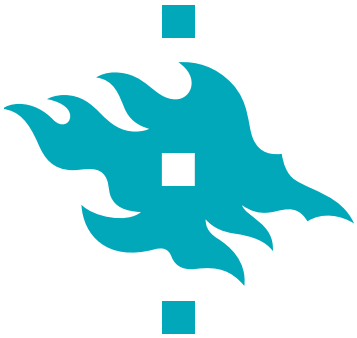

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ELINA S. RANTALA

METASTATIC UVEAL MELANOMA — DIAGNOSIS BY IMAGING AND STAGE-STRATIFIED OVERALL SURVIVAL

DEPARTMENT OF OPHTHALMOLOGY AND DEPARTMENT OF ONCOLOGY
FACULTY OF MEDICINE
DOCTORAL PROGRAMME IN CLINICAL RESEARCH
UNIVERSITY OF HELSINKI

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METASTATIC UVEAL MELANOMA – DIAGNOSIS BY IMAGING AND STAGE-STRATIFIED OVERALL SURVIVAL

Elina S Rantala

ACADEMIC DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, in Lecture Hall 1, Biomedicum, on the 21st of December, 2020 at 12 o'clock.

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To my daughter Ulla

Strange fishes glide in the depths,
unfamiliar flowers glow on the shore;
I have seen red and yellow and all the other colours, –
but the gaudy gay sea is the most dangerous to look upon,
it makes one thirsty and wide-awake for waiting adventures:
what happened in the fairy-tale will happen also to me!

Edith Södergran: Strange Sea
Dikter, 1916, translation David McDuff
(with permission)

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List of original publications

This thesis is based on the following publications, referred to in the text by their Roman numerals:

I Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. Melanoma Res. 2019; 29(6):561-568.

II Rantala ES, Peltola E, Helminen H, Hernberg M, Kivelä TT. Hepatic ultrasonography compared with computed tomography and magnetic resonance imaging at diagnosis of metastatic uveal melanoma. Am J Ophthalmol. 2020; 216:156-164.

III Rantala ES, Hernberg MM, Lundin M, Lundin J, Kivelä TT. Metastatic uveal melanoma managed with best supportive care. Acta Oncol. Accepted August 27, 2020.

IV Rantala ES, Kivelä TT, Hernberg MM. Impact of staging on survival outcomes: a nationwide real-world cohort study of metastatic uveal melanoma. Submitted August 28, 2020.

The results include unpublished results that are separately marked.

Abbreviations

AJCC	American Joint Committee on Cancer
ALT	alanine transaminase
AP	alkaline phosphatase
AST	aspartate aminotransferase
BCNU	bis-chloroethylnitrosourea
BOLD	bleomycin, vincristine (Oncovin), lomustine, and dacarbazine
BRAF	B-Raf proto-oncogene
BSC	best supportive care
CC-BY-4.0	Creative Commons Attribution License 4.0
CCS	comparative case series
CHT	conventional chemotherapy
CI	confidence interval
CIT	chemoimmunotherapy with interferon or interleukin
CNB	core-needle biopsy
COD	cause of death
CPI	check-point inhibitor
CT	computed tomography
CTLA	cytotoxic T-lymphocyte associated protein
DMFI	distant metastasis-free interval
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
FNAB	fine-needle aspiration biopsy
GM-CSF	granulocyte-macrophage colony-stimulating factor
GT	gamma-glutamyl transferase
HIA	hepatic intra-arterial chemotherapy
HMB-45	human melanoma black-45
HR	hazard ratio
IA	intra-arterial
IE	immunoembolisation
IFN	interferon
IHP	isolated hepatic perfusion
IL	interleukin
ImmTAC	immune-mobilising monoclonal T-cell receptor against cancer
IQR	interquartile range
IV	intravenous
LDH	lactate dehydrogenase
LDLM	largest diameter of the largest metastasis
LFT	liver function test

MBD4	methyl-CpG binding domain-4
MITF	microphthalmia transcription factor
MMC	mitomycin C
MRI	magnetic resonance imaging
N/A	not applicable
NC	no prior chemotherapy nor systemic treatment
ND	not defined
NR	not reported
NRCS	non-randomised controlled case series
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
PKI	protein kinase inhibitor
R0	microscopically complete liver surgery
R1	microscopically incomplete liver surgery
R2	macroscopically incomplete liver surgery
RFA	radiofrequency ablation
SIRT	selective internal radiation therapy
SOX10	SRY-related HMG-BOX gene 10
TACE	transarterial chemoembolisation
TNF	tumour necrosis factor
TNM	tumour, node, metastasis
TTP	time to progression
UNL	upper normal limit
US	ultrasonography
WF	Working Formulation

Country codes used in Chapter *2.5 Treatment*:

AU	Australia
AT	Austria
BE	Belgium
CA	Canada
CH	Switzerland
CN	China
CZ	Czech Republic
DE	Germany
DK	Denmark
FI	Finland
FR	France
GR	Greece
IL	Israel
IT	Italy
JP	Japan
NL	The Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
SE	Sweden
SP	Spain
UK	United Kingdom
USA	United States

Abstract

OBJECTIVES

Primary uveal melanoma is the most common intraocular malignant tumour in adults. It metastasises in more than half of patients, and even 35 years after the diagnosis of the primary tumour, metastatic uveal melanoma is the leading cause of death. However, no consensus exists regarding either screening or treatment of metastatic disease. The aims of this study are to provide a systematic review and meta-analysis of the current literature regarding the survival of actively treated patients with metastatic uveal melanoma; to describe a national cohort with metastatic uveal melanoma; and by means of this cohort, to analyse both the agreement of imaging modalities in diagnosis of metastatic disease and the stage-stratified survival of patients who received best supportive care (BSC) and active treatment.

METHODS

Study I was a systematic review and meta-analysis of original, peer-reviewed articles published between January 1, 1980 and March 29, 2017, reporting individual-level survival in Kaplan-Meier plot or numerical form. The survival graphs were digitised, and individual survival times were pooled. The median overall survival (OS) was calculated by treatment modality, and modalities were compared by the log-rank test and Cox regression, adopting conventional chemotherapy (CHT) as a reference.

For Studies II–IV, a nationwide cohort of patients was identified, whose metastases were diagnosed between January 1, 1999 and December 31, 2016 after the primary tumour had been managed in the Ocular Oncology Service, Helsinki University Hospital, which is a national referral centre. If a computed tomography (CT) or magnetic resonance imaging (MRI) was performed within 60 days of the upper abdominal ultrasonography (US), then the agreement of findings was studied regarding the presence and number of metastases (Study II). To study the survival of patients who received BSC (Study III) or active treatment (Study IV), they were assigned to stages IVa, IVb, and IVc, corresponding to predicted median OS of ≥12 months, <12–6 months, and <6 months, by using the Helsinki University Hospital Working Formulation (WF), previously validated by the European Ophthalmic Oncology Group (OOG). The primary endpoint was OS. It was compared with the Kaplan-Meier product-limit method and Cox proportional hazards regression analysis against BSC and between active treatment modalities (Study IV).

RESULTS

The meta-analysis included 2,494 patients from 78 studies, and the median OS was 13 months. Of the treatment modalities with >100 patients, the pooled median OS was 5–6 months longer with surgery and IHP and 4 months shorter with CPI than with CHT, for

which the median OS was 11 months ($P < 0.010$, log-rank test). However, OS was subject to identifiable confounding factors related to the heterogeneity in the included studies.

The nationwide cohort with metastatic uveal melanoma comprised 338 patients, of whom metastatic disease was diagnosed in 215 patients with US and CT/MRI within 60 days. The sensitivity of US in detecting metastases was 96% (95% confidence interval [CI], 92–98). Moreover, US detected metastases in 95% of the patients and agreed with a staging CT/MRI on their presence in 89% of patients, showing at least the same number of lesions as CT/MRI in 72% of patients, and in nine patients, it detected metastases that CT initially missed for various reasons.

In the nationwide cohort, 108 patients who were analysed received BSC and 216 active treatment. Of the patients who received BSC, 24%, 19%, and 55% represented WF stages IVa, IVb, and IVc, respectively. The median OS shortened with increasing stages, and calculated from the treatment decision (i.e. BSC), it was 12 months (95% CI, 9.4–21) for stage IVa, 5.7 months (95% CI, 0.7–11) for stage IVb, and 0.6 months (95% CI, 0.3–0.9) for stage IVc ($P < 0.001$, log-rank test for trend).

Of the 216 patients who received active treatment, 66%, 17%, and 15% represented WF stages IVa, IVb, and IVc, respectively. The median OS also shortened with increasing stages, and calculated from treatment decision, it was 18 months (95% CI, 16–21) for stage IVa, 6.9 months (95% CI, 4.8–9.7) for stage IVb, and 1.9 months (95% CI, 1.6–2.9) for stage IVc ($P < 0.001$, log-rank test for trend). In stage IVa, patients who received chemoimmunotherapy with interferon or interleukin (CIT) or local therapy, especially surgical resection, as their first-line treatment had a longer OS (18 and 27 months, respectively) than patients who received CHT (10 months) ($P < 0.020$). However, compared to BSC, OS after CIT in stage IVa was comparable ($P > 0.99$, corrected for multiple comparisons by stage), as was survival after selective internal radiation therapy (SIRT) ($P = 0.58$). Finally, we did not observe any convincing difference in OS relative to that after BSC in any comparison in stage-IVb or -IVc patients.

MAIN CONCLUSIONS

The meta-analysis suggested no clinically significant difference by treatment modality, although for patients with solitary hepatic metastases, surgery might have been more effective than CHT. However, the studies reviewed were heterogeneous. In the nationwide cohort, hepatic US was a sensitive follow-up modality, supporting its continued use as the primary imaging method for this purpose. The median OS was comparable to that of BSC patients with main treatment modalities—except with CHT and surgery in stage IVa, the former being associated with shorter and the latter with longer survival. Surgical resection may be superior but is available only for a minority of patients. No current treatment that is available for most patients with metastatic uveal melanoma is likely to appreciably prolong

OS. Furthermore, validated staging systems and proper historical control groups are crucial for correct interpretation of the outcomes in non-randomised trials.

KEYWORDS

uveal melanoma; uveal neoplasms; melanoma; metastasis; treatment; best supportive care; chemotherapy; surgery; chemoimmunotherapy; immunotherapy; targeted therapy; selective internal radiation therapy; isolated hepatic perfusion; transarterial chemoembolisation; ultrasonography; magnetic resonance imaging; computed tomography; survival; staging; meta-analysis; retrospective study

Summary in Finnish

TAUSTA

Suonikalvoston melanooma on yleisin aikuisten silmänsisäinen pahanlaatuinen kasvain. Yli puolet potilaista sairastuu levinneeseen tautiin, joka on yleisin kuolinsyy jopa 35 vuoden kuluttua emokasvaimen diagnoosista. Levinneen taudin seulomisesta tai sen hoidosta ei vallitse yhteisymmärrystä. Tavoitteeni oli selvittää systemoidun kirjallisuuskatsauksen ja meta-analyysin avulla levinnyttä suonikalvoston melanoomaa sairastavien aktiivisesti hoidettujen potilaiden elossaoloaika. Keräsin valtakunnallisen aineiston levinnyttä suonikalvoston melanoomaa sairastaneista potilaista ja tutkin sen avulla kuvantamismenetelmien yhtenevyyttä levinneen taudin diagnostiikassa sekä oireenmukaisesti ja aktiivisesti hoidettujen potilaiden elossaoloaikaa levinneisyysluokan mukaisesti.

MENETELMÄT

Osatyö I oli systemoitu katsaus ja meta-analyysi vertaisarvioiduista artikkeleista, jotka julkaistiin 1.1.1980 ja 29.3.2017 välisenä aikana PubMedissa, ja jotka sisälsivät potilaskohtaista tietoa eloonjäämisestä joko Kaplan-Meier -kuvaajan tai lukujen muodossa. Digitoin kuvaajat ja yhdistin elossaoloajat. Laskin mediaani elossaoloajan eri hoitomuodoille ja vertasin niitä perinteiseen kemoterapiaan Kaplan-Meierin menetelmällä ja Coxin suhteellisten riskitiheyksien regressioanalyysilla.

Osatyöt II–IV perustuivat valtakunnalliseen aineistoon potilaita, joiden levinnyt tauti oli todettu 1.1.1999 ja 31.12.2016 välisenä aikana, ja joiden emokasvain oli hoidettu Hyksin silmätautien klinikassa, johon suonikalvoston melanooman hoito on valtakunnallisesti keskitetty. Niiltä potilailta, joiden etäpesäkkeet oli havaittu kaikututkimuksella ja siitä 60 päivän sisällä tehdyllä tietokonetomografia (TT)- tai magneettitutkimuksella (MRI), tarkastelin kuvantamislöydösten yhtenevyyttä siltä osin, oliko etäpesäkkeitä havaittu ja jos oli, niin kuinka monta. Elossaoloaikaa tutkin jakamalla potilaat kolmeen ryhmään Euroopan silmäkasvainryhmän monikeskustutkimuksen validoiman Helsinki University Hospital Working Formulationin perusteella. Levinneisyysluokat IVa, IVb ja IVc edustavat elinajan odotetta ≥12, <12–6 ja <6 kuukautta. Tutkimuksen ensisijainen päätetapahtuma oli kokonaiselossaoloaika, jota vertasin oireenmukaisen hoidon sekä eri hoitomuotojen jälkeiseen elossaoloaikaan Kaplan-Meierin menetelmällä ja Coxin suhteellisten riskitiheyksien regressioanalyysilla.

TULOKSET

Meta-analyysiin löytyi 2494 potilasta 78 tutkimuksesta. Mediaani kokonaiselossaoloaika oli 13 kk. Niistä hoitomuodoista, joita sai >100 potilasta, isoloitu maksaperfuusio ja kirurgia pidensivät elossaoloaikaa 5–6 kk ja tarkistuspisteen estäjät lyhensivät sitä 4 kk verrattuna

perinteiseen kemoterapiaan, jonka jälkeen mediaani kokonaiselossaoloaika oli 11 kk. Meta-analyysiin sisältyvien julkaisujen heterogeenisyys paljasti tunnistettavissa olevia sekoittavia tekijöitä.

Valtakunnallinen aineisto koostui 338 potilaasta, joiden levinneistä taudeista 215 oli todettu kaikukuvauksella 60 päivän sisällä TT- tai MRI-tutkimuksesta. Kaikukuvauksen herkkyys havaita etäpesäke oli 96 % (95 % luottamusväli [LV], 92–98). Kaikukuvaus havaitsi etäpesäkkeet 95 %:lla potilaista ja oli 89 %:lla yhtenevä TT/MRI-tutkimuksen kanssa sen suhteen havaittiinko etäpesäkkeitä vai ei. Kaikukuvaus havaitsi 72 %:lla potilaista vähintään yhtä monta etäpesäkettä kuin TT/MRI, ja yhdeksällä potilaalla etäpesäkkeen, joka jäi TT-tutkimuksessa huomiotta. Tulokset tukevat kaikututkimuksen käytön jatkamista valtakunnallisena seulontamenetelmänä.

Koko aineistossa 108 potilasta sai oireenmukaista hoitoa. Heistä 24 % kuului levinneisyysluokkaan IVa, 19 % luokkaan IVb ja 55 % luokkaan IVc. Mediaani kokonaiselossaoloaika lyheni levinneisyysluokan mukaan ja oli 12 kk (95 % LV, 9.4–21) luokassa IVa, 5.7 kk (95 % LV, 0.7–11) luokassa IVb ja 0.6 kk (95 % LV, 0.3–0.9) luokassa IVc ($P < 0.001$, log-rank trenditesti).

Kahdestasadastakuudestatoista potilaasta, jotka saivat aktiivista hoitoa, 66 % kuului levinneisyysluokkaan IVa, 17 % luokkaan IVb ja 15 % luokkaan IVc. Mediaani kokonaiselossaoloaika oli sitä lyhyempi mitä korkeampi luokka oli: 18 kk (95 % LV, 16–21) luokassa IVa, 6.9 kk (95 % LV, 4.8–9.7) luokassa IVb, ja 1.9 kk (95 % LV, 1.6–2.9) luokassa IVc ($P < 0.001$, log-rank trenditesti). Luokan IVa kokonaiselossaoloaika oli pitempi, jos maksaetäpesäkkeiden ensilinjan hoito oli kemoimmunoterapia tai paikallishoito, erityisesti kirurgia, kuin jos se oli perinteinen solunsalpaajahoito (18 kk, 27 kk ja 10 kk, $P < 0.020$). Kemoimmunoterapialla ja maksan radioembolisaatiolla saatiin oireenmukaiseen hoitoon verrattava kokonaiselossaoloaika ($P > 0.99$ ja $P = 0.58$, log-rank testi). Levinneisyysluokkien IVb ja IVc potilaat eivät vakuuttavasti hyötyneet mistään hoitomuodosta.

PÄÄTELMÄT

Meta-analyysissa totesin, ettei kokonaiselossaoloaika millään hoitomuodolla paitsi mahdollisesti etäpesäkkeiden kirurgisella poistolla poikennut perinteisellä kemoterapialla saavutetusta. Analysoidut tutkimukset olivat heterogeenisiä. Valtakunnallisen aineiston perusteella ylävatsan kaikututkimus oli herkkä menetelmä toteamaan maksaetäpesäkkeet. Mediaani kokonaiselossaoloaika oli verrattavissa oireenmukaisesti hoidettujen potilaiden elossaoloaikoihin aktiivisilla hoitomuodoilla paitsi perinteisellä solunsalpaajahoidolla ja kirurgialla levinneisyysluokassa IVa, jossa se oli ensin mainitulla lyhyempi ja viimeksi mainitulla pidempi. Todennäköisesti mikään nykyinen hoito paitsi kirurgia ei pidennä useimpien levinnyttä uveamelanoomaa sairastavien potilaiden elossaoloaikaa. Kirurginen poisto on kuitenkin harvoin mahdollinen, koska maksassa on yleensä useampia etäpesäkkeitä. Validoidun levinneisyysluokituksen ja asianmukaisten verrokkien käyttäminen on välttämätöntä hoitotutkimusten oikealle tulkinnalle.

Introduction

Uveal melanoma is the most common primary malignant intraocular tumour in adults, with a mean age-adjusted incidence of 6.6 per million in Europe (as calculated from [1]) and 5.1 per million in the United States [2]. Most of uveal melanomas affect Caucasians, but the incidence varies by age, ethnicity, and latitude from 0.1 to 8.6 per million [1,3,4], with the incidence being highest in Scandinavia and northern latitudes of North America [4]. Furthermore, more than half of uveal melanomas result in clinical metastases [2,5,6], and thereafter, historically, the median overall survival (OS) was less than 6 months at a time when mainly liver function tests (LFTs) and chest radiography were used for follow-up [6].

In 90% of the patients, the liver is the first site of metastasis, followed by the lungs, bone, skin, and lymph nodes [6-8]. The liver remains the only site of metastasis in half of patients [5,7,8]. At the time of diagnosis of the primary tumour, only 1–3% have metastases; thus, it is a more frequent finding to detect benign hepatic abnormalities and synchronous primary cancers [9,10].

However, there is no agreement on follow-up. Each referral centre has its preferred imaging modality and frequency for screening for metastases. The frequency of imaging varies depending on participation in ongoing trials and perceived risk of dissemination indicated by tumour histology and its genetic profile, with high-risk patients often surveilled 4- to 6-monthly [11-15] based partly on the estimated tumour doubling times of metastases [16]. In Europe, hepatic ultrasonography (US) is widely used to screen for metastases, and computed tomography (CT) and magnetic resonance imaging (MRI) are scheduled if a suspicious new lesion is detected [17-20], although some large centres also prefer MRI for screening [11,21]. At some tertiary-referral centres in the United States, the follow-up is also done using MRI with a contrast agent for the liver and CT for the chest, abdomen, and pelvis [22]. US is used less frequently there because of its limitations in the obese [14], and fear of malpractice claims in the absence of practice guidelines also leads to a preference for surveillance with CT [23].

Given the small number of patients with metastatic uveal melanoma, few randomised controlled treatment trials have been conducted: hepatic intra-arterial (IA) versus intravenous (IV) fotemustine [24], selumetinib combined with dacarbazine versus placebo combined with dacarbazine [25], immunoembolisation versus bland embolisation [26], intrahepatic cisplatin with or without polyvinyl sponge [27], and a discontinuation trial with cabozantinib [28]. The largest one included 171 patients [24]. Retrospective cohort studies are frequent but often lack patient-level information about prognostic factors and specific treatments [29]. Patients who undergo surgery possibly have prolonged OS, but it necessitates an early detection of relatively few metastases [11]. In addition, new, more effective treatments for metastatic cutaneous melanoma [30,31] have not provided any survival benefit for patients with metastatic uveal melanoma [25], except possibly for those with loss-of-function variants in the methyl-CpG binding domain-4 (*MBD4*) gene;

however, their frequency among these patients is only 1% [32,33]. Unlike cutaneous melanoma, uveal melanoma rarely carries any mutation in B-Raf proto-oncogene (*BRAF*) [34,35]. Local treatments have been suggested to prolong survival [36-38], but no consensus exists on the treatment of metastatic uveal melanoma.

The objective of this thesis is to assess OS through a meta-analysis of published, peer-reviewed studies on metastatic uveal melanoma containing patient-level data. By means of a nationwide cohort, the aim is to evaluate the agreement of imaging modalities at the time of diagnosis of metastatic uveal melanoma to ascertain the most suitable method and to report stage-stratified OS, with a special interest in the survival of patients who received best supportive care (BSC) relative to those who received various active treatments.

