mm^3 in size (Eskelin and Kivelä, 2001), thus any imaging method capable of detecting such metastases would immediately cause a shift of focus from adjuvant treatment trials in high-risk patients to trials on treating actual minimal systemic disease. Tissue or blood-based predictive biomarkers, such as exosomes can be explored to facilitate surveillance and to further understanding on the characteristics of metastases.

7.3. Promoting staging

Using a validated staging system and a standard control group (e.g., data available in open access data repositories, see *7.6.* below), is important both in retrospective analyses and non-randomized one-arm trials trials. Staging is valuable as a stratification variable even in randomized trials. Regardless of trial type, analyzing and reporting results by stage will be more standardized, comparable, and informative. Staging systems should continuously develop based on accumulating evidence and data.

The HUH working formulation and the Veneto-Mayo and Institut Curie nomograms are validated devices for evaluating trials even in their present form; however, they have potential for being adjusted and improved, ideally through continuous international collaboration. Further prognostic factors, including gender that appears to have an association with OS in large datasets, could be considered, as well as exploring the possibility of adding LDH to the working formulation (Rantala et al., 2021b). The staging systems could be incorporated in electronic patient records and be a requirement for publishing in major journals. The current staging systems are designed and calibrated for either systemic treatment or for hepatic metastases. New systems need to be developed for other defined groups of patients with metastatic uveal melanoma.

7.4. Identifying predictive factors

Genetic profiling of metastases may eventually become a prognostic biomarker which will be implemented in the staging systems for metastatic uveal melanoma. Equally importantly, additional predictive biomarkers that identify subsets of patients who may benefit from specific immunomodulatory and targeted therapies are needed (see *6.5*, above) (Derrien et al., 2020; Johansson et al., 2019; Rodrigues et al., 2018). To facilitate this, international collaborative biobanking on a large scale is desirable.

7.5. Standardizing reporting

The recent meta-analysis highlighted the almost total lack of consistency in the ways in which results of treatment for metastatic uveal

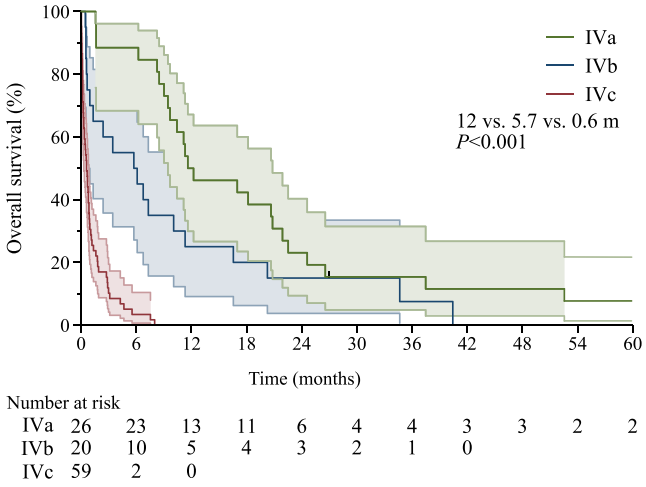


Fig. 21. Kaplan-Meier graph of overall survival (OS) from decision to treat with best supportive care for metastatic uveal melanoma. Graph is divided according to the Helsinki University Hospital working formulation stage (*see* 5.3.1.). Median OS and P-value from log-rank test for trend are shown. Published in (Rantala et al., 2021a), doi: 10.1080/0284186X.2020.1817978, CC BY license (http://creativecommons.org/licenses/by/4.0/), adapted colors.

melanoma are reported (Rantala et al., 2019). Detailed guidelines for consistent and informative reporting of prognostic studies and treatment trials are proposed in the supplement and these should be immediately adopted by major journals.