2 Review of the literature

2.1 EPIDEMIOLOGY

2.1.1 Frequency and timing of metastases

One half of patients with primary uveal melanoma develop metastases despite the relatively successful eradication—5–10% rate of local relapse—of the primary tumour without enucleating the eye [2,5]. A metastatic rate of 50% is reached in 10 years in studies using the Kaplan-Meier analysis and in 25 years if competing causes of death are taken into account [5]. Metastasis is most frequently observed within 2–5 years after the diagnosis of the primary tumour [6], and even after 35 years of follow-up, metastatic uveal melanoma is the most common cause of death (COD) for patients with primary uveal melanoma that was treated with enucleation—an approach that minimises the risk of local recurrence [5].

At the time of diagnosis of the primary tumour, only 1–3% of patients have metastases [9,10]. In a study of 4,070 patients with primary uveal melanoma, approximately 10% had a history of a reported malignancy before the diagnosis of the primary uveal melanoma [2]. Uveal melanoma disseminates hematogenously, and its propensity to home to the liver has been designated as one of the most unusual phenomena in tumour biology [39]. More than half of patients will develop their first metastasis in the liver—eventually 90% of patients have liver metastases—followed by the lungs, bone, skin, and lymph nodes [6,8,39-41].

2.1.2 Growth rate

The small number of metastases at the time of diagnosis and the fact that metastases from uveal melanoma are the most common COD, even after enucleation, indicate early subclinical metastasis in patients who have acquired the genetic events necessary for dissemination [5,16]. The mathematical background for the exponential growth of cells was published in 1956 [42]. In general, 30 doubling times are required for a single 10-μm cell to grow to a 10-mm^3 mass containing 1 billion cells [43]. There are at least two possible doubling time clones in uveal melanoma: one for the primary uveal melanoma and one for the metastasis [2,16]. In general, the doubling time of the primary tumour has been suggested to range from 154 to 511 days [44,45], and that of the metastasis from 30 to 80 days [16].

2.1.3 Lead time bias

Lead time bias refers to the phenomenon where early diagnosis of a disease makes it look like the patients would survive longer subsequently [46]. Lead time bias may result in a false impression of improved survival or treatment effect. It is consequently crucial that patients in trials are randomised or categorised according to a similar condition. Randomisation necessitates that the review for metastases has been constant. For categorisation, validated prognostic tools and staging systems are required [47].

2.2 DIAGNOSIS OF METASTASES

2.2.1 Justification for screening for metastases

Since the 1970s, screening for metastatic uveal melanoma has been recommended [39]; however, the justification for surveillance has also been questioned because of a lack of evidence that current treatment modalities prolong OS [48-50]. Despite mounting evidence that local treatments for liver metastases improve OS, those treatments are often impossible because of a high metastatic burden, which makes an early diagnosis of the metastases necessary [11,19,37,51-53]. Nonetheless, in two studies with frequent 6-monthly MRI-based screening, only 14% and 11% of patients were eligible for hepatic resection [11,54]. The psychological aspect of surveillance is a benefit that patients may appreciate [55], and uniform screening guidelines would improve patients' eligibility for treatment trials and their comparability [18,56]. While attempts have been made, there is still no consensus on the necessity of follow-up [48,57-61].

2.2.2 Follow-up strategies

In the 1970s, LFTs and chest radiographs were the modalities used for the follow-up of patients with primary uveal melanoma [39,62,63], and imaging of the liver—first with isotope scanning and later with US—became more common in the 1990s [18,40,64]. To date, each referral centre has its preferred imaging modality and frequency for early detection of metastases. The frequency of imaging varies depending on participation in ongoing trials and perceived risk of dissemination, informed by tumour histology and genetic profile, with high-risk patients often surveilled 4- to 6-monthly [11-15,18] based partly on the estimated tumour doubling times of metastases [16]. Clinical and histological features for high metastatic risk are as follows: large tumour size, involvement of the ciliary body, extraocular extension, high mitotic activity, and epithelioid cell type [65-67]. Moreover, genetic prognosticators that favour metastatic spread are monosomy of chromosome 3, chromosome 8q gain, *BAP1* loss, or class 2 gene expression profile [68,69].

In Europe, upper abdominal US is widely used for follow-up every 6–12 months for 10 to 15 years, and CT and MRI are scheduled if a suspicious new lesion is detected [17-20,56], although some large centres also prefer MRI for early detection of metastases [11,21]. At tertiary-referral centres in the United States, the surveillance is often done using MRI, with a contrast agent for the liver and CT for the chest, abdomen, and pelvis, with the frequency based on perceived risk of metastases [22]. Hepatic US is used less frequently because of its relatively higher dependence on operator skill [70], its limitations in the obese [14], and a fear of malpractice claims in the absence of national practice guidelines [23]. LFTs are also often included in the review protocols [58].

2.2.3 Imaging

2.2.3.1 Hepatic ultrasonography

The use of US as a surveillance tool is supported by its proven utility [14,18,71], even in the American population, although obesity makes it technically challenging and more time-consuming [14,70]. The tool is widely available and affordable, and it avoids the use of ionizing radiation [70]. A contrast agent can also be used for higher accuracy in characterising and detecting liver lesions [70]. There are only a few published studies on the role of US in the surveillance of hepatic metastases of uveal melanoma, and they report its sensitivity and specificity to be 96–100% and 14–88%, respectively (Table 1) [14,72]. The minimum diameter of detectable lesions in US has been suggested to be 5 mm [71]. Benign liver lesions, such as cysts or hemangiomas, were detected in 18% of surveilled patients with primary uveal melanoma [14]. Most centres with equivalent expertise in US and CT prefer US as a guide for percutaneous biopsy of suspicious liver lesions [70]. Furthermore, US can be used intraoperatively, and in a study that compared preoperative and intraoperative liver assessment with US, 30 metastases were detected by intraoperative US, compared to only 11 by preoperative US [64].

2.2.3.2 Computed tomography

A limitation of CT as a regular surveillance examination is the use of relatively large doses of ionizing radiation. A study using data from 1991 to 1996 suggested that 0.4% of all cancers in the United States can be traced back to radiation from CT scans and that radiation from such scans that are currently being performed may ultimately account for 2% of all cancers in the future [73]. Nevertheless, CT is a useful staging method when examining pulmonary metastases, large hepatic metastases, and patients in whom MRI is contraindicated because of allergy to gadolinium or specified foreign bodies [9,50], and a CT scan takes less time than MRI [70]. If one metastatic hepatic lesion is detected on CT imaging, 90% of patients have multiple metastases in the liver [50]. In a single-centre study, CT was performed within one month of the diagnosis of primary uveal melanoma, and it detected benign hepatic lesions in 55% of patients [9].

2.2.3.3 Magnetic resonance imaging

MRI with a contrast agent is the most specific imaging modality, and it is at least as sensitive as CT, with sensitivity ranging from 67–100% and specificity from 80–99% (Table 1) [13,17,74,75]. In a study of 100 patients with primary uveal melanoma who underwent a standard 1.5 Tesla MRI scan, the minimum diameter of the detectable hepatic lesions was as small as 1 mm [13]. Short T1 and long T2 patterns were reported in 27% of uveal melanoma patients, although short T1 and short T2 patterns were the most common [22,76]. However, MRI is more expensive and less accessible than CT and, especially, US. Although a global cost comparison is difficult because of differences in insurances and reimbursements, a rough estimation can be made from the Helsinki University Hospital price list for a self-paying patient: a hepatic US costs 93 €, while CT with contrast is 250 €,

and MRI with gadolinium and with a liver-specific contrast agent costs 350 € and 550 €, respectively.

2.2.3.4 Positron emission tomography

Metastases of uveal melanoma are 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG)-avid, similar to those of cutaneous melanoma. However, metastases of cutaneous melanoma most often home to the lymph nodes, whereas uveal melanoma typically disseminates to the liver, making the use of FDG-positron emission tomography (PET) less successful. Furthermore, normal mottled hepatic uptake of FDG obscures small FDG-avid lesions due to their poor target-to-background ratio [22], and consequently, MRI is more sensitive in detecting liver metastases than FDG-PET in uveal melanoma [17,75]. The sensitivity and specificity of PET are reported to be 45–100% and 67–100%, respectively (Table 1) [10,17,75,77-79]. A case series of 333 patients who underwent PET-CT for screening for metastases at the time of diagnosis of primary uveal melanoma found that PET-CT detected synchronous second primary cancers in 3% and benign hepatic lesions in 8% of the patients [10]. The use of PET-CT for regular follow-up is limited by the exposure to ionizing radiation [70].

2.2.3.5 Chest radiography

Early metastases to the lung are infrequent when hepatic US already shows abnormalities [12,18,56]. The chest radiograph was abandoned from the surveillance protocol in the Helsinki University Hospital already in the 1990s. The reason was a study that concluded that only 2 of 46 patients diagnosed with metastatic uveal melanoma had pulmonary metastases that occurred together with hepatic metastases, and another 344 patients who did not develop metastases underwent up to 900 chest radiographs [18]. Many other centres have since followed this decision.

Table 1. Specificity and sensitivity of imaging modalities in detecting hepatic metastases of uveal melanoma. Indications were heterogeneous and are given separately. No publications were available regarding CT.

Imaging modality	Indication	Sensitivity	Specificity	Diameter of metastases, range in mm	No. patients
Ultrasonography					
Hicks et al. 1998 [72]	Baseline	100%	14%	N/A	40
Choudhary et al. 2016 [14]	6-monthly surveillance	96%	88%	N/A	263

Table 1 cont.

Imaging modality	Indication	Sensitivity	Specificity	Diameter of metastases, range in mm	No. patients
Magnetic resonance imaging					
Servois et al. 2010 [17]	Suspected metastasis on surveillance US	67%	N/A	5 to >10	12
Orcurto et al. 2012 [75]	Biopsy-proven liver metastases	100%	N/A	0.3–1.1	10
Piperno-Neumann et al. 2015 [13]	6-monthly surveillance	100%	80%	1–35	100
Francis et al. 2019 [74]	Baseline	83%	99%	N/A	145
Positron emission tomography					
Kurli et al. 2005 [77]	Heterogeneous[a]	100%	100%	N/A	20
Francken et al. 2006 [78]	Suspected metastatic disease	100%	67%	N/A	22
Servois et al. 2010 [17]	Suspected metastasis on surveillance US	45%	N/A	5 to >10	12
Klingenstein et al. 2010 [79]	Heterogeneous[b]	100%	N/A	2.7–12	12[c]
Orcurto et al. 2012 [75]	Biopsy-proven liver metastases	100%	N/A	0.3–1.1	10
Freton et al. 2012 [10]	Baseline	100%	N/A	The smallest LDLM 9 mm	333

[a] Eighteen patients were imaged for staging and two before treatment of their primary uveal melanoma.
[b] Two patients were imaged for initial staging, one for a suspicious pulmonary finding, and nine for re-staging before or after local or systemic therapy for metastatic disease.
[c] Hepatic metastases were detected in 10 patients (83%), and two had bone or pulmonary metastases.

2.2.4 Liver function tests

LFTs, including alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and lactate dehydrogenase (LDH), are widely accepted in surveillance protocols, although the Collaborative Ocular Melanoma Study reported that LFTs, with a sensitivity of 14.7%, are poor surveillance tools [12,72]. These tests tend to become abnormal only when hepatic metastases reach an advanced stage, by which time any opportunities for prolonging life are usually lost [12,50]. However, LFTs have been reported to rise within the normal limits already during the half-year before metastases are detectable by imaging [80].

2.2.5 Histopathology

If a metastasis is suspected, then a US- or CT-assisted fine-needle aspiration biopsy (FNAB) or, preferably, a core-needle biopsy (CNB) is recommended. Following the modified Callender system, metastases of uveal melanoma are of spindle cells, epithelioid cells, or a mixed cell type (consisting of spindle cells and epithelioid cells) [81]. The cut points are arbitrarily chosen, but in the tumour, node, metastasis (TNM) classification a spindle cell melanoma is determined to consist of ≥90% spindle cells, while an epithelioid cell melanoma consists of ≥90% epithelioid cells, and all other tumours are mixed cell melanomas. This cytological information was included in one [82] of the recent large tertiary-centre or nationwide studies on metastatic uveal melanoma [21,83-86]. The protocol of the College of American Pathologists recommends that pigmentation, the degree of necrosis, and mitoses/mm^2 should be included in the report [67,87,88]. The positive immunohistochemical stains include human melanoma black-45 (HMB-45) antigen, S-100 protein, MelanA, and less frequently, vimentin (though non-specific), tyrosinase, SRY-related HMG-BOX gene 10 (SOX10), and microphthalmia transcription factor (MITF) [87,89-93]. Ki-67 is often used to estimate proliferation rate.

The differential diagnosis is straightforward based on histomorphology if melanin is present; however, it can be challenging if the tumour is amelanotic because melanoma may mimic various histological patterns, making immunohistochemical stainings important [5]. A histopathologic review found that 7–10% of original cancer diagnoses in patients with uveal melanoma were incorrect if immunohistochemistry was not performed [5]. MelanA and HMB-45 positivity are rare, occurring in <1% and 0% of patients with non-small-cell lung cancer, respectively [94]. Cytokeratin-20 positivity is commonly used to confirm diagnosis of colon cancer, as it is expressed in 94% of colon cancer specimens. In uveal melanoma, cytokeratin markers are negative, although focal staining for simple epithelial cytokeratins may appear, and immunopositivity for cytokeratin-20 is distinctly unusual [92,95]. S-100 protein is expressed in approximately 50%, MelanA in up to 20%, and HMB-45 in 2% of breast cancers [96-98]. It is advisable to use at least two immunohistochemical stainings for melanocytes such as HMB-45 and MelanA or S-100 protein in combination with epithelial markers, such as pan-cytokeratin, to exclude carcinoma if an amelanotic metastasis of uveal melanoma is suspected [87]. Finally, a mutation in *GNAQ* or *GNA11* is found in more than 90% of uveal melanomas [99,100]; however, *BRAF* mutation, which is present in 40–60% of patients with cutaneous melanoma, is almost entirely absent from uveal melanomas [34,35,101].

2.3 PROGNOSTIC FACTORS FOR SURVIVAL AFTER DIAGNOSIS OF METASTASES

2.3.1 Age and gender

Age [7,37,40,85,102,103] and gender [7,21,37,40,85,104] have not been consistently associated with OS, although several investigators have associated older age [41,82,105,106] and male gender [41,105-107] with shorter OS (Tables 2 and 3). Especially the survival of the oldest age group is potentially confounded because of lead time bias and competing causes of death that are usually statistically unaccounted for [5]. In the tabulated publications, the median age at the time of diagnosis of metastatic uveal melanoma was 61–65 years [7,37,40,85,102,103,106], paralleling how the age categories were defined.

Table 2. Age at the time of diagnosis of metastases as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if hazard ratio (HR), or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	Age, per 5-year increase	1.03 (0.93–1.14)	0.16
Gragoudas et al. 1991 [7]	145	<55 55–69 >69	Reference 1.7[b] (1.1–2.7) 1.6 (1.0–2.6)	'unrelated'
Khoja et al. 2019 [106]	912	<65 ≥65	Reference 1.21 (1.02–1.43)	0.01
Kodjikian et al. 2005 [102]	35	≤70 >70	Reference 1.84[c] (0.99–3.39)	0.06
Nicholas et al. 2018 [85]	132	Age, per 1-year increase	1.01 (0.996–1.03)	0.14
Pons et al. 2011 [103]	58	Age, per 1-year increase	0.99 (0.06–1.60)	>0.05
Pons et al. 2011 [103]	58	≤65 >65	Reference 0.92 (0.46–1.90)	>0.05
Pons et al. 2011 [103]	58	≤70 >70	Reference 0.77 (0.37–1.60)	>0.05
Xu et al. 2018 [37]	73	Age, per 1-year increase	0.996 (0.990–1.002)	0.15

[a] Not included in the table: did not report HR and *P*-value [41], [105]; reported HR and *P*-value only for multivariate analysis adjusted for age and gender, and in it, the *P*-value was 0.064 for age >65 years at first metastatic diagnosis [108].

[b] Rate ratio.

[c] Risk rate.

Table 3. Gender as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	Male Female	Reference 0.85 (0.56–1.29)	0.46
Gragoudas et al. 1991 [7]	145	Male Female	Reference 1.0 (0.72–1.5)	'unrelated'
Khoja et al. 2019 [106]	912	Male Female	Reference[b] 0.72 (0.63–0.85)	<0.001
Kivelä et al. 2003 [107]	24	Male Female	Reference 0.33 (0.13–0.81)	0.015
Kodjikian et al. 2005 [102]	35	Male Female	Reference 0.89[c] (0.52–1.55)	0.69
Mariani et al. 2019 [21]	224	Male Female	Reference 0.93 (0.69–1.26)	0.66
Nicholas et al. 2018 [85]	132	Male Female	Reference 0.83 (0.57–1.22)	0.35
Xu et al. 2018 [37]	73	Male Female	Reference 0.74 (0.45–1.22)	0.24

[a] Not included in the table: did not report HR and *P*-value [109], [105], [41].

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

[c] Risk rate.

2.3.2 Characteristics of the primary tumour

The baseline characteristics of the primary uveal tumour are often left unreported in studies on metastases published in oncological journals [110], and they may not be associated with OS (Table 4) [21,40,102,111]. Orange pigment was associated with OS in univariable analysis ($P = 0.005$) in a single-centre study with 99 patients, but it was not predictive in the final multivariate-adjusted logistic regression model and not evaluated in any other study. Therefore, the association should be regarded with caution [82].

Table 4. Characteristics of the primary tumour as a prognostic factor for OS in univariable analysis, tabulated according to different characteristics. Studies were included if HR, or equivalent, and *P*-value were reported.

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	Largest basal diameter, per 1-mm increase	0.98 (0.97–1.04)	0.54
Kodjikian et al. 2005 [102]	35	Tumour diameter ≤10 mm >10 mm	 Reference 1.04[a] (0.55–1.95)	 0.91
Mariani et al. 2019 [21]	224	Largest diameter <18 mm ≥18 mm	 Reference 1.14 (NR)	 0.41
Valpione et al. 2015 [111]	152	Larger basal diameter, per 1-mm increase	0.92 (0.80–1.05)	0.40
Kodjikian et al. 2005 [102]	35	Tumour thickness ≤5 mm >5 mm	 Reference 0.94[a] (0.50–1.78)	 0.85
Valpione et al. 2015 [111]	152	Tumour thickness, per 1-mm increase	1.07 (0.91–1.27)	0.46
Lorenzo et al. 2018 [82]	99	Orange pigment over tumour	4.20[b] (1.48–11.9)	0.005
Kodjikian et al. 2005 [102]	35	Ciliary body involvement No Yes	 Reference 1.70[a] (0.92–3.11)	 0.09
Mariani et al. 2019 [21]	224	Ciliary body involvement No Yes	 Reference 1.42 (1.03–1.96)	 0.03
Valpione et al. 2015 [111]	152	Ciliary body involvement No Yes	 Reference 0.71 (0.35–1.44)	 0.34
Mariani et al. 2019 [21]	224	Extrascleral extension No Yes	 Reference 0.74 (0.40–1.37)	 0.34
Valpione et al. 2015 [111]	152	TNM category[c] T4 T3 T2 T1	 Reference 0.30 (0.01–3.80) 0.33 (0.03–3.91) 0.71 (0.01–3.80)	 0.20 0.38 0.26
Valpione et al. 2015 [111]	152	Cell type Spindle cell Mixed Epitheloid	 Reference 1.52 (0.26–1.64) 4.30 (0.01–100)	 0.125 0.98

[a] Risk rate.

[b] Odds ratio.

[c] The edition of a staging manual on which the TNM category is based, was not reported.

2.3.3 Distant metastasis-free interval

A longer distant metastasis-free interval (DMFI) might be a survival benefit (Table 5) [21,41,52,82,108,109,111,112]. However, lead time bias possibly influences the results [113].

Table 5. Distant metastasis-free interval as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Kodjikian et al. 2005 [102]	35	≤24 months >24 months	Reference 0.96[b] (0.55–1.66)	 0.87
Lorenzo et al. 2018 [82]	99	≤40 months >40 months	Reference 2.61[c] (1.08–6.31)	 0.03
Mariani et al. 2009 [52]	255	>24 months ≤24 months	Reference 1.94 (1.47–2.63)	 <0.0001
Mariani et al. 2019 [21]	224	>24 months 12–24 months 6–12 months 0–6 months	Reference 1.74 (1.19–2.53) 1.54 (0.97–2.44) 2.35 (1.35–4.1)	 0.004 0.07 0.003
Nicholas et al. 2018 [85]	132	DMFI, per 1-month increase	0.998 (0.996–1.00)	0.015
Pons et al. 2011 [103]	58	>24 months ≤24 months	Reference 1.71 (0.87–3.40)	 >0.05
Valpione et al. 2015 [111]	152	DMFI, per 1-month increase	0.9 (NR)	<0.001
Xu et al. 2018 [37]	73	DMFI, per 1-month increase	0.996 (0.990–1.002)	0.15

[a] Not included in the table: did not report HR and *P*-value [112], [109], [41]; reported HR and *P*-value for the final step of multivariate analysis already adjusted by age and gender [108].

[b] Risk rate.

[c] Odds ratio.

2.3.4 Performance status

A better Eastern Cooperative Oncology Group (ECOG) performance status (Table 6), which is a measure of the general well-being and daily life activities of a patient with cancer, confers a survival advantage (Table 7) [21,40,82,85,86,103,106,108,111]. The European Organisation for Research and Treatment of Cancer (EORTC) multicentre phase II study with 24 patients reported no significance of performance status measured with the Karnofsky index (Table 6); however, this index was 100 for seven patients, 90 for 11 patients, and 80 for six patients, and no patient had a Karnofsky index score less than 80 [107].

Table 6. Comparison of ECOG performance status and Karnofsky index scale [114-116].

ECOG grade	Karnofsky grade	Status
0	90–100	Fully active, able to carry on all pre-disease 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 a bed or chair ≥50% of waking hours
4	10–20	Completely disabled. Cannot carry on self-care.

Table 7. Performance status (PS) as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	ECOG PS 0 1–2	 Reference 3.40 (2.23–5.18)	 <0.001
Jochems et al. 2019 [86]	175	ECOG PS 0-1 ≥2	 'ECOG >1 seemed to be associated with poorer survival'	 NR
Khoja et al. 2019 [106]	912	ECOG PS 0 ≥1	 Reference 1.49 (1.25–1.78)	 <0.001
Kivelä et al. 2003 [107]	24	Karnofsky index, per 10-unit decrease in index	1.33 (0.78–2.27)	0.30
Lorenzo et al. 2018 [82]	99	Higher ECOG PS Lower ECOG PS	Reference 0.34[b] (0.15–0.74)	 0.007
Mariani et al. 2019 [21]	224	ECOG PS 0 1 2 3	 Reference NR 1.87 (0.95–3.67) NR	 NR 0.07 NR
Nicholas et al. 2018 [85]	132	ECOG PS 0 ≥1	 Reference 1.88 (1.10–3.22)	 0.022
Pons et al. 2011 [103]	58	ECOG PS 0 1–2	 Reference 1.32 (0.65–2.70)	 ≥0.05[c]

Table 7 cont.

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Valpione et al. 2015 [111]	152	ECOG PS 0 1 2–3	 Reference 1.5 4.5	<0.001[d]

[a] Not included in the table: reported HR and *P*-value for the final step of multivariate analysis already adjusted by age and sex, not for the univariable analysis [108].

[b] Odds ratio.

[c] In multivariate analysis, $P < 0.05$.

[d] Only one *P*-value is given in the original publication.

2.3.5 Size of metastases

The largest diameter of the largest metastasis (LDLM) [40,82,85,106,107], larger percentage [111], larger area [21], and larger volume [40] of the metastases on baseline imaging are associated with a shorter OS (Table 8).

Table 8. Size of metastases as prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	LDLM, per 1-cm increase	1.16 (1.10–1.24)	<0.001
Eskelin et al. 2003 [40]	91	Estimated total metastatic burden, per 1,000-cm^3 increase	1.51 (1.18–1.92)	<0.001
Khoja et al. 2019 [106]	912	LDLM <3 cm >3 cm	 Reference 1.65 (1.41–1.93)	 <0.001
Kivelä et al. 2003 [107]	24	Median LDLM, per 10-mm increase	1.13 (1.01–1.26)	0.032
Lorenzo et al. 2018 [82]	99	Smaller largest diameter of the largest liver metastasis Larger largest diameter of the largest liver metastasis	Reference 1.03[a] (1.01–1.06)	 0.034
Mariani et al. 2019 [21]	224	Largest liver metastasis size 1–500 mm^2 501–800 mm^2 801–1,200 mm^2 1,201 mm^2–	 Reference 1.17 (0.74–1.86) 2.56 (1.56–4.19) 3.28 (2.14–5.02)	 0.51 <0.001 <0.001
Nicholas et al. 2018 [85]	132	Largest liver metastasis size, per 1-mm increase	1.07 (1.03–1.12)	0.0010
Valpione et al. 2015 [111]	152	Liver substitution, per <20%, 20≤50%, 50%≤ increase[b]	1.6	<0.001

[a] Odds ratio; for consistency, the larger largest diameter of the largest liver metastasis was tabulated as a reference.

[b] Equivocal what was used as a reference, but the authors state that increasing liver substitution was associated with a worse OS.

2.3.6 Sites of metastases

The presence of liver metastases has been reported to be associated with shorter survival (Table 9) [41,85,86,105]. Moreover, concomitant extrahepatic and hepatic metastases have been associated with worse survival [21,37]. Bone metastases were an adverse prognostic factor only in multivariable analysis, unlike in cutaneous melanoma; however, the number of patients who had bone metastases was small, and it was not studied by other researchers [85]. In addition, a higher number of liver metastases [102,103] were associated with a shorter OS.

Table 9. Sites of metastases as a prognostic factor for OS in univariable analysis. Studies were included if HR, or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Jochems et al. 2019 [86]	175	Liver metastases No Yes	 Reference 2.09 (1.07–4.08)	 0.03
Nicholas et al. 2018 [85]	132	Liver metastases No Yes	 Reference 2.81 (1.30–6.89)	 0.0086
Kodjikian et al. 2005 [102]	35	Number of liver metastases ≤10 >10	 Reference 4.02[b] (1.85–8.73)	 <0.001
Pons et al. 2011 [103]	58	Number of liver metastases <5 ≥5	 Reference 3.06 (1.36–6.87)	 <0.05
Mariani et al. 2019 [21]	224	Extrahepatic and hepatic metastases No Yes	 Reference 2.03 (1.31–3.16)	 0.002
Xu et al. 2018 [37]	73	Extrahepatic and hepatic metastases No Yes	 Reference 2.28 (1.07–4.88)	 0.033
Pons et al. 2011 [103]	58	Extrahepatic metastases No Yes	 Reference 1.50 (0.70–3.20)	 ≥0.05
Nicholas et al. 2018 [85]	132	Pulmonary metastases No Yes	 Reference 0.94 (0.59–1.49)	 0.78
Nicholas et al. 2018 [85]	132	Bone metastases No Yes	 Reference 1.32 (0.71–2.46)	 0.39
Nicholas et al. 2018 [85]	132	Brain metastases No Yes	 Reference 0.93 (0.29–2.92)	 0.89

[a] Not included in the table: did not report HR and *P*-value [105], [41].

[b] Risk rate.

2.3.7 Liver function tests

Elevated AP [40,85,106,112] and LDH [21,40,82,85,86,106,108,111] are mostly strongly associated with a shorter OS, but associations with elevated AST [40,82], ALT [40,82], gamma-glutamyl transferase (GT) [108], and neutrophil lymphocyte ratio [85] have also been reported (Tables 10–13). The EORTC multicentre phase II study, which reported no association with AP level, included only one patient whose AP level was >2.5 x the upper normal limit (UNL) [107]. For comparability, the level of liver enzymes in serum or plasma was best expressed as a fraction of the upper normal limit for the specific enzymes in the laboratory where testing was performed [110].

Table 10. AP as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	AP, per 100-IU/L increase	1.49 (1.30–1.71)	<0.001
Eskelin et al. 2003 [40]	91	AP <2.5 x UNL ≥2.5 x UNL	 Reference 7.67 (2.60–22.6)	 <0.001
Khoja et al. 2019 [106]	912	AP ≤1.0 x UNL >1.0 x UNL	 Reference 2.76 (2.27–3.36)	 <0.001
Kivelä et al. 2003 [107]	24	AP, relative to the UNL (per 1x increase)	1.75 (0.97–3.15)	0.061
Lorenzo et al. 2018 [82]	99	AP ≤1.0 x the UNL >1.0 x the UNL	 Reference 20.41[b] (2.55–166.67)	 <0.001
Nicholas et al. 2018 [85]	132	AP, per 1-unit[c] increase	1.003 (1.002–1.004)	<0.0001

[a] Not included in the table: did not report HR and *P*-value [112].

[b] Odds ratio.

[c] Scale not mentioned.

Table 11. LDH as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	LDH, per 100-IU/L increase	1.06 (1.03–1.08)	<0.001
Eskelin et al. 2003 [40]	91	LDH <2.5 x UNL ≥2.5 x UNL	 Reference 6.42 (2.88–14.3)	 <0.001
Jochems et al. 2019 [86]	175	LDH Normal 250–500 U/L >500 U/L	 Reference 1.8 (1.07–3.01) 9.0 (5.63–14.35)	 <0.001
Khoja et al. 2019 [106]	912	LDH ≤1.0 x UNL >1.0 x UNL	 Reference 2.64 (2.11–3.30)	 <0.001
Lorenzo et al. 2018 [82]	99	LDH ≤1.0 x UNL >1.0 x UNL	 Reference 4.63[b] (1.77–12.05)	 0.001
Mariani et al. 2019 [21]	224	LDH ≤1.0 x UNL >1.0 x UNL–≤1.5 x UNL >1.5 x UNL	 Reference 1.30 (0.93–1.83) 4.15 (2.71–6.33)	 0.13 <0.001
Nicholas et al. 2018 [85]	132	LDH, per 1-unit[c] increase	1.00 (1.00–1.00)	<0.0001[d]
Valpione et al. 2015 [111]	152	LDH, x UNL, per 1-unit increase	1.6	0.014

[a] Not included in the table: reported HR and *P*-value for the final step of multivariate analysis already adjusted by age and sex [108].

[b] Odds ratio.

[c] Scale not mentioned.

[d] Seems statistically implausible.

Table 12. AST as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	AST, per 10-IU/L increase	1.25 (1.14–1.36)	<0.001
Eskelin et al. 2003 [40]	91	AST <2.5 x UNL ≥2.5 x UNL	 Reference 7.84 (2.18–28.2)	 0.002
Lorenzo et al. 2018 [82]	99	AST ≤1.0 x UNL >1.0 x UNL	 Reference 9.17[a] (2.46–34.48)	 <0.001

[a] Odds ratio.

Table 13. ALT as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	ALT, per 10-IU/L increase	1.23 (1.13–1.33)	<0.001
Eskelin et al. 2003 [40]	91	ALT <2.5 x UNL ≥2.5 x UNL	 Reference 3.39 (1.21–9.55)	 0.021
Lorenzo et al. 2018 [82]	99	ALT ≤1.0 x UNL >1.0 x UNL	 Reference 6.90[a] (1.85–25.64)	 0.002

[a] Odds ratio.

2.3.8 Presence of symptoms

Symptoms attributable to metastases are associated with a shorter OS (Table 14) [37,40,82], but lead time bias and small numbers of patients with symptoms (10–41 patients per study) might affect the results.

Table 14. Symptoms as a prognostic factor for OS in univariable analysis, tabulated alphabetically by author. Studies were included if HR, or equivalent, and *P*-value were reported.

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	Asymptomatic Symptomatic	Reference 1.69 (1.05–2.73)	 0.031
Lorenzo et al. 2018 [82]	99	Asymptomatic Symptomatic	Reference 3.61[a] (1.36–9.55)	 0.008
Xu et al. 2018 [37]	73	Asymptomatic Symptomatic	Reference 2.72 (1.36–5.44)	 0.005

[a] Odds ratio.

2.3.9 Attendance to regular follow-up

Attendance to regular review for metastases may be statistically associated with survival (Table 15) [40,41,82], but the effect of lead time bias is likely significant, albeit difficult to analyse because of inconsistent surveillance protocols.

Table 15. Attendance to follow-up as a prognostic factor for OS in univariable analysis. Studies were included if HR, or equivalent, and *P*-value were reported.[a]

Study	No. patients in the study	Variable	HR (95% CI)	*P*-value
Eskelin et al. 2003 [40]	91	Participation in annual review No Yes	 Reference 0.60 (0.36–1.07)	 0.084
Lorenzo et al. 2018 [82]	99	Metastasis diagnosis by surveillance testing[b] Yes No	 Reference 2.90[c] (1.04–8.04)	 0.037

[a] Not included in the table: did not report HR and *P*-value [41].

[b] The frequency of follow-up was not reported.

[c] Odds ratio.

2.4 STAGING SYSTEMS

Staging is universally recommended for prognostication, for research purposes, and to identify patients who may benefit from therapies [58]. The most common cancer classification system was developed by the International Union Against Cancer, the American Joint Committee on Cancer (AJCC), and the American College of Surgeons [117]. It is known as TNM classification, and it has been published since 1977, and for uveal melanoma since 1983 [118]. TNM staging is currently performed according to its 8th edition, published in Chicago, USA, and effective as of 2017.

Additionally, three dedicated staging systems have been developed to refine the prognostication of metastatic disease: 1) the Helsinki University Hospital Working Formulation (WF) in 2003, 2) the prognostic nomogram for metastatic uveal melanoma from the Veneto Oncology Institute and the Mayo Clinic in 2015, and 3) the recent prognostic nomogram for hepatic metastases of uveal melanoma from the Institut Curie in 2019 [21,40,111,119].

2.4.1 Tumor, Node, Metastasis staging

The current TNM classification for ciliary body and choroidal melanomas, the AJCC Staging Manual, 8th edition [67], is essentially identical to the 7th edition but is only validated as regards the primary tumour. The classification for the 7th edition was empirically derived from a collaborative database of 7,359 patients [120]. Furthermore, regarding the primary tumour, it was independently validated by a study of 3,217 patients [118] and is supported by several large single-centre studies [121,122].

The classification is based on the anatomical extent of the primary tumour (T), including the presence of regional lymph node metastases (N) and the presence of systemic metastases (M).

Primary ciliary body and choroidal melanomas are classified in categories T1a–T4d according to tumour size and involvement of the ciliary body and extrascleral tissues up to 5 mm in diameter [67,120]. In addition, T4 includes a subcategory for extrascleral extensions >5 mm in diameter (T4e).

These T-categories are combined to form stages—I, IIA–B, IIIA–C, and IV—that differ from one another in terms of survival [67]. Of ciliary body and choroidal melanomas, 21–32% are classified as stage I, 32–34% as stage IIA, 22–23% as stage IIB, 9–17% as stage IIIA, 3–7% as stage IIIB, 1% as stage IIIC, and 2% as stage IV [118,120]. Stage IV includes patients who either have invasion of regional lymph nodes or discrete tumour deposits in the orbit that are not contiguous to the eye or have distant metastases.

The invasion of regional lymph nodes—preauricular, submandibular, or cervical—and discrete tumour deposits in the orbit are denoted as N1-category and are rare [67].

Patients with metastases (M1) are categorised into subcategories M1a–M1c by the LDLM, where M1a denotes an LDLM ≤3 cm, M1b indicates an LDLM of 3.1–8.0 cm, and M1c classifies an LDLM ≥8 cm. The subcategories M1a–M1c correlate strongly with OS [67]. These subcategories are not used to create substages to stage IV.

Information on cytogenetic prognosticators, gene expression profiling, and molecular genetic prognosticators are not yet included in the AJCC staging system because they have only recently emerged, and the follow-up of patients with genetic data is short. A few studies have recently reported that AJCC staging can be supplemented with chromosome status [123,124] or gene expression profile status [125].

2.4.2 Helsinki University Hospital Working Formulation

The WF was the first substaging system to predict survival after metastatic uveal melanoma to improve the design, analysis, and reporting of trials [40,119]. The WF is based on a multivariable model—built with 91 patients by using Cox proportional hazards regression—that identified the Karnofsky index/ECOG performance status, LDLM, and serum or plasma AP level as independent predictors for survival [40]. The strongest prognostic factor in the WF was the LDLM, which was later incorporated into the 7th edition of the AJCC as the M1a–M1c subcategories [40,67]. Additionally, it was adjusted for time on chemotherapy.

The multivariable model is used to calculate individual predicted survival for newly diagnosed patients with metastatic uveal melanoma and to assign them to stages IVa, IVb, and IVc. These stages correspond to a predicted survival ≥12 months, <12 to 6 months, and <6 months after diagnosis of metastases, respectively.

The WF was validated by the European Ophthalmic Oncology Group (OOG) [119]. Members of the OOG from seven medical and ocular oncology services provided data of 249 consecutive patients who died of metastatic uveal melanoma. The diagnosis of metastases was based on autopsy, biopsy, or typical clinical course (progressive hepatic metastases in the absence of second cancer). One hundred and sixty-eight patients had received single-agent or combination chemotherapy; four patients had undergone chemoembolisation; six patients had received interferon (IFN) usually with tamoxifen; 11 patients had received BSC; 47 patients had undergone surgical resection with or without systemic therapy; nine patients had been immunised with tumour vaccine; and four patients had received various other treatments. Of the patients, 44%, 44%, and 12% were staged to IVa, IVb, and IVc, respectively. The corresponding median OS was 19, 11, and 4.6 months, respectively, and it shortened with an increasing stage ($P < 0.001$). The 12- and 24-month survival rates were 53% and 22%, respectively. The median OS of 47 patients with surgical resection was 28 months for stage IVa and 26 months for stage IVb, and only one patient in stage IVc survived 17 months ($P = 0.69$). The median OS of 201 patients without surgical resection was 17, 10, and 4.6 months ($P < 0.001$) for stage IVa, IVb, and IVc, respectively.

2.4.3 Staging nomograms

The first prognostic nomogram for disseminated uveal melanoma was built with the data of 152 patients from the prospective melanoma database at the Melanoma Oncology Unit of the Veneto Oncology Institute, Padova, Italy, and it was validated by a dataset from Mayo Clinic, Rochester, Minnesota, comprising 102 patients [111]. This nomogram includes LDH, DMFI, percentage of liver involvement, and ECOG performance status, and it predicts 6-, 12-, and 24-month survival. The 12- and 24-month survival rates for the building dataset were 63% and 35% and for the validation dataset 62% and 36%, respectively.

The second prognostic nomogram was modelled with the data of 224 patients from the Institut Curie, Paris, France [21]. The following four factors were selected for the nomogram: DMFI, the number of liver metastases, the area of the largest metastasis, and LDH. The nomogram predicts 6-, 12-, and 24-month survival, and the survival rates were 88%, 68%, and 26%, respectively.

2.4.4 Similarities and differences between staging systems for metastastic disease

The WF [40,119], Veneto-Mayo [111], and Curie [21] nomograms share components—the size of metastases [21,111,119], LFT [21,111,119], and performance status [111,119]—but these components are assessed differently.

The WF and the Veneto-Mayo nomogram are modelled regardless of metastatic site, whereas the Curie nomogram includes only patients with liver metastases, although concomitant extrahepatic disease is also allowed, and it requires that a liver MRI at the time of diagnosis of metastases is available.

The WF includes AP level because it displayed a stronger association with survival than LDH; however, the LDH level was known for <50% of patients, which possibly influenced the statistics. In the Veneto-Mayo nomogram, LDH was chosen over AP for the final model, although AP was also tested but omitted from the results. In the Curie nomogram, LDH was included, and AP was not analysed. LDH is also included in the TNM staging of cutaneous melanoma.

The liver involvement was measured as percentage of liver in the Veneto-Mayo nomogram, based on their hypothesis that it is the best indicator of the effective volume of hepatic disease. LDLM was analysed but left unreported. In the WF, the percentage of liver involvement was not reported, but LDLM was analysed and found to be at least as good as metastatic burden. The Curie nomogram analysed only the surface area of the largest metastasis, assuming that the total number of hepatic metastases is associated with the surface of the largest metastasis, leaving LDLM and the percentage of hepatic invasion unreported because the latter would 'be a time-consuming task'.

DMFI was analysed in the building dataset of the WF, but proved not to be an independent prognostic factor, whereas it was included in the other two systems.

According to my Scopus citation search on May 04, 2020, the Veneto-Mayo and Curie nomograms have not been applied to stage patients in any published article, and the WF has been used in three publications [107,126,127].

2.5 TREATMENT

2.5.1 National guidelines

There is no consensus on the treatment of metastatic uveal melanoma. Few national guidelines exist: those in Canada [57], France [59], the United Kingdom [58], Scotland [61], and the United States [60]. All of them are evidence-based, and none was developed based on an expert consensus only; however, in a recent systematic analysis of the guidelines [57,58,60] consistently poor values were achieved for the usability of the recommendations for clinical practice [128]. There is also no shared opinion on the best first-line treatment modality in the present guidelines.

2.5.2 Selection of endpoint in treatment trials

Several endpoints have been used in oncological clinical trials: OS, progression-free survival (PFS), and time to progression (TTP). OS is defined as the time from enrolment or treatment initiation 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 might be affected by subsequent therapies if such a treatment that affects the prognosis exists [129,130]. Importantly, OS possibly includes deaths due to other reasons, such as second synchronous cancer or other unrelated medical conditions [5].

PFS is defined as the time from randomisation until objective tumour progression or death from any cause, whichever occurs first [130]. PFS can be assessed earlier and with a smaller sample size than OS, and it is generally based on defined assessment criteria [131]. However, especially if not masked, it is potentially subject to assessment bias. The definition of PFS can also vary among studies, and frequent radiological or laboratory examinations are needed.

TTP is defined as the time from randomisation until objective tumour progression. It does not include deaths that are censored [130].

Both the United States' Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) require that the investigational product provides clinical benefit [130,132]. The FDA considers OS as the most reliable endpoint in cancer research, and PFS and TTP may support either regular or accelerated approval [129,130]. For the EMEA, acceptable primary endpoints include OS and PFS. If PFS is the selected primary endpoint, then OS should be reported as a secondary one [132]. From the patient's point of view, OS may be a more meaningful outcome than PFS or TTP [113].

2.5.3 Systemic therapy

2.5.3.1 Conventional chemotherapy

The chemotherapy regimens used for metastatic uveal melanoma are often adopted from protocols for cutaneous melanoma. Fifteen studies reported individual-level data on conventional chemotherapy (CHT) to treat metastatic uveal melanoma, including 411 patients, with five to 85 patients per study (Table 16). CHT was used as the control for another regimen in 33% of the studies [24,25,133-135].

Chemotherapy agents included dacarbazine, temozolomide, fotemustine, and docosahexaenoic acid–paclitaxel, as well as combinations of gemcitabine and treosulfan; temozolomide and bevacizumab (anti-vascular endothelial growth factor); cisplatin, dacarbazine, and vinblastine; and gemcitabine, treosulfan, and cisplatin. No less than 10 studies were prospective—two of them randomised ones, and one being a large multicentre randomised trial of the EORTC that used fotemustine intravenously in one arm [24]. Fostemustine is selectively absorbed by the liver and not registered in Finland where a combination of temozolomide, lomustine, and vincristine was typically chosen in the 2010s [136,137].