7.6. Promoting trials

Multicenter studies, both prospective and retrospective, will be of increasing value, and the progress of digitalization with a trend toward deidentified, open access data repositories will aid in integration of previous single center data for research purposes and for data mining through artificial intelligence and other computational methods. The inclusion of patients with metastatic uveal melanoma to so-called basket studies that allow studying of specific therapeutic agents across different tumor types as long as they contain the same molecular aberration are to be promoted (e.g., the basket study NCT03947385 enrolling metastatic uveal melanoma in addition to cutaneous melanoma, colorectal cancer, and other solid tumors), and the use of Bayesian method to take into account previously obtained information, are proposed (Billingham et al., 2016). Again, biopsy and analysis of metastases, like that of primary tumors, must become commonplace as a translational goal of trials, first to explore and gain understanding of the factors that determine progression of metastases, and then to individualize trial enrollment and, eventually, treatment. Ideally one can compare data between the primary tumor and its metastases to understand progression events better. The analysis of the primary tumor is promoted also to predict later metastasis behavior in order to develop adjuvant studies (Damato, 2018; Smit et al., 2020). A rapid expansion of knowledge on cytogenetic and molecular genetic data on primary uveal melanoma has taken place in the past decade and efforts have been made to extend it to metastases. Obstacles include, but are not limited to, the rarity of this cancer, logistically separated and often decentralized treatment by medical and surgical oncologists, and differential funding and interest – both clinical and research related – for what is the most common primary intraocular cancer in Caucasians. A high public support for, and trust expressed in, increasingly frequent biobanking (Yip et al., 2019) furthers whereas governmental privacy and data security concerns complicate, and may even stall attempts to share data and specimens for joint research purposes (OECD, 2015).

Additional to focusing on the metastatic cascade, investigations of the biology and genomics of the immune system, including immune microenvironment, and other host defenses against neoplasia, including those that may promote dormancy of micrometastases, will be critical to recognize potential biomarkers that might guide the selection of a first line or supporting treatment utilizing complementary mechanisms. This would further facilitate development of personalized treatment. Rigorous steps to demonstrate and validate clinical effect of any new biomarkers are required. The results of immuno-oncological therapies are less favorable in uveal melanoma than in cutaneous melanoma in part because the eye is an immune-privileged site (Jager et al., 2020; Niederkorn, 2009; Smit et al., 2020).

Currently, no standard of care exists for metastatic uveal melanoma. The choice of treatment should be discussed in expert center multidisciplinary boards and patients should be informed about ongoing trials. As of December 2021, 40 active studies for metastatic uveal melanoma are registered in the National Institutes of Health ClinicalTrials.gov database. These trials include one ImmTAC tebentafusp expanded access program (NCT04960891) and numerous projects in progress regarding immunotherapy trials. Networking between tertiary referral centers managing patients with metastatic uveal melanoma should work in close collaboration to allow wide enrollment of patients to trials in order to speed discovery.

8. Conclusions

1. US and MRI are the most sensitive surveillance methods to detect hepatic metastases in patients with uveal melanoma. When US and LFTs are used for surveillance, an MRI scan should be scheduled if any new lesion is detected by US, or if LFTs are newly elevated. High risk patients may be followed by 6-month liver MRI for early detection of those who may benefit from microscopically complete (R0) liver surgery, but a head-to-head comparison with US would be valuable because no level 1–2 evidence yet exists. Surveillance can be recommended for 10–15 years.
2. Patient-level data from meta-analyses provide no convincing evidence for a longer median OS for patients with metastatic uveal melanoma from any reported systemic treatment with the possible exception of surgical resection. A small group of patients who have an *MBD4* loss of function mutation in their metastases may respond to checkpoint inhibitors. Results from a randomized study with tebentafusp in HLA-A*02:01–positive patients suggest a 6 months longer median OS in interim analysis and are worth of attention.
3. Most of the variability in reported OS probably is attributable to surveillance, selection, reporting, and publication bias.
4. The median OS is 10–13 months for actively treated patients who receive systemic therapy. Surgical resection and tebentafusp may provide 6 months longer median OS in specific groups of patients.
5. Staging of metastases is crucial for analyzing and interpreting results of retrospective surveys and prospective trials alike. The median OS of the most favorably staged patients is about 18 months with local or systemic therapy, and 14 months with BSC.
6. The Helsinki University Hospital working formulation and Veneto-Mayo nomogram, both of which are externally validated devices, and the internally validated Curie Institute nomogram are available for staging. The working formulation also predicts the survival of patients receiving BSC but not that of patients who undergo surgical resection.

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Declaration of interest statement

Tero T. Kivelä reports personal fees from Santen Finland; Micaela M. Hernberg reports fees from BMS, MSD, Novartis, Roche, Sanofi, and Varian. The other authors have no conflicts of interest to declare.

Note

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CRediT author contributions

Elina S. Rantala:,Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization,

Project administration, Funding acquisition. Micaela M. Hernberg: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision. Sophie Piperno-Neumann: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision. Hans E. Grossniklaus: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision. Tero T. Kivelä: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

Author contributions

Percentage of work contributed by each author in the production of the manuscript is as follows: Elina S. Rantala 35%, Micaela M. Hernberg 15%, Sophie Piperno-Neumann 10%, Hans E. Grossniklaus 10%, Tero T. Kivelä 30%.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preteyeres.2022.101041.

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