The reported median OS ranged from 4.6 to 17.0 months, and none of the studies applied staging, although a prospective study tabulated the parameters needed for staging by the WF [138].

Table 16. Studies of CHT with individual-level survival data. The search was conducted in PubMed with the following string: (uveal melanoma OR choroidal melanoma OR ciliary body melanoma OR ciliochoroidal melanoma OR iridociliary melanoma OR iris melanoma OR intraocular melanoma OR ocular melanoma) AND (metast* OR stage IV) AND (treatment) AND ('1980/01/01' [PDAT] : '2020/01/01' [PDAT]) for Tables 16–27. The table is strongly modified from [139] by Creative Commons Attribution License 4.0 (CC-BY-4.0). OS definition in the ninth column of the table reports whether either the date of diagnosis of the metastases, the enrolment, or the start of treatment was defined as the start-point for OS. Country codes are found at the end of the list of abbreviations in Chapter *Abbreviations*.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Temozolomide	Bol [133]	2019	Retrospective case series	32	32 (100%)	0 (0%)	NR	Treatment	5.7	NL
Dacarbazine	Carling [134]	2015	Retrospective CCS	14	NR	NR	2.5 (0.6-4.7)	Treatment	4.6	NO
Dacarbazine	Carvajal [25]	2018	Prospective randomised trial phase III (SUMIT)	32	NR	NR[a]	NR	Enrolment	NR; 8.6[b]	USA, FR, NL, IL, CA, SP, BE, UK, DE
Gemcitabine + treosulfan	Corrie [140]	2005	Prospective NRCS phase I	5	4 (80%)	0 (0%)	NR	NR	12.2	UK
Docosahexaenoic acid-paclitaxel	Homsi [141]	2010	Prospective NRCS phase II, open label	22	13 (59%) NC	NR	NR	Enrolment	9.8	USA
Fotemustine	Leyvraz [24]	2014	Prospective randomised trial EORTC multicentre	85	85 (100%)	0 (0%)	NR	Enrolment	13.8 (10.2–17.2)	CH, FR, BE, PL, IT, UK, DE
Temozolomide or dacarbazine	Luke [135]	2020	Prospective randomised phase II trial	15	0 (0%)	NR[c]	NR	Treatment	7.2 (5.6–ND)	USA
Multiple[d]	Nicholas [85]	2018	Retrospective case series	35	35 (100%)	0 (0%)	NR	Diagnosis	9.4 (6.0–13.3)	CA
Gemcitabine + treosulfan	Pföhler [142]	2003	Retrospective case series	14	1 (7%)	0 (0%)	NR	Enrolment	14 (12–31)	UK, DE

Table 16 cont.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Temozolomide + bevacizumab	Piperno-Neumann [143]	2016	Prospective trial phase II	35	35 (100%)	0 (0%)	NR	Treatment	10 (8–15)	FR
Multiple[e]	Pons [103]	2011	Retrospective CCS	25	0 (0%)	0 (0%)	NR	NR	10.83 (5.35–16.30)	PT, SP
Cisplatin + dacarbazine + vinblastine	Schinzari [144]	2017	Prospective NRCS phase II	25	25 (100%)	0 (0%)	NR	Treatment	13.0	IT
Gemcitabine + treosulfan + cisplatin	Schmittel [145]	2005	Prospective NRCS phase II	19	19 (100%) NC	NR	NR	Treatment	7.7 (1.9–13.8)	DE
Gemcitabine + treosulfan 2500 or 3000 mg/m^2	Schmittel [146]	2005	Prospective NRCS phase II	14	12 (86%) NC	NR	NR	Treatment	6.0 (4–8)	DE
Gemcitabine + treosulfan 3500 or 4000 mg/m^2				19	16 (84%) NC	NR	NR	Treatment	9.0 (0–18)	
Gemcitabine + treosulfan	Terheyden [138]	2004	Prospective NRCS phase II	20	8 (40%)	0 (0%)	NR	Treatment	NR; 17.0 (9.0–31.0)[f]	DE

[a] No systemic anticancer therapy, but prior surgery and intrahepatic or other non-systemic therapies were permitted.

[b] Approximated from the provided Kaplan-Meier graph.

[c] All patients had undergone prior surgery or radiation.

[d] Carboplatin and paclitaxel, dacarbazine, temozolomide, and the Dartmouth Protocol: dacarbazine, cisplatin, carmustine, and tamoxifen. Due to multiple different therapies, the patients were included in the CHT group, but they could not be organised under a specific chemotherapy agent.

[e] Thirteen patients received dacarbazine, five received temozolomide with or without interferon, five received fotemustine, and two received carboplatin/dacarbazine/interferon-alpha/interleukin (IL)-2. Due to multiple different therapies, the patients were included in the CHT group; however, they could not be organised under a specific chemotherapy agent.

[f] No OS reported; digitised Kaplan-Meier estimate.

2.5.3.2 Chemoimmunotherapy with interferon or interleukin

Six studies reported individual-level data on chemoimmunotherapy with IFN or IL (CIT), including 107 patients, with three to 48 patients per study (Table 17). The median OS ranged from 3.7 to 41 months. Three of the studies were conducted in Finland and were the only ones that applied staging of metastases [107,126,127]. The EORTC phase II study with bleomycin, vincristine, lomustine, and dacarbazine (BOLD) with IFN was conducted to confirm the reported response rate of 15–20% [126,147]; however, it suggested no major benefit in OS [107].

Table 17. Studies of CIT with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Fotemustine IA/IV + IL2+ IFN-alpha2	Becker [148]	2002	Prospective NRCS	48	NR	NR	NR	Treatment	12 (11.4–12.8)	DE
BOLD + IFN-alpha2b	Kivelä [107]	2003	Prospective non-randomised trial phase II EORTC multicentre	24	24 (100%)	0 (0%)	NR	Treatment	10.6 (6.9–16.4)	FI, SE, DE, NL, BE, UK
BOLD + leucocyte IFN	Pyrhönen [126]	2002	Prospective non-randomised trial phase II	22	18 (82%)	0 (0%)	NR	Treatment	12 (8–22)	FI
Thalidomide + IFN-alpha2b	Solti [149]	2007	Prospective NRCS pilot study	6	0 (0%)	NR	NR	Treatment	NR; 3.7 (0.9–ND)[a]	USA
Fotemustine IV + IL2 + IFN-alpha2b	Terheyden [150]	1998	Retrospective case series	3	3 (100%)	0 (0%)	2 (2–4)	Treatment	NR; 41.0 (10.0–ND)[a]	DE
Dacarbazine + IFN- alpha2a + bevacizumab	Vihinen [127]	2010	Prospective trial phase II	4	4 (100%)	0 (0%)	NR	Treatment	NR; 10.8 (6.5–ND)[a]	FI

[a] No OS reported; digitised Kaplan-Meier estimate.

2.5.3.3 Immunotherapy

Immunotherapy boosts the immune system with the aim of destroying the cancer cells. Twenty-one publications incorporating 704 patients, with five to 83 patients per study, evaluated anti-cytotoxic T-lymphocyte associated protein (CTLA)-4, anti-programmed cell death (PD)-1, anti-programmed cell death ligand-1 (PD-L1), immune-mobilising monoclonal T-cell receptor against cancer (ImmTAC) platform, or dendritic cell vaccine (Table 18). Anti-CTLA-4 antibodies included ipilimumab with 275 patients, the largest number of patients, and tremelimumab. Anti-PD-1 antibodies included nivolumab and pembrolizumab, while the anti-PD-L1 antibodies tested were atezolizumab and avelumab. The combination of ipilimumab and nivolumab was administered to 27 patients, ipilimumab and pembrolizumab to nine patients, and ipilimumab and nivolumab or pembrolizumab to 79 patients. Tefentafusp and vaccine were tested in 14 patients each. Ten studies were prospective, and none were randomised; 42% were first-line treatments; none were staged; and the median OS ranged from 4.6 to 20 months for all studies. For combined ipilimumab + anti-PD-1 or PD-L1 treatments, the median OS ranged from 14 to 19 months [151-155], and only one of these studies concerned a first-line treatment [151]. While most patients do not seem to benefit from immunotherapies, evidence has recently emerged that molecular targeted immunotherapy might benefit a small subset of patients who carry an *MBD4* mutation [33,156].

Table 18. Studies of immunotherapy with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Pembrolizumab or nivolumab or atezolizumab	Algazi [157]	2016	Retrospective case series	56	8 (14%)	0 (0%)	NR	Treatment	7.7 (0.7–14.6)	USA, SP
Dendritic cell vaccine	Bol [158]	2014	Prospective NRCS	14	8 (57%)	3 (21%)	NR	Treatment	19.2	NL, DE
Ipilimumab or pembrolizumab or combined ipilimumab + nivolumab	Bol [133]	2019	Retrospective case series	24 43 19	24 (100%) 43 (100%) 19 (100%)	0 (0%)	NR	Treatment	9.9 10.3 18.9	NL
Ipilimumab	Danielli [159]	2012	Prospective NRCS	13	0 (0%)	NR	NR	Treatment	8.3	IT, UK
Ipilimumab + nivolumab or pembrolizumab	Heppt [152]	2019	Retrospective multicentre case series	64	50 (78%)	31 (48%)	NR	Treatment	16.1 (12.9–19.3)	DE
Pembrolizumab Nivolumab Ipilimumab + nivolumab or pembrolizumab	Heppt [154]	2017	Retrospective multicentre case series	54 32 15	35 (65%) 23 (72%) 6 (40%)	} 9 (10%) 2 (13%)	NR	Treatment	14.0 10.0 Not reached[a]	DE
Pembrolizumab	Johnson [156]	2019	Prospective trial phase II	5	3 (60%)	0 (0%)	NR	Treatment	Not reached[b]	USA
Tremelimumab	Joshua [160]	2015	Prospective trial phase II	11	NR[c]	3 (27%)	NR	Enrolment	12.8 (3.8–19.7)	CA
Ipilimumab + nivolumab	Karivedu [153]	2019	Retrospective case series	8	4 (50%)	2 (25%)	NR	Treatment	14.2	USA
Pembrolizumab	Karydis [161]	2016	Retrospective case series	25	0 (0%)	3 (12%)	11.3 (3.7–65.1)	Treatment	NR; 9.5 (5.0–14.1)[d]	UK
Avelumab	Keilholz [162]	2019	Prospective trial phase Ib	16	NR	NR	NR	Treatment	Not reached (3.6–ND)	DE
Ipilimumab	Kelderman [163]	2013	Retrospective case series, WIN-O	22	0 (0%)	NR	NR	Treatment	5.2; 4.6 (2.3–10.8)[e]	NL

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Ipilimumab + pembrolizumab	Kirchberger [155]	2018	Retrospective case series	9	1 (11%)	0 (0%)	NR	Treatment	18.4	DE
Nivolumab or pembrolizumab	van der Kooij [164]	2017	Retrospective case series	17	8 (47%)	NR	NR	Treatment	8.8	NL
Ipilimumab	Luke [165]	2013	Retrospective case series	39	0 (0%)	NR	NR	Treatment	9.6 (6.3–13.4)	USA, CH
Ipilimumab	Maio [166]	2013	Prospective NRCS	83[f]	0 (0%)	NR	NR	NR	6.0 (4.3–7.7)	IT
Multiple[g]	Nicholas [85]	2018	Retrospective case series	6	6 (100%)	0 (0%)	NR	Diagnosis	19.5 (8.0–47.1)	CA, UK, AU
Pembrolizumab	Rossi [167]	2019	Prospective NRCS	16	12 (75%)	4 (25%)	NR	Treatment	Not reached[h]	IT
Ipilimumab	Rozeman [168]	2019	Prospective phase Ib/II	41	41 (100%)	0 (0%)[i]	NR	Enrolment	12.4	NL
Tefentafusp	Sato [169]	2018	Prospective NRCS phase I/II	19	NR[j]	NR	NR	Treatment	Not reached, follow-up 15.9[k]	USA
Ipilimumab	Zimmer [170]	2015	Prospective trial phase II	53	8 (15%)	NR	NR	Treatment	6.8 (3.7–8.1)	DE

[a] Median follow-up was 3.9 months for patients who died and 3.3 months for those who stayed alive.
[b] Median overall survival was not reached (median follow-up: 11.1 months; range, 0.4–25.5 months).
[c] Three patients had undergone surgery, three palliative radiation therapy, one transarterial chemoembolisation (TACE), and three systemic chemotherapy.
[d] No OS reported; digitised Kaplan-Meier estimate.
[e] The reported median survival of 5.2 months appears to be arithmetically calculated and not a Kaplan-Meier estimate; therefore, the digitised Kaplan-Meier estimate of 4.6 months is also reported.
[f] Of 83 patients, 1 was lost in follow-up, and in the Kaplan-Meier plot, 82 patients are depicted.
[g] Anti-CTLA-4, anti-PD-L1, and dacarbazine with anti-CTLA-4.
[h] The median OS of the entire cohort was not reached. The OS for patients with clinical benefit and for patients with progression was 12.8 months and 3.1 months, respectively.
[i] All patients underwent radiofrequency ablation of one liver lesion on Day 1 and subsequently received four courses of ipilimumab every 3 weeks in a 3 + 3 design.
[j] Median of four prior therapies (0–8).
[k] One-year OS rate of 74% in phase I; the median OS has not been reached (median follow up of 15.9 months).

2.5.3.4 Targeted therapy

In 11 studies, 294 patients (eight to 97 patients per study) received targeted therapy (Table 19). The drugs included imatinib, sorafenib, sunitinib, cabozantinib, selumetinib, and ganetespib, and in three studies, they were combined with a conventional chemotherapeutic agent. Nine studies were prospective, and three of them were randomised. Targeted therapy was applied as the first-line treatment in 28% of the patients, and the median OS ranged from 6.3 to 16 months. Furthermore, the SUMIT trial—the first-ever clinical trial in metastatic uveal melanoma designed to register a drug with a regulatory body—tested selumetinib in combination with dacarbazine; however, it failed to document improved outcomes [25,171]. Immunotherapy and targeted therapy have revolutionised the treatment of metastatic cutaneous melanoma, but in metastatic uveal melanoma, their effect is limited, probably due to the lower mutational load and different driver mutations [101,172,173], and although c-KIT is often expressed in uveal melanoma, it does not translate into clinical efficacy of imatinib [174].

Table 19. Studies of targeted therapy with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Sorafenib + carboplatin + paclitaxel	Bhatia [175]	2012	Prospective trial phase II	24	20 (83%)	NR	NR	Enrolment	11 (7–14)	USA
Selumetinib + dacarbazine	Carvajal [25]	2018	Prospective randomised double-blind trial phase III (SUMIT)	97	NR	NR[a]	NR	Enrolment	10.1[b]	USA, FR, NL, IL, CA, SP, BE, UK, DE
Cabozantinib	Daud [28]	2017	Prospective randomised discontinuation trial	23	NR[c]	NR	NR	Treatment	12.6	USA, IL, BE
Imatinib	Hofmann [174]	2009	Prospective NRCS	12	8 (67%)	NR	NR	Treatment	6.8; 5.5 (2.6–8.7)[d]	DE
Cabozantinib	Luke [135]	2020	Prospective randomised phase II trial	31	0 (0%)	NR[e]	NR	Treatment	6.3 (5.5–10.3)	USA
Sunitinib	Mahipal [176]	2012	Prospective NRCS pilot study	20	3 (15%)	3 (15%)	NR	Treatment	8.2	USA
Sorafenib	Mouriaux [177]	2016	Prospective trial phase II	32	19 (59%)	0 (0%)	NR	Treatment	NR; 7.8 (4.3–11.4)[f]	FR, CA
Multiple[g]	Nicholas [85]	2018	Retrospective case series	17	17 (100%)	0 (0%)	NR	Diagnosis	15.5 (6.9–35.6)	CA, UK, AU
Sorafenib + fotemustine	Niederkorn [178]	2014	Retrospective case series	8	2 (25%)	NR	NR	Treatment	15.9	AT
Imatinib mesylate	Penel [179]	2008	Prospective trial phase II	13	6 (46%)	0 (0%)	NR	Treatment	10.8	FR
Ganetespib	Shah [180]	2018	Prospective trial phase II	17	7 (41%)	NR	NR	Treatment	7.0	USA

[a] No systemic anticancer therapy, but prior surgery and intrahepatic or other non-systemic therapies were permitted.
[b] Approximated from the provided Kaplan-Meier graph.
[c] Reported for all patients, not specifically for uveal melanoma patients.
[d] The reported median survival of 6.8 months appears to correspond to mean survival [(1.59 + 2.62 + 3.60 + 4.57 + 4.57 + 5.55 + 5.67 + 6.59 + 6.65 + 8.66 + 10.73 + 20.73)/12 = 6.8 months, from the digitised Kaplan-Meier plot]; the digitised Kaplan-Meier estimate is 5.5 months.
[e] All patients had undergone prior surgery or radiation.
[f] No OS reported; digitised Kaplan-Meier estimate.
[g] Targeted treatment included the following: anti-HDAC, multitargeted receptor tyrosine kinase inhibitor, MEK inhibitors, dacarbazine with MEK inhibitor, and tyrosine kinase inhibitor with stereotactic body radiation therapy.

2.5.3.5 Immunosuppressant

A total of 14 patients were analysed in a prospective non-randomised phase II trial with a median OS of 11 months (Table 20). The used immunosuppressant was everolimus combined with pasireotide.

Table 20. Studies of immunosuppressants with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Everolimus + pasireotide	Shoushtari [181]	2016	Prospective trial phase II	14	0 (0%)	NR	NR	Treatment	11	USA

2.5.4 Local therapy

2.5.4.1 Surgical resection

Local therapies, especially radical surgical resection (R0) is considered the best treatment whenever possible, while chemotherapy is recommended if a patient is not eligible for local therapies [107]. Regrettably, the number of patients eligible for local therapies is limited because of diffuse disease burden or poor overall performance status [11,182]. Eleven studies reported the results of surgical resection incorporating 528 patients, with five to 157 per study (Table 21). The median OS ranged from 11 to 90 months and was prolonged if the resection was more complete. Although a complete resection is preferred, only 25–50% of the patients underwent a radical resection [19,52,104,183,184]. Surgical resection was applied to metastases located in the liver, lung, stomach, bone, adrenals, and lymph nodes. Of the patients with liver metastases, 6–44% underwent metastatic debulking [11,52,104,184,185]. In a Dutch nationwide study, 22% of the patients with metastatic uveal melanoma received local treatment regimens [86].

Table 21. Studies of surgical resection with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Resection	Aoyama [182]	2000	Retrospective case series	12	8 (67%)	0 (0%)	NR	Treatment	NR; 27 (23–ND)[a]	USA
Resection[b] R0 R1/R2	Frenkel [184]	2009	Retrospective CCS	 14 23	 NR NR	 0 (0%) 0 (0%)	 NR NR	 Diagnosis Diagnosis	 NR; 65.2 (11.2–ND)[a] NR; 16.3 (7.6–25.3)[a]	GR
Resection[c]	Gomez [11]	2014	Retrospective CCS	18	NR	NR	NR	Treatment	27	UK
Resection	Hsueh [185]	2004	Retrospective CCS	24	NR[d]	NR	NR	Diagnosis	38	USA
Resection + fotemustine IA or cisplatin IA R0 R2[e]	Kodjikian [104] / Rivoire [19]	2005	Retrospective CCS	 14 14	 14 (100%) 14 (100%)	 0 (0%) 0 (0%)	 NR NR	 Treatment Treatment	 25 16	FR
Resection Resection + RFA	Mariani [53]	2016	Retrospective CCS	57 13	57 (100%) 13 (100%)	0 (0%) 0 (0%)	NR NR	Treatment Treatment	27 28	FR
Resection[f] R0 R1 R2	Mariani [52]	2009	Retrospective comparative case series	 76 22 157	 76 (100%) 22 (100%) 157 (100%)	 0 (0%) 0 (0%) 0 (0%)	 NR NR NR	 Treatment Treatment Treatment	 27 17 11	FR
Resection	Nicholas [85]	2018	Retrospective case series	12	12 (100%)	0 (0%)	NR	Diagnosis	82.4 (15.6–ND)	CA, UK, AU

Table 21 cont.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Resection + fotemustine IA or dacarbazine IA + cisplatin IA	Salmon [183]	1998	Prospective non-randomised comparative case series							FR
Curative resection				19	19 (100%)	0 (0%)	NR	NR	22	
Tumour reduction				34	34 (100%)	0 (0%)	NR	NR	NR; 8.1 (5.3–10.1)[a]	
Resection, R0[g]	Servois [186]	2019	Retrospective case series	14	14 (100%)	0 (0%)	NR	Diagnosis	90[h]	FR
Resection, partial[i]	Yang [187]	2013	Retrospective case series	5	NR	NR	NR	Treatment	11.5 (7.5–15.8)	CN

[a] No OS reported; digitised Kaplan-Meier estimate.

[b] The authors state, 'Some patients received chemotherapy intravenously or through an intra-arterial hepatic port, and some received adjuvant immunotherapy'.

[c] One radiofrequency ablation (RFA).

[d] Of 112 treatments, 13 were first-line, but the numbers are not reported separately for the 24 patients who underwent surgery; in addition, some resections were combined with immunotherapy, systemic chemotherapy, and hepatic perfusion.

[e] Three patients received no chemotherapy.

[f] The authors state, 'Postoperative chemotherapy was mandated in every patient during the first years of our experience, but since 2005 has been reserved for randomised patients in the intra-arterial arm of the European trial'; in addition, eight patients underwent RFA during laparotomy to attain R0 resection.

[g] After R0 resection, all patients relapsed and underwent RFA (10 patients) or RFA + metastasectomy (four patients).

[h] Survival at 5 years was 0.70 (range, 0.49–1.0), and at 10 years, it was 0.35 (range, 0.13–0.92); 90 months is approximated from the Kaplan-Meier graph.

[i] Of the five patients, two received adjuvant therapy with TACE with or without immunotherapy.

2.5.4.2 Hepatic intra-arterial chemotherapy

Liver metastases obtain their blood supply primarily via the hepatic artery, and the normal liver tissue obtains its supply via the portal vein, allowing the chemotherapeutic agent to be delivered selectively to the cancer cells via the hepatic artery. Eleven studies evaluated hepatic intra-arterial chemotherapy (HIA) in 370 patients, with seven to 101 patients per study (Table 22). Five studies were prospective, with one randomised controlled trial. The chemotherapeutic agents included predominantly fotemustine and melphalan, but carboplatin; and combinations of cisplatin, vinblastine, and dacarbazine were also applied. The EORTC multicentre randomised controlled trial with 86 patients in the HIA arm found no difference in OS between intravenous and intra-arterial fotemustine [24]. The median OS ranged from 2.9 to 22 months.

Table 22. Studies of HIA with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Melphalan	Boone [188]	2018	Retrospective case series	14	4 (29%)	NR	NR	Treatment	2.9	USA
Carboplatin	Cantore [189]	1994	Prospective NRCS phase II	8	5 (63%)	NR	NR	Treatment	12.0 (7.0–20.0); 15[a]	IT
Fotemustine	Egerer [190]	2001	Prospective NRCS pilot study	7	5 (71%)	0 (0%)	2 (1–10)	Treatment	18[b]; 20.0 (3.0–ND)	DE
Fotemustine or carboplatin	Farolfi [191]	2011	Retrospective case series	18	NR[c]	NR	NR	Treatment	21 (8–39)	IT
Melphalan	Heusner [192]	2011	Retrospective CCS	38	For all: 43 (70%) NC	NR	3.3 (0.5–2), mean	Treatment	10.3 (5.01–15.59)	DE
Melphalan and additional agents[d]				23		NR			8.7 (8.07–9.32)	
Fotemustine	Leyvraz [24]	2014	Prospective randomised trial EORTC multicentre	86	86 (100%)	0 (0%)	NR	Enrolment	14.6 (10.2–15.4)	CH, FR, BE, PL, IT, UK, DE
Fotemustine	Leyvraz [64]	1997	Prospective NRCS	31	31 (100%) NC	NR	NR	Diagnosis	14	CH
Cisplatin + vinblastine + dacarbazine	Melichar [193]	2009	Retrospective case series	10	7 (70%)	0 (0%)	1.4 (0.5–9.5)	Treatment	16	CZ
Fotemustine or dacarbazine + cisplatin, after biopsy[e]	Salmon [183]	1998	Prospective non-randomised comparative case series	16	16 (100%)	0 (0%)	NR	NR	NR; 6.2 (1.0–10.1)[f]	FR

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Fotemustine	Siegel [194]	2007	Retrospective case series	18	NR	0 (0%)	2 (6–63)	Treatment	22	DE
Fotemustine[g]	Peters [195]	2006	Retrospective case series	101	101 (100%) NC	39 (39%)[h]	1.9 (0.1–45)	Diagnosis	15 (12.1–17.6)	CH, IT, IL, DE, BE, FR

[a] The median survival is 12 months when calculated from Table 1 in the original article; the reported median survival of 15 months appears to correspond to mean survival [(7 + 8 + 8 + 12 + 16 + 18 + 20 + 29)/8=15 months].

[b] The reported median survival of 18 months appears to be arithmetically calculated and not a Kaplan-Meier estimate; 20.0 months is a digitised Kaplan-Meier estimate.

[c] Reported for all patients, not specifically for uveal melanoma patients.

[d] Dacarbazine, doxorubicin, fotemustine, gemcitabine, and mitomycin (MMC).

[e] Patients received fotemustine or dacarbazine for at least two months and cisplatin after biopsy.

[f] No OS reported; digitised Kaplan-Meier estimate.

[g] In addition, 38 patients underwent debulking surgery at the time of catheter placement. In the Kaplan-Meier plot, 100 patients were depicted.

[h] As prior treatment, 39 patients had undergone surgery; the prior treatment of 11 patients was unknown.

2.5.4.3 Transarterial chemoembolisation

In transarterial chemoembolisation (TACE), the blood supply of the tumour from the hepatic artery is cut off, and a chemotherapeutic agent is then trapped within the tumour. While a gelatin sponge was the most common material used to cut off the blood supply, polyvinyl alcohol particles, starch microspheres, and drug-eluting beads were also used. Sixteen studies reported on 522 patients (10 to 125 per study), and none were staged (Table 23). Six studies were prospective, with a maximum of 30 patients, and two of them were randomised. The most commonly used chemotherapeutic agents included cisplatin and fotemustine. The oldest study that the whole search strategy caught involved TACE [196]. The median OS ranged from 5.1 to 28.8 months.

Table 23. Studies of TACE with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Cisplatin w/wo polyvinyl sponge[a]	Agarwala [27]	2004	Prospective randomised trial phase I/II	19	13 (68%)	0 (0%)	NR	NR	8.5	USA
Irinotecan-eluting beads	Carling [134]	2015	Retrospective CCS	14	11 (79%)	1 (7%)	4.1 (1.2–12.7)	Treatment	9.4	NO
Cisplatin + doxorubicin + MMC + gelatin sponge	Dayani [197]	2009	Retrospective case series	21	17 (81%)	1 (5%)	NR	Treatment	NR; 5.1 (3.3–8.2)[b]	USA
Fotemustine + polyvinyl alcohol particles	Edelhauser [198]	2012	Retrospective case series	21	2 (10%)	0 (0%)	NR	Diagnosis	NR; 28.8 (9.9–ND)[b]	AT
Irinotecan-eluting beads	Fiorentini [199]	2009	Prospective trial phase II	10	0 (0%)	0 (0%)	44 (24–84)	Treatment	NR[c]	IT
BCNU + gelatin sponge	Gonsalves [200]	2015	Retrospective case series	50[d]	50 (100%)	0 (0%)	NR	Treatment	7.1	USA
Cisplatin[e] + gelatin sponge or polyvinyl alcohol particles	Gupta [201]	2010	Retrospective case series	125	82 (66%)	NR	7 (1–122), mean	Treatment	6.7 (4.9–8.5)	USA
Cisplatin or carboplatin + polyvinyl alcohol particles	Huppert [202]	2010	Prospective NRCS pilot study	14	8 (57%)	1 (7%)	4.5 (1–38)	Treatment	11.5	DE
Fostemustine[f]	Itchins	2017	Retrospective case series	37	34 (92%)	3 (8%)	2.3 (0–12.9)	Diagnosis	17.0 (12–26)	IT, NZ
Cisplatin + polyvinyl sponge	Mavligit [196]	1988	Retrospective case series	30	19 (63%)	0 (0%)	NR	Diagnosis	11 (9–18)	USA
BCNU + gelatin sponge	Patel [203]	2005	Prospective trial phase II	30	24 (80%)	0 (0%)	NR	Treatment	5.2	USA
Fotemustine or cisplatin + starch microspheres	Schuster [204]	2010	Retrospective case series	25	0 (0%)	NR	9 (2–24)	Treatment	6 (5–7)	DE

Table 23 cont.

Cisplatin + gelatin sponge	Shibayama [205]	2017	Retrospective case series	29	27 (93%)	1 (3%)	NR	Treatment	23	JP
CPT-11 charged microbeads	Valpione [206]	2015	Retrospective CCS	58[g]	58 (100%)	0 (0%)	NR	Treatment	15.5	IT
Bland embolisation + gelatin sponge	Valsecchi [26]	2015	Prospective randomised trial phase II	27	NR	NR	NR	Treatment	17.2 (11.9–22.4)	USA
MMC + iodised oil + microspheres	Vogl [207]	2007	Prospective NRCS pilot study	12	0 (0%)	4 (33%)	NR	Treatment	21	DE

[a] Of 19 patients, 10 were treated with TACE.

[b] No OS reported; digitised Kaplan-Meier estimate.

[c] The median overall survival was not reached; that is, the cumulative survival plot did not fall below 50%.

[d] Fifty patients met the inclusion criteria, but 49 were included in the Kaplan-Meier analysis.

[e] Two patients additionally received paclitaxel, and one patient received doxorubicin + MMC.

[f] Eleven patients received only TACE, while 19 received TACE and immunotherapy, and eight received only immunotherapy because they died before TACE.

[g] In addition, 49 patients received intravenous fotemustine 3 weeks after TACE.

2.5.4.4 Immunoembolisation

The two studies that included patient-level survival data on immunoembolisation (IE) incorporated embolisation of the hepatic artery with granulocyte-macrophage colony stimulating factor (GM-CSF) instead of a cytotoxic agent. Both were of a prospective nature—a phase I and a phase II study—including 59 patients with a median OS of 14 and 22 months (Table 24).

Table 24. Studies of IE with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Immuno-embolisation with GM-CSF	Sato [208]	2008	Prospective trial phase I	34	28 (82%)	3 (9%)	NR	Treatment	14.4[a]	USA
Immuno-embolisation with GM-CSF	Valsecchi [26]	2015	Prospective randomised double-blind trial phase II	25	NR	NR	NR	Treatment	21.5 (18.5–24.8)	USA

[a] The median OS is reported for 34 patients in intent-to-treat analysis, whereas the Kaplan-Meier plot includes 31 radiographically assessable patients.

2.5.4.5 Isolated hepatic perfusion

In isolated hepatic perfusion (IHP), the liver is temporarily isolated from the blood circulation and perfused with high doses of a chemotherapeutic agent. The by-passing of the liver is achieved by placing a catheter into the hepatic artery and another catheter into the vein that drains blood from the liver. IHP, whether open or percutaneous, is a complex procedure, and although it has been under clinical investigation for six decades, its application has been limited because of high morbidity and mortality [209,210]. A Swedish study reported a 1-month mortality of 7%, but recently, with refinement of the technique and patient selection, the rate decreased to 2% [211,212]. Nine studies from seven research groups included a total of 266 patients, with three to 61 patients per study (Table 25). Two of the studies were prospective, and none were randomised. The chemotherapeutic agent that was utilised was melphalan with or without tumour necrosis factor (TNF)-α or oxaliplatin. The median OS ranged from 9.6 to 27 months.

Table 25. Studies of IHP with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Melphalan	Alexander [213]	2003	Prospective trial phase I/II	29	22 (76%)	0 (0%)	NR	Enrolment	12.1	USA
Melphalan	Artzner [214]	2019	Retrospective case series	16	8 (50%)	1 (6%)	NR	Treatment	27.4 (3.4–27.4)	DE
Melphalan w/wo TNF-alpha or cisplatin	Ben-Shabat [211]	2016	Retrospective case series	61	Majority	A few	NR	Treatment	22.4	SE
Melphalan with buffer without buffer	Ben-Shabat [212]	2017	Retrospective case series	36 16	36 (100%) 16 (100%)	0 (0%) 0 (0%)	NR NR	Treatment	24.2 26.0	SE
Melphalan	de Leede [215]	2016	Retrospective case series	31	27 (87%)	0 (0%)	2.3 (0.9–13.3)	Treatment	10	NL
Melphalan	Forster [216]	2014	Retrospective case series	5	4 (80%)	0 (0%)	NR	Treatment	NR; 14.2 (10.0–ND)[a]	USA
Oxaliplatin + melphalan	van Iersel [217]	2014	Prospective trial phase I	3	2 (67%)	0 (0%)	NR	Treatment	NR; 18.7 (7.8–ND)[a]	NL
Melphalan	Karydis [218]	2018	Retrospective case series	51	NR	9 (18%)	NR	Treatment	15.3	UK, USA
Melphalan	Vogl [219]	2017	Retrospective case series	18	7 (39)	5 (28)	NR	Treatment	9.6	DE

[a] No OS reported; digitised Kaplan-Meier estimate.

2.5.4.6 Selective internal radiation therapy

In selective internal radiation therapy (SIRT), microspheres composed of resin or glass particles bound to yttrium-90, which is a high-energy beta-emitting isotope, are implanted into the hepatic arterial circulation. The resin bead microspheres are small enough to enter the tumour circulation and emit radiation that destroys cancer cells but too large to enter capillaries and spread to the lungs, which must be tested before treatment on a patient level. Six studies evaluated SIRT incorporating 124 patients, with eight to 50 patients

per study (Table 26). No prospective studies have been published on SIRT. The median OS ranged from 2.8 to 19 months. In a nationwide Finnish study, 18 patients without extrahepatic metastases and ineligible for surgical resection received SIRT as a first-line or salvage therapy, and the median OS after SIRT was 2 months longer than for the historical chemotherapy group (P = 0.047); moreover, the procedure was well tolerated. In recent years, SIRT has become the primary local treatment modality of liver metastases not eligible for surgical resection in Finland [51,136].

Table 26. Studies of SIRT with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
SIRT, ^{90}Y resin microspheres	Eldredge-Hindy [220]	2016	Retrospective case series	50	13 (18%) [a]	NR	9.8	Treatment	NR; 14.9 (9.7–17.2)[b]	USA
SIRT, ^{90}Y resin microspheres	Klingenstein [221]	2013	Retrospective case series	13	2 (15%)	1 (8%)	5 (1–49)	Treatment	7	DE
SIRT, ^{90}Y resin microspheres[c]	Levey [222]	2019	Retrospective case series	24	22 (92%)	1 (4%)	NR	Treatment	18.6 (14.3–46.6)	USA
SIRT, ^{90}Y glass microspheres	Schelhorn [223]	2015	Retrospective case series	8	0 (0%)	0 (0%)	17.1 (6.4–23.2)	Treatment	2.8	DE
SIRT, ^{90}Y resin microspheres	Tulokas [51]	2018	Retrospective case series	18	14 (78%)	0 (0%)	NR	Treatment	13.5 (3.6–44.8)	FI
SIRT, ^{90}Y resin microspheres[c]	Zheng [224]	2018	Retrospective case series	11	2 (18%)	0 (0%)	9.0 (2.0–37.5)	Treatment	17.0 (1.8–32.2)	USA, CN

[a] Prior treatment reported for all 58 patients, and not specifically for the 50 patients who had a pre-treatment PET-CT and were included in the Kaplan-Meier plot.

[b] No OS reported; digitised Kaplan-Meier estimate.

[c] TARE, Transarterial radioembolisation.

2.5.4.7 Liver-directed thermotherapy

Thermal destruction of liver metastasis is induced by stereotactic radiofrequency ablation (RFA) and laser-induced thermotherapy. Two studies evaluated the use of liver-directed thermotherapy in uveal melanoma hepatic metastases incorporating 25 patients (Table 27). The reported OS ranged from 29 to 38 months, and both studies were retrospective.

Table 27. Studies of liver-directed thermotherapy with individual-level survival data.

Intervention	Study	Year	Study design	No. patients with uveal melanoma	No. patients who received first-line treatment (%)	No. surgically treated patients (%)	Median time from metastasis to treatment months (range)	OS definition	Median OS, published Kaplan-Meier estimate months (95% CI)	Region(s)
Stereotactic RFA	Bale [225]	2016	Retrospective case series	6	0 (0%)	0 (0%)	NR	Treatment	38; 36.2 (15.7–ND)[a]	AT
Laser-induced thermotherapy	Eichler [226]	2014	Retrospective case series	18	NR[b]	NR	4 (22)	Diagnosis	29.2; 29.2 (12.5–43.0) [c]	DE

[a] In the original publication, the median survival was reported as 38 months; according to personal communication, this was calculated by the actuarial method and is 36.3 months by the Kaplan-Meier method.

[b] The authors state, 'Limitations of our study are the small number of patients and the inhomogenous population concerning various treatments prior to the laser-induced thermotherapy like immunochemotherapy and TACE'.

[c] Digitised Kaplan-Meier estimate approved by personal communication.

2.5.5 Best supportive care

Seven studies reported individual-level survival data on patients with metastatic uveal melanoma who received BSC (Table 28). Altogether, they comprised 518 patients (11–191 patients per study), and four studies omitted prognostic factors on a patient level [7,11,37,83,85,86,103]. Of all patients included in these studies, 15–88% received BSC. Patients were often older and had more advanced disease, making comparison without staging, which was not included in any of the studies, unfeasible. The publications lacked a detailed description of BSC / palliative treatment / no treatment—a common issue in medical literature [227].

Table 28. Studies reporting individual-level survival data on BSC.

Study	No. patients with BSC/all (%)	Prognostic factors	Median OS (months)
Gragoudas et al. 1991 [7]	44/145 (30)	No	2.0
Pons et al. 2011 [103]	23/58 (40)	Yes	8.03 (95% CI, 5.35–16.30)
Gomez et al. 2014 [11]	137/155 (88)	No	8 (range, 1–30)
Lane et al. 2018 [83]	191/620 (31)	No	1.7 (IQR, 0.66–3.5)
Xu et al. 2019 [37]	11/73 (15)	Yes	4.9
Nicholas et al. 2018 [85]	43/132 (33)	No	3.8 (95% CI, 1.9–5.9)
Jochems et al. 2019 [86]	69/175 (39)	Yes	6[a]

[a] No OS mentioned; approximated from Kaplan-Meier graph.

2.5.6 Adjuvant therapy

Given the assumption that dormant micrometastases harbour in the liver or in bone marrow, as recently postulated, years before the clinical diagnosis can be made, adjuvant therapy would be a logical strategy in uveal melanoma [228,229]. Attempts have been made with dacarbazine, IFN [230], combined dacarbazine and IFN [231], intra-arterial fotemustine [232], sunitinib [233], ipilimumab [234], and dendritic cell vaccine [235]. However, the studies either failed to demonstrate a longer OS [230-232], were very small (≤20 patients) [234,235], or did not include a proper control group [233].

2.5.7 Time trends of overall survival

Survival rates in different time periods were compared in three retrospective single-centre studies. A large study, which included 661 consecutive patients with metastatic uveal melanoma, reported no improvement in survival rate between the periods 1982–1991, 1992–2001, and 2002–2009 [83], nor did a study of 73 patients with uveal melanoma metastatic to the liver between 2004–2011 and 2012–2016 [37]. However, an assessment of the experience of a single institution with uveal melanoma metastatic to the liver suggested that a shift from CHT to liver-directed treatment improved survival. It included 730 consecutive patients from the time periods 1971–1993, 1998–2007, and 2008–2017; between the first versus second and the first versus third time periods, OS improvement was observed ($P < 0.001$) [84]. However, this analysis might be subject to both lead time bias, from changes in surveillance methods, and selection bias.

2.5.8 Issues with treatment trials

Given the small number of patients resulting from the rarity of uveal melanoma, few randomised trials have been conducted: hepatic IA versus IV fotemustine [24], selumetinib plus dacarbazine versus placebo plus dacarbazine [25], immunoembolisation versus bland

embolisation [26], intrahepatic cisplatin with versus without polyvinyl sponge [27], and cabozantinib [28,135]. The largest trial included 171 patients [24].

Furthermore, a few studies on the real-life outcomes of metastatic uveal melanoma in tertiary care centres have been published with 89–730 actively treated patients per study [10-12,15], including only one nationwide study with 175 patients [86]. However, they often have considerable gaps in reporting patient-level prognostic factors and treatments administered, or they lack proper control groups [110,236,237]. Additionally, lead time bias poses a problem in interpreting results [48,84]. Unless the review for metastases is similar in the centres, comparing the results of treatment modalities is impossible, even in otherwise controlled trials.

Researchers often fit multivariate models *ad hoc* for metastatic uveal melanoma, typically by a data-driven, forward or backward stepwise approach, ignoring prior knowledge [21, 37,40,82,85,103,104,108,111]. Such models typically fit a small sample but are unlikely to be repeatable. Alternatively, researchers plot survival according to single predictors. Bias from other factors makes comparisons between studies difficult, if not impossible [110]. For all considerations above, the staging of patients is essential. Nevertheless, only three studies reported any staging [107,126,127], and an additional one provided the information to calculate it [138].

3 Aims of the study

The goal of this thesis is to advance the analysis and interpretation of OS in metastatic uveal melanoma.

The specific aims of this study are as follows:

I To provide a meta-analysis of OS in published, peer-reviewed studies on metastatic uveal melanoma containing patient-level data (Study I).

II To describe a nationwide cohort whose metastatic disease was diagnosed between 1999 and 2016 (Studies II, III, and IV).

III To evaluate the agreement of radiological screening modalities at the time of diagnosis of metastatic uveal melanoma in the nationwide cohort to ultimately advance the formulation of a nationally and potentially universally acceptable screening strategy for metastases, consequently enhancing comparability in treatment trials in the future (Study II).

IV To evaluate the OS, stratified by validated prognostic stages, of patients who only received BSC in the nationwide cohort in order to publish a historical benchmark to facilitate correct interpretation of OS outcomes in trials (Study III).

V To report the stage-stratified OS and treatment modalities of actively treated patients in the nationwide cohort so as to identify any treatment modalities that might be associated with a shorter- or longer-than-average survival (Study IV).

4 Patients and methods

4.1 PATIENTS AND DATA COLLECTION (I–IV)

4.1.1 Study I

I planned the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines [238]. I searched PubMed for literature published between January 1, 1980 and March 29, 2017 for the terms uveal melanoma, choroidal melanoma, ciliary body melanoma, ciliochoroidal melanoma, iridociliary melanoma, iris melanoma, intraocular melanoma, and ocular melanoma, and for the additional terms metast* or stage IV, and treatment. Patient-level data were required in either Kaplan-Meier plot or numerical form. Kaplan-Meier plots were digitised; then, the patient-level survival times of each treatment modality were constructed and pooled, and the median OS times were reported and analysed. The analysis included 78 peer-reviewed studies, with 2,494 patients treated for metastatic uveal melanoma.

4.1.2 Studies II–IV

Studies II–IV enrolled consecutive patients with primary uveal melanoma, managed in the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital, Finland, who developed metastases between January 1999 and December 2016. Common exclusion criteria for Studies II–IV were no diagnosis until autopsy, metastases not consistent with uveal melanoma, and concurrent active second cancer. For a detailed description of the exclusions, see Figure 1.

Patients who underwent CT, MRI, or both within 60 days of upper abdominal US were eligible for Study II.

Patients eligible for Study III were those who received only BSC, including palliative radiotherapy to control pain in five patients.

Patients who received active treatment were eligible for Study IV.

I obtained charts from all hospitals that participated in the management of metastatic uveal melanoma, and I recorded the following: gender, age, date of diagnosis of the primary tumour and metastases, TNM stage [67,118,120], participation in regular follow-up to detect metastases early [18], symptoms of metastases, LFTs, LDLM, sites of metastases, ECOG performance status [114], date of treatment decision (including decision on BSC), WF [40,119], modality of treatment, and date of death and registered COD. Surveillance included annual LFTs and US, followed by MRI or CT when metastases were suspected. Since 2014, surveillance has been semi-annual for patients representing TNM stage III.

For Study II, I recorded whether the original US and CT/MRI imaging reports described the presence and number of metastases consistently. If US or CT/MRI examination was interpreted as metastatic whereas the other one was not, then an experienced radiologist reviewed the CT/MRI images.

For Study IV, patients were divided by first-line treatment strategy (systemic versus local). Based on my previous meta-analysis (Study I), I prospectively identified the following systemic modalities: CHT, CIT, checkpoint inhibitors (CPI), protein kinase inhibitors (PKI), and vaccine therapies. Additionally, data on patients treated with IFN/IL monotherapy were available. Prospectively identified local treatments were surgery, SIRT, TACE, and other liver-directed therapies (stereotactic RFA, brachytherapy).

Follow-up ended on December 31, 2018.

4.2 VERIFICATION OF METASTASES (II–IV)

I aimed to include as many patients with histologically confirmed metastasis as possible and adapted the definitions of the Collaborative Ocular Melanoma Study to ascertain whether metastatic uveal melanoma was present [5,239]. Samples of metastases were obtained from biobanks and institutes of pathology.

The code 'dead with melanoma metastases, confirmed metastases' was used if the original pathology report mentioned moderate to heavy melanin or either HMB-45 or MelanA/MART-1 immunopositivity. If the original pathology report mentioned none of these characteristics and was not an FNAB, then I obtained the original specimen for review. Moreover, if melanin was equivocal, then I ordered HMB-45, MelanA/MART-1, and pan-cytokeratin immunostainings [5]. The code 'suspected metastases' was used if only an FNAB was available or no histopathologic confirmation had been sought but clinical findings (hepatomegaly, elevated LFT, liver imaging) were consistent with progressive metastases. The code 'possible metastases' was used if the death certificate specified metastatic melanoma as the COD but clinical data were inconclusive, or if the specified COD was other than metastases but clinical findings were consistent with metastases. Finally, the code 'dead, not consistent with melanoma metastases' was used if the histopathology was not diagnostic of metastatic melanoma, clinical data were inconclusive, and the patient was excluded—this applied to one patient in the cohort (Figure 1).

In Study II, metastases were biopsy-confirmed in 67% of patients, whereas a biopsy was not performed on 33% of patients (largely those who were offered BSC because of their advanced age or poor general health). The COD was relevant for Studies III and IV, whereas for Study II, which concentrated on diagnostics, it was irrelevant. After central review with an experienced ophthalmic pathologist, 47% had confirmed metastasis, 46% suspected metastasis, and 7% possible metastasis in Study III, compared to 71%, 27%, and 2%, respectively, in Study IV.

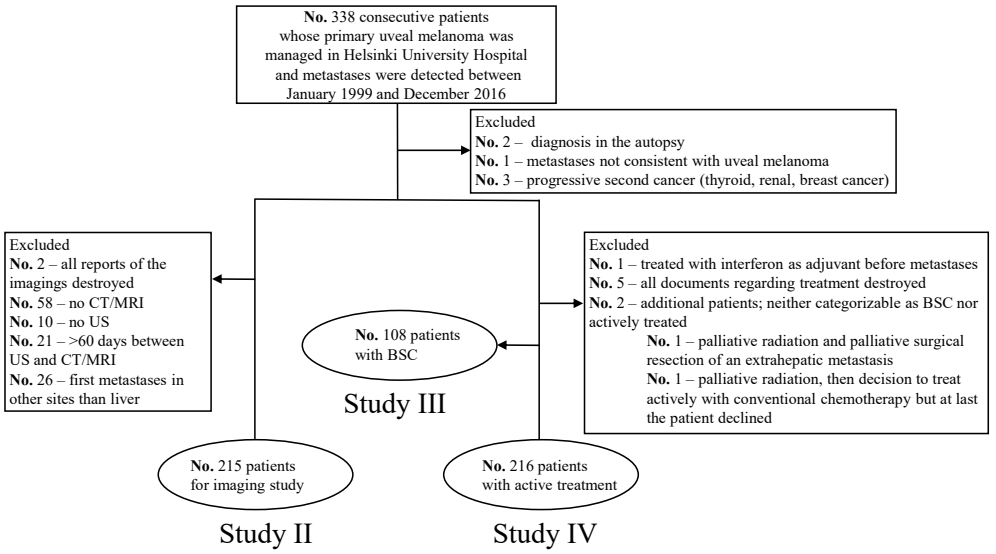


Figure 1. Study flow chart.

4.3 STAGING OF METASTASES (II–IV)

I used the WF validated by the OOG for the calculation of the individually predicted median OSs to stage the patients at the time of treatment decision as common in treatment trials (as opposed to the time of diagnosis of metastases in the original building and validation datasets) for Studies III–IV [40,119,130-132,139]. The patients were assigned to stages IVa, IVb, and IVc, originally corresponding to median predicted OSs of ≥12 months, <12–6 months, and <6 months, respectively (online calculator available at http://www.prognomics.org/huhwf.aspx). The ECOG performance status, LDLM, or AP level were missing for 16 patients in Study III and for 12 patients in Study IV, thus preventing calculation; however, the WF stage was assignable for 13 and nine patients, respectively, by using the prognostic table published with the building dataset [40]. In both Studies III and IV, three patients were not stageable.

4.4 HISTORICAL BENCHMARK (I, III)

I provide two historical control survival curves to be used for comparing observed OS data from a new trial: one curve of the pooled data on 78 articles with 2,494 patients from Study I (for active treatment in doi: 10.5281/zenodo.1490563) and one curve of data on 108 patients from Study III (for BSC in doi: 10.5281/zenodo.3369090).

I constructed the historical control OS distribution for a phase II trial using as an example a large cutaneous melanoma study that included data from 1,200 patients [240].

The historical control curve is given by

$$\bar{S}(t) = \frac{1}{n}\sum_{i=1}^{n} S_i(t)$$

where

$$S_i(t) = [S_0(t)]^{exp(SUM_i)}$$

$S_0(t)$ is given for active treatment in doi: 10.5281/zenodo.1490563 and for BSC in doi: 10.5281/zenodo.3369090.

n is the number of patients in the phase II trial.

At the time of analysis of a new phase II trial, the survival curve of this trial based on *n* patients is compared with the historical survival curve [240]. Somewhat arbitrarily, the endpoint was chosen to be 1 year. If the *P*-value is <0.01, then the new drug could be pursued further.

4.5 STATISTICAL ANALYSIS (I–IV)

Analysis was performed with Stata (version 15 and 16, Stata Corp., College Station, TX, USA). The significance was set at <0.05, and all *P*-values are two-tailed. I report the median with range and interquartile range (IQR) for continuous variables.

In Study I, I compared individual studies on each treatment modality to evaluate heterogeneity, and I then compared studies within each treatment modality according to the agents used. Thereafter, I compared each treatment modality against CHT and, finally, first-line treatments, if possible.

In Study II, I used a non-parametric test for trend to compare continuous variables between ordered groups. The sensitivity of US for detecting metastases was then calculated.

For Studies III and IV, the primary endpoint was OS from the date of treatment decision of metastatic disease to death, as is usual in clinical trials [130-132,139]. The secondary endpoint was OS from the date of diagnosis of metastases to death to allow for comparisons with the validation dataset of the OOG, because that definition was originally used when building and validating the staging by the OOG [119]. Study III used OOG data for comparisons (E. R. et al. partly unpublished results) whereas Study IV used BSC (i.e. Study III data) as the comparison basis.

Time trends in OS were analysed in Studies I and IV.

I estimated OS using the Kaplan-Meier product-limit method, reported the median OS with a 95% CI, and compared unordered and ordered categories with the log-rank test and test for trend, respectively. I also adjusted with Bonferroni correction for multiple comparisons.

In addition, I used Cox proportional hazards regression to probe whether additional prognostic factors identified from the literature might help to predict OS together with the WF stage. I allowed independent variables in models if $P < 0.10$, tested the assumption of proportional hazards using the scaled adjustment of Schoenfeld residuals [40,241], and compared models using the deviance test.

4.6 ETHICAL CONSIDERATIONS (I–IV)

Study I was a systematic literature review and meta-analysis, and no institutional review board approval was needed. Studies II–IV were approved by the institutional review board of the Head and Neck Centre of the Hospital District of Helsinki and Uusimaa, the National Institute for Health and Welfare, and the National Supervisory Authority for Welfare and Health, Finland. Informed consent for participation was not required by Finnish law because the studies were based on past patient records, and nearly all eligible patients had already died.

5 Results

5.1 META-ANALYSIS OF OVERALL SURVIVAL (I)

The search identified 1,663 publications on metastatic uveal melanoma and 78 of them contained original data digitisable for a pooled Kaplan-Meier graph, resulting in an analysis of 2,494 patients. The patients were categorisable to 13 treatment modalities (Table 29; Table 1 in Study I). The median OS was 13 months (95% CI, 12–14) for the entire cohort, and the cumulative proportion of surviving patients declined rapidly from 52% at 12 months, to 25% at 24 months, and 13% at 36 months.

The OSs of CIT, HIA, TACE, PKI, and SIRT were comparable with CHT (P = 0.13–0.80; Figure 2 in Study I). Surgery, IHP, and IE were associated with longer OSs ($P < 0.001$, P = 0.004, and P = 0.008, respectively), whereas CPI was associated with a shorter OS than CHT ($P < 0.001$).

However, upon closer analysis, only approximately 8% of treatments with CPI were first-line treatments. IE might not be generalisable as superior because the data were solely derived from a single-centre phase I and a subsequent phase II trial with a total of 59 patients. Moreover, the OS benefit of IHP depended entirely on one study with an exceptionally long OS [211].

The analysis could not be limited only to first-line treatments, because such patient-level data were available solely for CHT, CIT, HIA, and TACE. In addition, the WF staging was reported in 4% of the studies and 2% of the patients and could not be used for analysis. The interval from diagnosis of metastases to the initiation of study treatment also varied widely, and no more than 18% of the studies diligently reported all the components of OS from diagnosis of metastases to death or censoring.

The trend in OS over the past four decades has exhibited no improvement (log-rank test for trend, P = 0.66). The 2,494 patients were included in the historical benchmark published in an open access data repository doi: 10.5281/zenodo.3369090.

Table 29. Treatment modalities with number of actively treated patients and median OS in meta-analysis (Study I) and nationwide cohort (Study IV; shaded columns).

Treatment modality	No. patients in meta-analysis (*n*)	No. first-line treatments in meta-analysis / patients with reported therapy line [*n*/*n* (%)]	No. patients in articles with only first-line treatments (*n*)	No. patients in nationwide cohort *(n)*	Median OS years (95% CI) for meta-analysis		Median OS years (95% CI) for nationwide cohort
					For all patients	For first-line treatments	
TOTAL	2494	1034/1696 (61)	510	216	1.07 (1.00–1.13)	1.03 (0.95–1.14)	1.03 (0.89–1.13)
CHT	272	185/238 (78)	139	43	0.91 (0.77–1.03)	0.94 (0.83–1.15)	0.42 (0.25–0.67)
CIT	107	49/59 (83)	31	104	1.06 (0.93–1.36)	0.90 (0.57–1.36)	1.08 (0.83–1.37)
IFN/IL monotherapy	-	-	-	14	-	-	0.75 (0.24–1.50)
HIA	355	294/320 (92)	233	-	1.16 (1.03–1.27)	1.17 (1.02–1.32)	-
TACE	484	311/458 (68)	107	3	0.84 (0.75–0.92)	0.90 (0.71–1.07)	1.32; 3.42; 1.00[a]
IHP	147	62/86 (84)	0	-	1.34 (1.15–1.68)	-	-
CPI	318	24/307 (8)	0	8	0.59 (0.53–0.71)	-	1.08 (0.34–N/A)
PKI	132	58/109 (53)	0	1	0.86 (0.63–0.95)	-	0.81[a]
SIRT	71	15/71 (21)	0	22	0.94 (0.62–1.25)	-	1.32 (0.75–2.50)
IE	56	28/34 (82)	0	-	1.63 (1.27–1.86)	-	-
Immunosuppressant	14	0/14 (0)	0	-	0.91 (0.45–1.47)	-	-
Liver-directed thermotherapy	24	0/24 (0)	0	2	2.50 (1.22–3.02)	-	2.58; 6.08[a]
Vaccine	14	8/14 (57)	0	-	1.62 (0.56–3.18)	-	-
Surgery	500	-	-	19	1.43 (1.32–1.66)	-	2.0 (1.32–6.09)

[a] Median not calculable; individual survival given.

5.2 CHARACTERISTICS OF THE NATIONWIDE COHORT (II–IV)

Of the 324 patients eligible for studies analysing treatment, 49% were female (Table 30). Of the primary uveal melanomas, 8% were categorised as small (T1), 38% medium-sized (T2), 45% large (T3), and 9% very large (T4), and 45% extended from the choroid to the ciliary body or extraocularly.

The median DMFI was 28 months (range, 0–265; IQR, 13–52). The follow-up for metastases was regular for 97% of the patients. Asymptomatic at the time of detection of metastases were 64% of them; 41% of those who received BSC and 76% of the patients who received active treatment, respectively.

At the time of treatment decision, 93% of the patients had liver metastases with or without other sites. The median LDLM was 30 mm (range, 2–270), and categorised according to TNM, it was M1a in 48%, M1b in 31%, and M1c in 12% of the patients.

The AP exceeded the UNL in 38% of the 313 patients whose AP was available, and the ECOG performance status was 0–1 for 67%, 2 for 12%, and 3–4 for 20% of the patients. For patients who received BSC and active treatment, the ECOG performance status was 0–1 for 32% and 83%, 2 for 12% and 11%, and 3–4 for 51% and 4%, respectively. According to the WF, 52%, 18%, and 28% were assigned to stages IVa, IVb, and IVc, respectively (Figure 2). The median interval from diagnosis of metastases to treatment decision was 29 days (range, 0–758; IQR, 7.5–63) in the BSC dataset and 56 days (range, 0–1,059; IQR, 34–92) in actively treated patients (if more than 90 days, see Table 31 for reasons; E. R. et al. unpublished results).

The median age at treatment decision was 68 years (range, 21–95), with one of the BSC patients and 14 of the actively treated patients being alive at the end of the follow-up. The audited COD was metastatic uveal melanoma for all others. The follow-up time was 3.2 years (range, 0.2–17) for patients who received BSC and 3.8 years (range, 0.1–24) for actively treated ones.

Table 30. Basic characteristics of the patients in the treatment studies (Studies III–IV) according to the treatment group (active treatment and BSC) and the WF stage. In both Studies III and IV, three patients were not stageable.

Variable	All patients *n* = 324	BSC *n* = 108			Actively treated *n* = 216		
		Stage IVa *n* = 26 (24%)	Stage IVb *n* = 20 (19%)	Stage IVc *n* = 59 (55%)	Stage IVa *n* = 143 (66%)	Stage IVb *n* = 37 (17%)	Stage IVc *n* = 33 (15%)
Gender, *n* (%)							
Female	159 (49)	14 (54)	11 (55)	27 (46)	73 (51)	14 (38)	19 (58)
Male	165 (51)	12 (46)	9 (45)	32 (54)	70 (49)	23 (62)	14 (42)
TNM stage, *n* (%)							
I	27 (8)	4 (15)	2 (10)	3 (5)	11 (8)	3 (8)	4 (12)
IIA	57 (18)	5 (19)	2 (10)	13 (22)	24 (17)	6 (16)	7 (21)
IIB	65 (20)	6 (23)	4 (20)	10 (17)	30 (21)	7 (19)	7 (21)
IIIA	86 (27)	7 (27)	6 (30)	16 (27)	39 (27)	12 (32)	3 (9)
IIIB	53 (16)	2 (8)	3 (15)	12 (20)	22 (15)	5 (14)	8 (24)
IIIC	8 (2)	1 (4)	2 (10)	3 (5)	0 (0)	1 (3)	1 (3)
IV	28 (9)	1 (4)	1 (5)	2 (3)	17 (12)	3 (8)	3 (9)
Primary tumour extent, *n* (%)							
Limited to choroid	179 (55)	16 (62)	10 (50)	31 (53)	82 (57)	18 (49)	20 (61)
With ciliary body involvement	136 (42)	10 (38)	9 (45)	27 (46)	58 (41)	17 (46)	12 (36)
Extraocular extension	9 (3)	0 (0)	1 (5)	1 (2)	3 (2)	2 (5)	1 (3)
Distant metastasis-free interval, *n* (%)							
<2.0 years	138 (43)	7 (27)	10 (50)	25 (42)	60 (42)	19 (51)	12 (36)
2.0–3.5 years	75 (23)	7 (27)	4 (20)	16 (27)	34 (24)	10 (27)	4 (12)
>3.5 years	111 (34)	12 (46)	6 (30)	18 (31)	49 (34)	8 (22)	17 (52)
Follow-up for metastases, *n* (%)							
None	2 (1)	0 (0)	0 (0)	1(2)	0 (0)	0 (0)	1(3)
Irregular	7 (2)	1 (4)	0 (0)	4 (7)	0 (0)	0 (0)	2 (6)
Regular	314 (97)	25 (96)	20 (100)	53 (90)	143 (100)	37 (100)	30 (91)
Unknown	1 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

Table 30 cont.

Variable	All patients *n* = 324	BSC *n* = 108			Actively treated *n* = 216		
		Stage IVa *n* = 26 (24%)	Stage IVb *n* = 20 (19%)	Stage IVc *n* = 59 (55%)	Stage IVa *n* = 143 (66%)	Stage IVb *n* = 37 (17%)	Stage IVc *n* = 33 (15%)
Symptoms from metastasis, *n* (%)							
No	208 (64)	20 (77)	14 (70)	10 (17)	131 (92)	19 (51)	13 (39)
Yes	110 (34)	6 (23)	6 (30)	47 (80)	11 (8)	18 (49)	19 (58)
Unknown	6 (2)	0 (0)	0 (0)	2 (3)	1 (1)	0 (0)	1 (3)
Histologic confirmation, *n* (%)							
By local pathologist	193 (60)	9 (35)	7 (35)	36 (61)	96 (67)	23 (62)	20 (61)
By review	43 (13)	5 (19)	1 (5)	4 (7)	23 (16)	5 (14)	4 (12)
Not available	88 (27)	12 (46)	12 (60)	19 (32)	24 (17)	9 (24)	9 (27)
Location of metastases at the time of diagnosis, *n* (%)							
Liver only	227 (70)	19 (73)	10 (50)	44 (75)	105 (73)	20 (54)	25 (76)
Liver and other sites	74 (23)	6 (23)	8 (40)	13 (22)	25 (18)	15 (41)	7 (21)
Other sites only	23 (7)	1 (4)	2 (10)	2 (3)	13 (9)	2 (5)	1 (3)
Median largest diameter of the largest metastasis, mm (range, IQR)	30 (2–270, 20–55)	20 (2–34, 10–30)	40 (8–104, 20–60)	50 (15–270, 20–150)	23 (2–90, 16–34)	57 (10–125, 41–80)	65 (13–196, 35–118)
TNM M1 category, *n* (%)							
≤30 mm (M1a)	156 (48)	22 (85)	9 (45)	11 (19)	99 (69)	7 (19)	6 (18)
31–80 mm (M1b)	99 (31)	3 (12)	10 (50)	19 (32)	37 (26)	19 (51)	11 (33)
>80 mm (M1c)	40 (12)	0 (0)	1 (5)	14 (24)	3 (2)	10 (27)	11 (33)
Unknown	29 (9)	1 (4)	1 (5)	15 (25)	4 (3)	1 (3)	5 (15)

Table 30 cont.

Variable	All patients *n* = 324	BSC *n* = 108			Actively treated *n* = 216		
		Stage IVa *n* = 26 (24%)	Stage IVb *n* = 20 (19%)	Stage IVc *n* = 59 (55%)	Stage IVa *n* = 143 (66%)	Stage IVb *n* = 37 (17%)	Stage IVc *n* = 33 (15%)
Liver function tests, *n* (%)							
AST							
<1.0 x UNL	121 (37)	7 (27)	6 (30)	9 (15)	73 (51)	20 (54)	5 (15)
1.0–2.0 x UNL	45 (14)	2 (8)	6 (30)	10 (17)	16 (11)	6 (16)	3 (9)
>2.0 x UNL	43 (13)	0 (0)	0 (0)	21 (36)	4 (3)	4 (11)	13 (39)
Unknown	115 (35)	17 (65)	8 (40)	19 (32)	50 (35)	7 (19)	12 (36)
ALT							
<1.0 x UNL	195 (60)	15 (58)	13 (65)	27 (71)	101 (71)	24 (65)	11 (33)
1.0–2.0 x UNL	57 (18)	2 (8)	4 (20)	15 (25)	18 (13)	6 (16)	12 (36)
>2.0 x UNL	28 (9)	1 (4)	0 (0)	10 (17)	5 (3)	4 (11)	7 (21)
Unknown	44 (14)	8 (31)	3 (15)	7 (12)	19 (13)	3 (8)	3 (9)
AP							
<1.0 x UNL	180 (56)	17 (65)	13 (65)	16 (27)	114 (80)	14 (38)	4 (12)
1.0–2.0 x UNL	51 (16)	0 (0)	1 (5)	16 (27)	10 (7)	15 (41)	7 (21)
>2.0 x UNL	57 (18)	1 (4)	4 (20)	24 (41)	2 (1)	5 (14)	20 (61)
Unknown	36 (11)	8 (31)	2 (10)	3 (5)	17 (12)	3 (8)	2 (6)
LDH							
<1.0 x UNL	82 (25)	14 (54)	4 (20)	3 (5)	57 (40)	4 (11)	1 (3)
1.0–2.0 x UNL	77 (24)	2 (8)	8 (40)	11 (19)	37 (26)	14 (38)	3 (9)
>2.0 x UNL	45 (14)	1 (4)	4 (20)	11 (19)	3 (2)	9 (24)	15 (45)
Unknown	120 (37)	9 (35)	4 (20)	34 (57)	46 (32)	10 (27)	14 (42)
ECOG performance status, *n* (%)							
0–1	217 (67)	25 (96)	8 (40)	2 (3)	140 (98)	27 (73)	13 (39)
2	38 (12)	0 (0)	8 (40)	5 (8)	3 (2)	10 (27)	11 (33)
3–4	64 (20)	1 (4)	4 (20)	50 (85)	0 (0)	0 (0)	8 (24)
Unknown	5 (2)	0 (0)	0 (0)	2 (3)	0 (0)	0 (0)	1 (3)

Table 30 cont.

Variable	All patients *n* = 324	BSC *n* = 108			Actively treated *n* = 216		
		Stage IVa *n* = 26 (24%)	Stage IVb *n* = 20 (19%)	Stage IVc *n* = 59 (55%)	Stage IVa *n* = 143 (66%)	Stage IVb *n* = 37 (17%)	Stage IVc *n* = 33 (15%)
Age, median (range, IQR), y							
Primary tumour	65 (18–92, 56–74)	79 (63–92, 66–83)	77 (45–86, 66–83)	73 (39–90, 52–85)	58 (18–85, 52–67)	64 (32–82, 57–69)	63 (19–81, 50–68)
Metastatic disease	68 (20–95, 59–77)	83 (63–95, 72–91)	79 (47–90, 70–85)	76 (48–94, 57–87)	62 (20–86, 56–71)	67 (34–82, 60–72)	65 (24–85, 55–72)
Treatment decision	68 (21–95, 59–78)	83 (64–95, 72–91)	79 (48–90, 70–85)	77 (48–94, 57–87)	63 (21–86, 56–71)	68 (34–82, 60–72)	65 (24–85, 55–73)
Death	69 (22–97, 61–78)	84 (65–97, 73–92)	80 (48–92, 70–85)	77 (49–95, 57–87)	65 (22–87, 58–72)	68 (34–83, 62–73)	65 (24–85, 56–73)

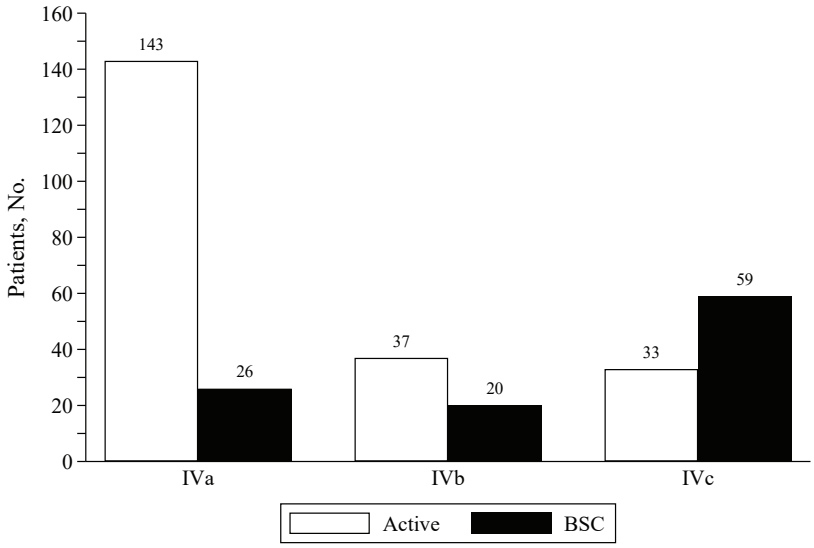


Figure 2. The WF stage according to active treatment or BSC.

Table 31. Reasons for a delay of more than 90 days from diagnosis of metastasis to treatment decision for patients who received BSC or active treatment. E. R. et al. unpublished results.

Reason	Active *n* = 59 (%)	BSC *n* = 17 (%)	Both *n* = 76 (%)
Initially negative FNAB or CNB result	21 (36)	4 (24)	25 (33)
Unfavourable performance status	0 (0)	3 (18)	3 (4)
Patient preference	2 (3)	2 (12)	4 (5)
Administrative reasons	1[a] (2)	1[b] (6)	2 (3)
Considered for SIRT but eventually not eligible	1 (2)	2 (12)	3 (4)
Other	0 (0)	1[c] (6)	1 (1)
Not specified	34 (58)	4 (24)	38 (50)

[a] Waiting for a trial opening.

[b] The US report was mistakenly not read by the managing physician.

[c] The managing oncologist decided that because of simultaneous prostate adenocarcinoma, no active treatment is indicated.

5.3 AGREEMENT BETWEEN IMAGING MODALITIES IN FOLLOW-UP (II)

Altogether, 215 patients with liver metastases were included in the analysis, with 215 US, 167 CT, and 69 MRI examinations. The first imaging modality was US for 91% of patients, CT for 8%, and MRI for 1%. The median interval from the first to the second imaging modality was 17 days (range, 0–56).

US detected metastases in 95% of the patients, and it was consistent regarding the presence of metastases with CT and MRI in 89% of patients but showed quantitatively less metastases in 56% and more in 12% of them. US was inconsistent with CT/MRI in 23 patients (11%) (Figure 3). In nine patients, US detected metastases that were left undetected by CT for various reasons, and in another nine patients, US failed to suggest metastases. Among the latter nine patients, a newly detected lesion was present in US in seven patients, and LFTs were elevated in five patients. If a newly detected lesion in US or an elevated LFT was an indication to follow-up MRI, metastases would not have remained undetected in any of the nine patients.

The sensitivity of US against CT/MRI for findings that raised suspicion of metastases was 96% (95% CI, 92–98); 215 US scans were true-positives, and 10 were false-negatives.

In 215 patients, MRI detected more metastases than US in 54% of scans and less in 3%. In comparison, CT detected more metastases than US in 31% and less in 16% of scans. When both MRI and CT were done, as was the case for 18 patients, then MRI detected more metastases than CT in 33% and less in 6% (Figure 4). The median OS from diagnosis of metastases was 12 months (range, 0–166).

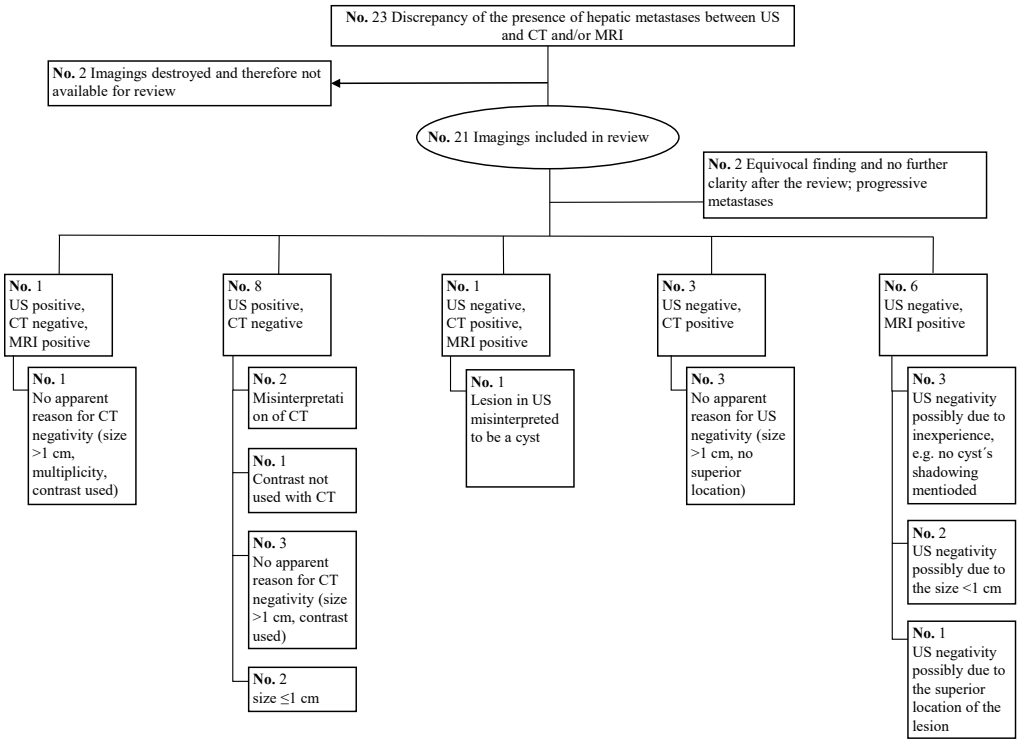


Figure 3. Flow chart that shows patients whose US was inconsistent with CT/MRI. Reproduced by CC-BY-4.0 from [242].

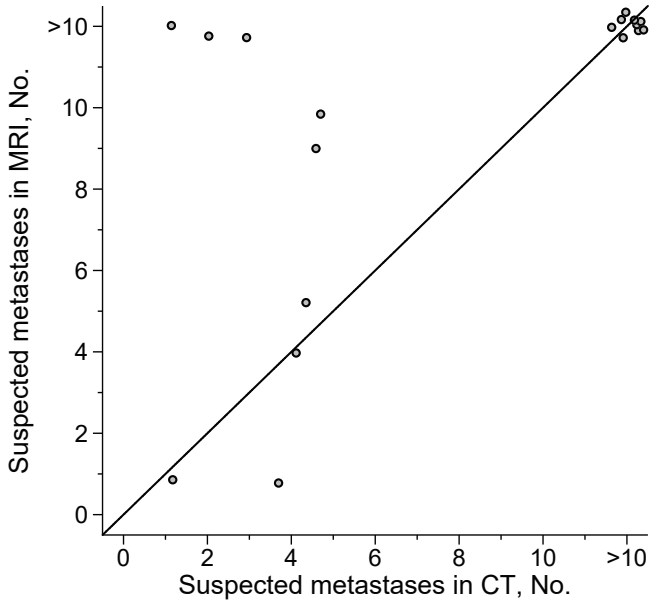


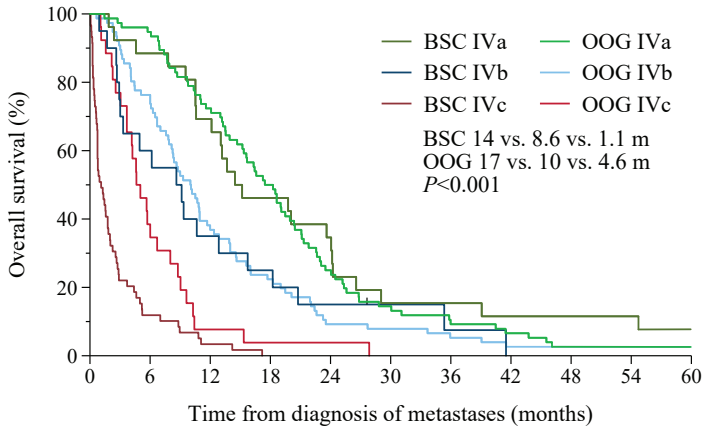
Figure 4. Number of reported metastases in CT compared to MRI. Reproduced by CC-BY-4.0 from [242].

5.4 SURVIVAL WITH BEST SUPPORTIVE CARE (III)

Of the 108 eligible patients, 24%, 19%, and 55% represented stages IVa, IVb, and IVc, respectively (Figure 2, Figure 5). The median OS was 1.6 months from the BSC decision for the entire cohort, and the 1-, 2-, and 3-year survival rate was 17%, 8%, and 5%, respectively. The median OS shortened with an increasing stage and was 12 (95% CI, 9.4–21) for stage IVa, 5.7 (95% CI, 0.7–11) for stage IVb, and 0.6 months (95% CI, 0.3–0.9) for stage IVc ($P <$ 0.001, log-rank test for trend). In stage IVa, 50% of patients survived ≥12 months, whereas in stage IVb, 50% survived ≥6 months and 25% ≥12 months. Meanwhile, in stage IVc, 97% died within 6 months.

The weighted kappa for agreement between the observed and predicted OS categories was 0.614 and 0.615 (agreement 84% versus 59% expected, $P < 0.001$ and 83% versus 57% expected, $P < 0.001$, Figure 6), calculated from the treatment decision and diagnosis of metastases, respectively.

Regarding comparison to those patients who received systemic, non-surgical treatment in the OOG validation dataset (described in Chapter *2.4.2 Helsinki University Working Formulation*), the OS for stages IVa and IVb was comparable to that after BSC ($P = 0.41$ and$P = 0.75$; Figure 5; E. R. et al. unpublished results). In stage IVc, the OS was shorter with BSC than with treatment ($P < 0.001$).



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					

Figure 5. Kaplan-Meier graph of overall OS from the date of diagnosis of metastasis to death for patients who received BSC and for patients from the OOG validation dataset who received systemic, non-surgical treatment [8], according to the WF stage. E. R. et al. unpublished results.

5.5 SURVIVAL OF ACTIVELY TREATED PATIENTS (IV)

Of the 216 eligible patients, 66%, 17%, and 15% represented stages IVa, IVb, and IVc, respectively (Figure 2). The median OS was 12 months (95% CI, 11–14; range, 0.2–162) from the treatment decision of metastasis for the entire cohort, and the 6-, 12-, 24-, and 36-month survival rates were 73%, 52%, 24%, and 13%, respectively. The median OS shortened with an increasing stage and was 18 months (95% CI, 16–21) for stage IVa, 6.9 months (95% CI, 4.8–9.7) for stage IVb, and 1.9 months (95% CI, 1.6–2.9) for stage IVc ($P < 0.001$, log-rank test for trend). In stage IVa, 73% of patients survived ≥12 months, whereas in stage IVb, 57% survived ≥6 months and 19% ≥12 months, and in stage IVc, 88% died within 6 months.

The weighted kappa for agreement between the observed and predicted OS categories was 0.549 and 0.603 (agreement 81% versus 58% expected, $P < 0.001$ and 85% versus 62% expected, $P < 0.001$, Figure 6), calculated from the treatment decision and diagnosis of metastases, respectively.

Of the 216 patients, 104 (48%) received first-line CIT, 43 (20%) CHT, 19 (9%) surgery, 22 (10%) SIRT, 14 (6%) IFN/IL monotherapy, 8 (4%) CPI, 3 (1%) TACE, 2 (1%) other liver-directed therapies, and 1 PKI (Table 29). Moreover, out of 104 patients who received CIT, 48 (46%) received the traditional (in Finland) combination of bleomycin, vincristine, lomustine, and dacarbazine (BOLD) with IFN [107,126,147].

Only 12 (6%) of patients participated in four treatment trials (NCT02599402, NCT01974752, NCT00154388, and NCT00308607).

The median OS with CIT in stage IVa was 18 months (95% CI, 15–21). The OS was longer in stage IVa for patients who received CIT ($P = 0.013$, with Bonferroni correction for three comparisons), but not in stages IVb and IVc, compared to CHT (Figure 7).

Considering local treatments, the median OS of surgery was 27 months (95% CI, 17–73) in stage IVa; only one patient each was assigned to stage IVb and IVc. Surgery was associated with a longer OS in stage IVa than SIRT ($P = 0.010$, Bonferroni correction). No difference in OS was observed between CIT and SIRT ($P > 0.99$, Bonferroni correction) (Figure 7). Using BSC as a reference, OS after SIRT was comparable with BSC ($P = 0.58$, Bonferroni correction), and OS after CIT was comparable to BSC in stages IVa and IVb, and it was slightly longer (1.9 versus 0.6 months) in stage IVc ($P = 0.003$, Bonferroni correction).

To determine whether the treatment outcome has improved over time, I compared the time periods 1999–2010 (124 patients), and 2011–2016 (92 patients), and I observed no improvement in survival ($P = 0.81$, log-rank test; E. R. et al. unpublished results).

By univariable Cox regression, the WF expectedly predicted a shorter OS [119]. Regarding components of the WF, a higher AP level, larger LDLM (by M1 category), and poorer ECOG performance status were associated with a shorter OS ($P < 0.001$ for each). Gender, age, DMFI, and the site of initial metastases were not associated with OS ($P = 0.15–0.70$, Cox regression). The presence of symptoms from metastases and LDH >2.0 x the UNL emerged as candidates for further modelling ($P = 0.003$ and $P < 0.001$, respectively).

In bivariable models with the WF stage, only LDH >2.0 x the UNL was associated with a shorter OS ($P = 0.002$). The model with LDH fitted better with the data than the WF stage alone (–2 log likelihood = 427.89 versus 734.35, $P < 0.001$, df = 2).

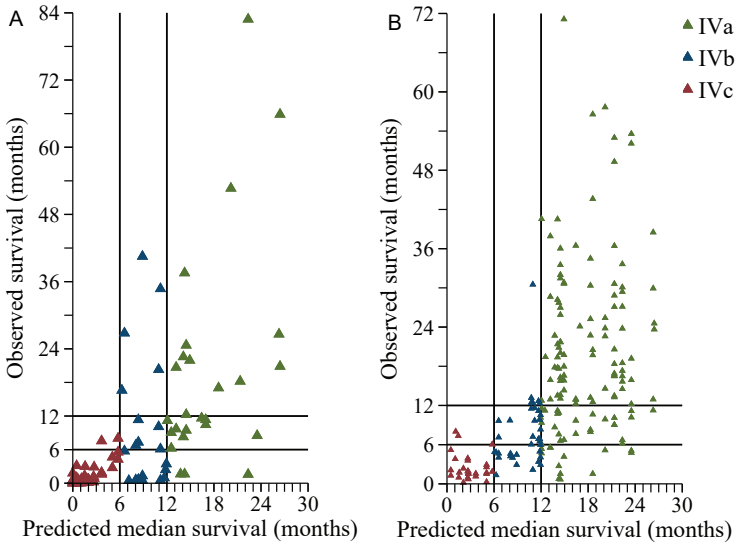


Figure 6. Scatterplot of the predicted median OS time against the observed OS by the WF for patients who (A) received BSC (Study III) and (B) received active treatment.

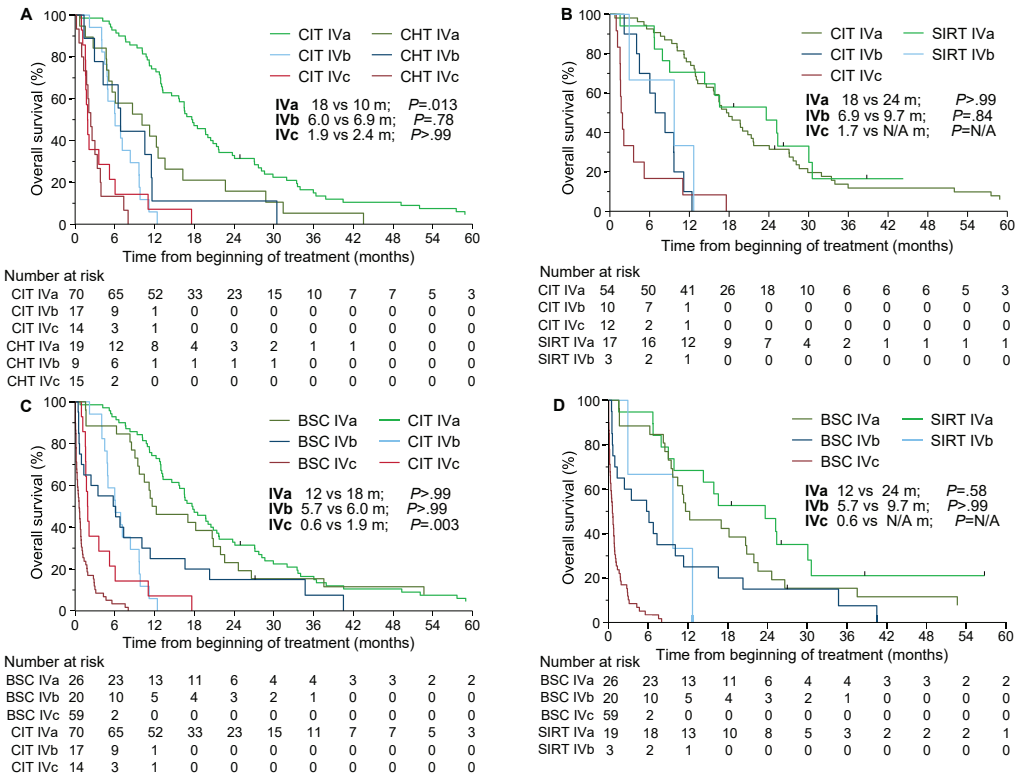


Figure 7. Kaplan-Meier graph of OS from treatment decision to death staged with the WF for (A) CIT against CHT, (B) CIT against SIRT if only liver metastases, (C) BSC against CIT, and (D) BSC against SIRT.

6 Discussion

6.1 META-ANALYSIS OF OVERALL SURVIVAL

In my meta-analysis (Study I), the median OS was 13 months for all 2,494 patients and essentially identical to my nationwide cohort (Studies II–IV) (Figure 8). Of the treatment modalities with >100 patients in Study I, surgery and IHP had a 5–6-month longer OS, and CPI had a 4-month shorter OS than CHT, for which the median OS was 11 months. These survival differences might disappear, as discussed below, if selection and lead time bias could be eliminated and if the analysis could be limited to first-line treatments, but patient-level data on first-line treatment analyses were available only for CHT, CIT, HIA, and TACE.

To my knowledge, this review and meta-analysis was the first to summarise unrestricted patient-level data for treatment of metastatic uveal melanoma extracted from survival graphs. A review with 841 patients from 40 studies with metastatic uveal melanoma previously reported an objective response rate but did not analyse OS, and 70% of the articles in my meta-analysis were not included [243]. Another review tabulated the median OS from 36 articles but did not pool data [110].

After my meta-analysis was published, the International Rare Cancers Initiative reported a meta-analysis with individual patient variables and survival outcomes from 29 phase Ib/III trials in metastatic uveal melanoma from 2000 to 2016 [106]. They collected original study data of all treated patients directly from the trial investigators. It therefore follows that compared with the International Rare Cancers Initiative meta-analysis, mine did not include six studies because of missing patient-level OS data [244-249] and one study because of OS data inseparable between uveal and cutaneous melanoma [250]. Moreover, OS data were available for 912 patients, compared to 2,494 patients in my meta-analysis; the International Rare Cancers Initiative's median OS was 10 months, compared with 13 months in my meta-analysis; and the PFS was 3.3 months. The 6-month PFS rates and the 1-year OS rates for each treatment group were plotted against the group sample size. The International Rare Cancers Initiative suggested that liver-directed treatments provide longer PFS and OS than immunotherapy, anti-angiogenic agents, kinases, and chemotherapy; however, neither the line of therapy nor the impact of imaging or early diagnosis of metastases was evaluated. The International Rare Cancers Initiative also carried out univariable and multivariable analyses that I could not perform because my analysis was based on published records in which patient-level prognostic data were not presented.

Regarding the treatment modalities with a significantly longer OS, IHP is even now offered only in selected centres, and one of those centres was responsible for the OS benefit in the

subanalysis and also reported lower mortality with its refined technique for IHP than what was the case earlier [211,212]. Systemic chemotherapy is frequently pursued in patients with heavy tumour burden, whereas patients who receive IHP more often have metastases limited to the liver.

The median OS with surgery was 17 months, including some long-term survivors [184] (Study I). The surgically treated patients were overrepresented among those long-term survivors in my national cohort (Study IV), paralleling previous findings [37,41,109]. Unfortunately, few patients are eligible for surgery because most patients have widespread metastases [11].

Of the patients treated with CPI, only 8% received it as their first-line treatment, likely leading to a biased result (Study I). After my meta-analysis, the OSs for 133 patients who received various CPIs as their first-line treatment have been published in three papers, and the median OS in them ranged from 10 to 20 months [85,133,168]. Only eight patients received first-line CPI in my national cohort (Study IV; Table 29). Patients with loss-of-function mutation in *MBD4* are likely to benefit from CPI. The loss-of-function allele frequency in *MBD4* among patients with uveal melanoma has been suggested to be 1%; however, in a recent Finnish series of 440 patients with uveal melanoma, no loss-of-function variants were identified [32,33,251,252].

My meta-analysis provides clinicians with a rough comparison of the treatment options for metastatic uveal melanoma and supports earlier assumptions that no clinically significant improvement in OS exists, regardless of the mode of treatment. Much, if not most, of the perceived differences in survival between individual studies are likely attributable to surveillance, selection, and publication bias rather than treatment-related prolongation in OS.

Based on my experience in extracting data for this meta-analysis, I also suggest guidelines for reporting a trial on treatment for metastatic uveal melanoma (Supplemental Digital Content 5 in Study I). The benchmark data published as open-access data, based on this study and including the data of 2,494 patients, are to be used for comparing observed OS data from a new single-arm, early phase trial.

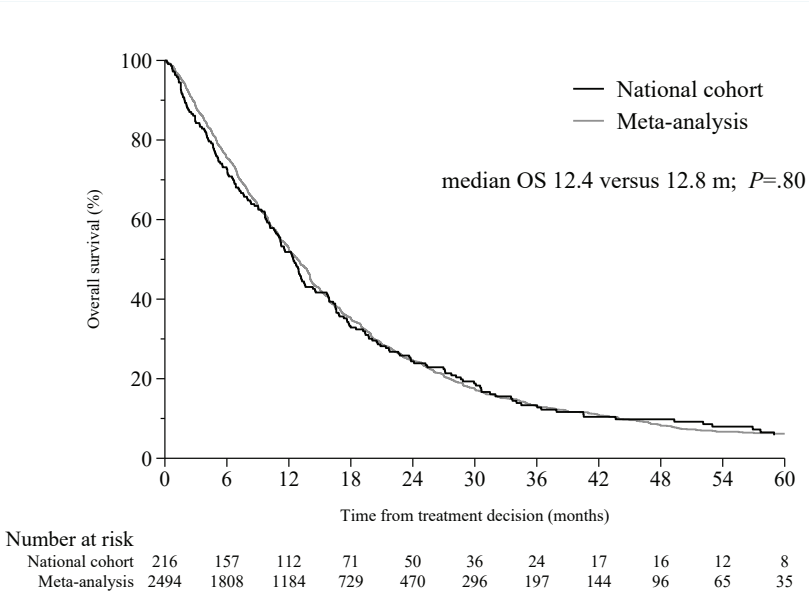


Figure 8. Kaplan-Meier graph of OS after metastatic uveal melanoma for actively treated patients from the nationwide cohort (Study IV) compared against meta-analysis (Study I). *P*-value is calculated using the log-rank test.

6.2 COMPLETENESS OF NATIONAL DATA

In my national cohort, the ECOG performance status was missing for 2% of patients, AP for 11%, and LDLM for 9%. I was able to assign a stage for 98% of the patients, and the treatment modality was known for all eligible patients.

In the International Rare Cancers Initiative meta-analysis with data requested directly from the investigators [106], 21% of the 912 patients lacked information on their ECOG performance status, 35% on AP, 35% on LDLM, and 19% on the line of therapy. Furthermore, in the only nationwide study prior to my study, 36% of the Dutch patients who received local therapy lacked an ECOG performance status, and neither the staging nor median OS was reported [86]. Meanwhile, in the largest single-institution report, the information regarding specific treatments was available only for 30% of patients [83]. Finally, only three studies reported staging at all [107,126,127].

6.3 ULTRASONOGRAPHY AS SCREENING MODALITY FOR METASTASES

Our population-based study of the agreement of hepatic US with staging CT/MRI revealed that US can be used in detecting metastases in patients with primary uveal melanoma in a real-life setting. The sensitivity of US in detecting metastases was 96%—US detected

metastases in 95% of the patients and agreed with a staging CT/MRI on their presence in 89% of patients, showing at least the same number of lesions as CT/MRI in 72% of the patients, and it detected metastases that CT initially missed for various reasons in nine patients. If US does not show metastases but any new lesion is detected, or if LFTs are newly elevated, then an MRI scan should be scheduled. Our findings suggest that a subsequent MRI is a more sensitive staging modality than CT in detecting hepatic metastases from uveal melanoma.

The sensitivity of US has been reported as 96–100%, in line with our study (Table 1) [14,72]. US and LFTs did not reveal hepatic metastases in four patients (2%), comparable to earlier published results (4%) [18]. However, in three of these patients, US detected a new lesion—although not specified as a suspected metastasis —that led to a confirmatory scan suggesting that in case of any newly-detected lesion, it should be considered a metastasis until proven otherwise [253]. Moreover, benign liver lesions, cysts, and hepatic steatosis are common at baseline, which must be taken into account during follow-up [9,10,14].

A review recommended that MRI should soon replace CT as the standard modality in liver imaging in uveal melanoma [22], and my study provides evidence that MRI outperforms CT in staging. MRI with a contrast agent is the most specific modality, and with a sensitivity of 67–100% and a specificity of 80–99% (Table 1), it is at least as sensitive as CT [13,17,74]. Additionally, the use of CT as a follow-up imaging method is limited by the fact that it uses ionizing radiation, while the utility of MRI might be limited by expense. Only a rough cost analysis was included in our study because of global differences in reimbursement systems. In North America, many centres prefer CT to US and MRI—a practice based partly on insurance policies that might possibly change based on my results and others that support MRI [22].

A single-centre study compared the survival of 90 patients diagnosed as having metastatic uveal melanoma before the onset of symptoms with annual LFTs, and of 259 patients after the onset of symptoms. The median time from diagnosis of primary uveal melanoma to death was similar to my study: 45 versus 45 months (Figure 9, schematic representation) [49]. A single-centre cohort study with 30 patients evaluating the utility of US for liver metastases reported that the median time from diagnosis of primary uveal melanoma to death was 36 months (Figure 9) [14]. Whether the difference in survival between the studies is dependent on the lead time bias, given the treatment or a different case mix, is impossible to assess. A similar surveillance strategy and staging would facilitate this comparison.

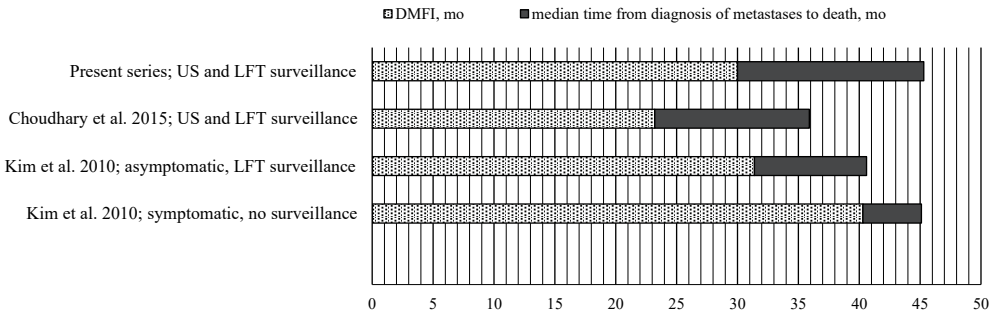


Figure 9. Schematic representation of survival of uveal melanoma patients with surveillance (Choudhary et al. [14] with 30 patients and Kim et al. with 90 patients [49]) and without surveillance (Kim et al. [49] with 259 patients) (E. R. et al. unpublished figure).

6.4 OVERALL SURVIVAL WITH BEST SUPPORTIVE CARE

The WF that was previously validated almost exclusively for actively treated patients also differentiates by OS patients receiving only BSC. In the validation dataset of the OOG, 11 patients received BSC [119]. More importantly, the median OS for both stages IVa and IVb was comparable to that of systemically treated patients in the validation dataset.

In our national cohort, 33% of the patients received BSC, which is comparable to 39% reported in the national cohort from the Netherlands—the sole nationwide study prior to my report [86]. Notably, these real-life percentages are comparable to recent studies from tertiary referral centres [83,85], although one might have hypothesised that active treatment would have been preferred in them and that patients with less favourable performance status would not have been referred to the tertiary centres by the managing physicians in the first place (Table 31).

I present the third largest cohort of patients who received BSC for metastatic uveal melanoma [11,83] and the first one to stage them. Three studies with 11 [37], 23 [103], and 69 patients [86] reported prognostic factors for patients who received BSC (Table 28). Paralleling these studies, the patients in my series were older and had a poorer ECOG performance status [86,103] than actively treated patients; however, I cannot confirm that they had a shorter follow-up [37] or more elevated LDH [86]. The components of the WF—ECOG performance status, AP level, and LDLM—were also expectedly significant predictors of OS in my BSC cohort.

Of patients who received BSC, 24%, 19%, and 55% were assigned to WF stages IVa, IVb, and IVc, respectively, as opposed to 44%, 44%, and 15% of the patients receiving active treatment in the OOG validation dataset and 66%, 17%, and 15% of the actively treated patients in my national cohort (Study IV). The migration towards stage IVc in the BSC

dataset represents their poorer ECOG performance status because 44% of the BSC patients versus 99% of the actively treated ones presented a performance status of 0–2. This also reflects the fact that most treatment trials require a performance status of 0–1 [227], and in the few trials that reported the WF stage, it was stage IVa in 46% [107], 50% [126], and 100% [127] of the patients.

Expectedly, the median OS was appreciably shorter (1.6 months), in aggregate, for patients who received BSC, compared to 13 months for the actively treated patients in the meta-analysis (Study I) and 12 months for the actively treated patients in my national cohort (Study IV). The OS has repeatedly been claimed, or at least assumed, to be longer with active treatment as compared to BSC [7,11,37,83,85]; only rarely, the difference has been suggested to be related to patient characteristics rather than to a treatment effect [103,110]. Nevertheless, if staged, the median OS with BSC and active treatment appeared to be comparable for stages IVa and IVb. The stages IVa and IVb, included the majority (94%) of the patients whose ECOG performance status was 0–1. In stage IVc, OS was longer for actively treated patients. For this stage, a survival benefit can neither be rejected nor be confirmed because a probable bias was found: 85% of the patients had an ECOG performance status of 3–4 and hence were normally ineligible for active treatment.

According to my study, using a validated staging system and a proper control group, especially in retrospective analyses and in non-randomised one-arm trials (e.g. the data that I published in an open-access data repository), is of paramount importance when analysing the results in an informative way. Indeed, it is likely that most trials continue to be non-randomised, given the relative rarity of metastatic uveal melanoma.

6.4 OVERALL SURVIVAL OF ACTIVELY TREATED PATIENTS

In stage IVa, patients who received CIT or local therapy as their first-line treatment—especially surgical resection—had a longer OS than patients who received CHT in my nationwide cohort. However, compared to BSC, the outcome after CIT was comparable, and survival after SIRT was also comparable to that after CIT and BSC. Consequently, I did not observe any convincing difference in OS in any comparison in patients whose WF stage was IVb or IVc. CHT might not have been the best reference group against which to compare other treatments, unlike what has repeatedly been done [24,25,51,134,135].

Due to encouraging pilot reports [147,254], the prospective EORTC multicentre study in 2003 analysed the efficacy of BOLD chemotherapy plus recombinant IFN alpha-2b, which is a form of CIT, but did not confirm its efficacy [107], nor did the pooled survival data from five CIT studies confirm any difference between CHT and CIT ($P = 0.80$; Study I). However, as mentioned, in my national cohort, OS with CIT was longer than with CHT in stage IVa ($P = 0.013$; Study IV), but this difference resulted from a shorter OS with CHT. I could not find any possible bias by comparing the prognostic factors of patients assigned to

stage IVa who received CIT or CHT: 97% versus 95% had ECOG performance status 0–1; 77% versus 74% had solely liver metastases; 61% versus 79% were from the M1a category (median LDLM 30 mm [range, 9–160; IQR, 20–50] versus 26 mm [range, 9–182; IQR, 15–56]); and 77% versus 78% had elevated LDH, respectively. Analysis of the prognostic factors of patients assigned to stage IVa who received CHT or BSC revealed mainly that patients with CHT had more frequently elevated LDH: 95% versus 96% had ECOG performance status 0–1; 74% versus 73% had solely liver metastases; 79% versus 85% were from the M1a category; and 78% versus 54% had elevated LDH, respectively.

Local treatment for metastatic uveal melanoma limited to the liver has been suggested to prolong survival, based on a median OS of 18–35 months in non-controlled series [36-38,84]. The presumably longer survival has been assumed to be secondary to better overall functional status [37], and I did not confirm the prolonged survival if stratified by stage.

Lately, in Finland, SIRT has become the preferred first-line local treatment for metastatic uveal melanoma restricted to the liver in patients for whom surgical resection is unfeasible because of the number or distribution of metastases [51]. However, the present results suggest that as a first-line treatment, SIRT may not be superior to previously predominating CIT or, indeed, BSC, when considering stage-specific OS.

Of note, only 12% of the actively treated patients in my cohort participated in a clinical trial, compared to 50% of patients in the nationwide study from the Netherlands [86]. Some national guidelines state that patients with metastatic uveal melanoma should be considered for clinical trials wherever possible and be informed of available trial options at other centres [57,58,60]. Likewise, in the Finnish cohort, only 9% of patients received local first-line treatment, compared to the 22% in the Netherlands, reflecting national differences in choosing first-line treatments.

The agreement between the WF-predicted and observed OS according to weighted kappa was actually stronger in my BSC (0.615) and the active treatment dataset (0.603) than in the validation dataset of the OOG (0.388) [119].

In the multivariable analysis stratified by stage, LDH improved the model fit, as has been proposed [21,111]. Although the LDH level was available only for a subpopulation of my patients, the data suggest that the WF staging might benefit from considering an elevation in LDH >2.5 x the UNL in addition to AP levels.

To determine whether OS had improved over time, I compared the periods 1999–2010 and 2011–2016, corresponding to the marketing authorisation of ipilimumab throughout the European Union in 2011 and equalling a recent single-centre study analysing OS before and after the introduction of CPI [37]. Unfortunately, my results from the meta-analysis (Study I) and national cohort (Study IV) both confirm that the survival outcome has not improved over time [37,83,139]. A single-centre study with 730 patients suggests that the

median OS was shortest for patients who were treated between 1971 and 1993, and it is similar in cohorts who were treated between 1998 and 2007 and between 2008 and 2017 [84]. The latter two cohorts parallel my study period and results.

6.6 RELIABILITY AND VALIDITY

In Study I, the major limitation was the heterogeneity of the study populations. Most of the studies were retrospective, were small in sample size, and had different surveillance strategies, if any. The treatment was sometimes administered to treatment-naïve patients, sometimes as salvage therapy. To control for bias, I reported the percentage of first-line treatments and whether prior surgical resection was performed. Other causes of bias, such as variable ECOG performance status, sites and size of metastases, and LFTs were reported highly inconsistently and not at patient-level, and this unavoidably adds to the bias when combining data. Differences in methods between the original publications posed an additional challenge: the method by which the median OS was calculated was not always reported, and at-risk tables and censored observations were often missing from Kaplan-Meier graphs.

The limitations in Studies II–IV include their retrospective nature, which shows in varying imaging protocols (Study II) and in the variability in the selection of patients for treatments (Studies III and IV). The lag between the diagnosis of metastases and the treatment decision was >90 days in 28% of the actively treated patients, possibly further confounding the results. The geographically long distances in Finland make the follow-up for metastases and their treatment solely in the tertiary-centre challenging. The lack of information on genetic prognosticators is an additional limitation. However, these genetic prognosticators had not yet been identified and defined for most of the study period.

In Study II, the maximum interval of 60 days between the US and CT/MRI scans may have biased the comparison of the imaging modalities because the doubling time of untreated metastases has a median of 63 days [16]. Nonetheless, in my study, the median observed interval was 17 days (IQR, 8–27), and this bias should favour CT/MRI rather than US.

6.7 FUTURE DIRECTIONS

Given the rarity of uveal melanoma, it is difficult to conduct randomised controlled trials. Therefore, multicentre studies—both prospective and retrospective—will be of great value, and the progress of digitalisation will aid in the integration of registries for research purposes so as to extract and aggregate data from electronic medical records or 'data lakes'.

To improve comparability, the establishment of a globally applicable follow-up strategy would be important. The imaging method used for review should be chosen based on sensitivity, specificity, availability, expenses, radiation exposure, and population characteristics. Considering the present results, a study comparing US and MRI head-to-

head as a follow-up tool in high-risk patients with a cost-benefit analysis based on stage-specific OS outcomes would be a logical follow-up to move international surveillance guidelines forward.

Furthermore, based on the summary of the delays of more than 90 days between the suspicion of metastases and the treatment decision (Table 31), further analysis is required in Finland to determine whether the delay shortens OS as well as how to reduce the delay and improve national clinical processes.

In the past decade, a significant expansion of knowledge regarding cytogenetic and molecular genetic data on uveal melanoma has taken place that may help to identify genetic subsets of patients who could benefit from certain therapies. The first subset of patients who may benefit from currently existing immunomodulatory therapies has already been recognised: patients with germline or somatic loss-of-function *MBD4* mutation [32,33,251]. With time, genetic data with the most reliable and cost-effective biomarkers could possibly also be implemented in the staging systems for metastatic uveal melanoma.

As outlined in my study, it is crucial to use proper control groups and staging when interpreting the results of non-randomised studies. The WF is confirmed as a useful, validated device in evaluating trials, even in its present form; however, the data also suggest that it has the potential to be adjusted with further prognostic factors, especially LDH.

7 Conclusions

1. Patient-level data aggregated from peer-reviewed reports provide no convincing evidence of a longer median OS for patients with metastatic uveal melanoma by any reported treatment modality, except surgical resection, or by decade. Most of the differences in reported OS are likely attributable to surveillance, selection, and publication bias.

2. US is a sensitive imaging method for detecting new hepatic metastases in patients with primary uveal melanoma. If US does not reveal definite metastases but any new lesion is detected, or if LFTs are newly elevated, then an MRI scan of the liver should be scheduled. Continued use of US as a surveillance method is supported by these data; however, a head-to-head comparison with MRI would be valuable.

3. The Helsinki University Hospital WF differentiates by OS also patients receiving BSC.

4. Analysis of the Finnish national cohort confirms that no current treatment available for most patients with metastatic uveal melanoma is likely to appreciably prolong OS. While surgical resection may be superior, it is available only for a minority of patients.

5. Validated staging systems and proper control groups are crucial for correct interpretation of outcomes in non-randomised trials.

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