Discovering biomarkers and druggable targets in uveal melanoma

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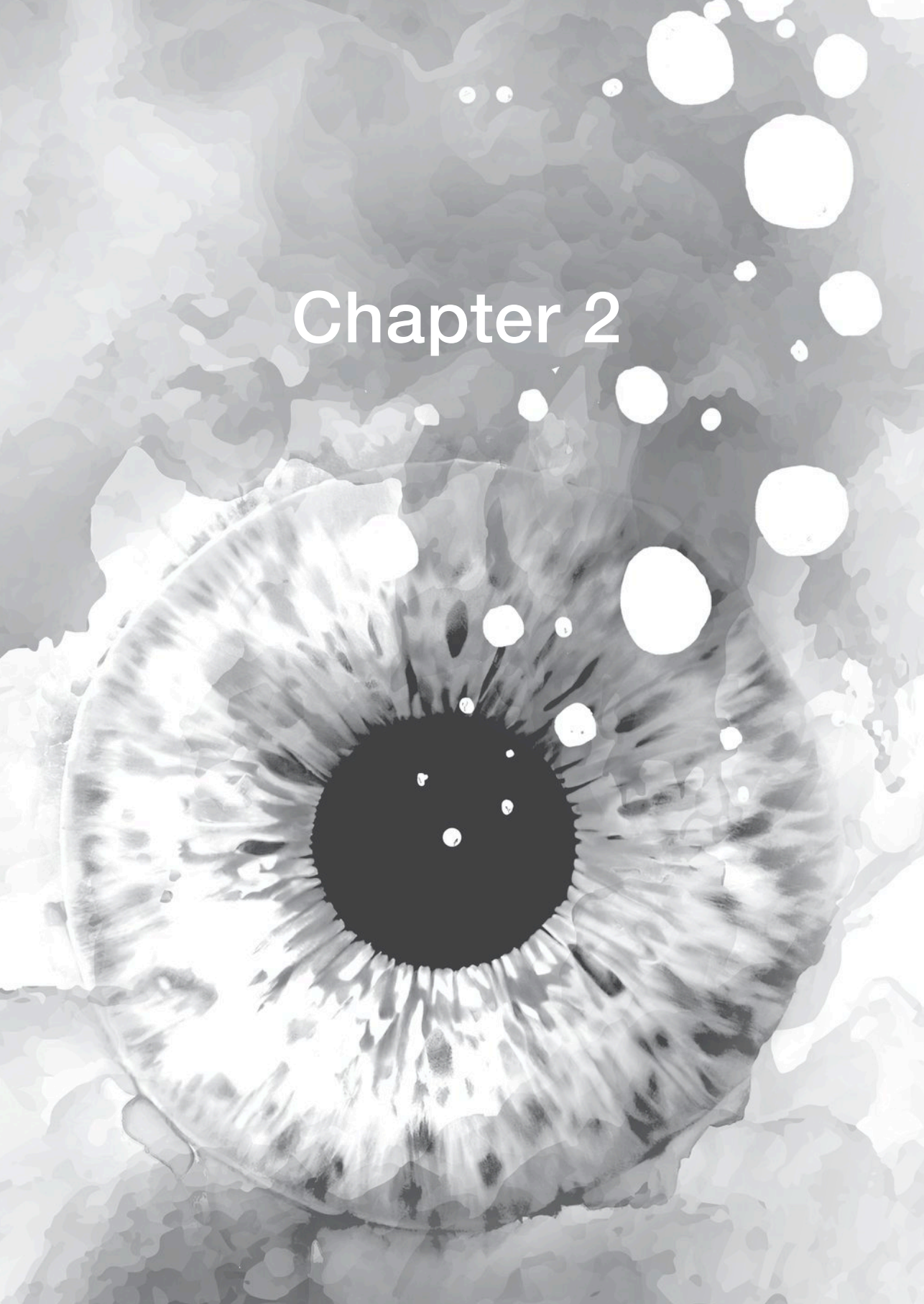
Chapter 2

Five decades of enucleations for Uveal Melanoma in one center: more tumors with high risk factors, no improvement in survival over time.

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Abstract

Background: In order to improve medical care for uveal melanoma (UM) patients, we need to monitor disease and survival to guide our research efforts. We analyzed the data of UM patients who underwent enucleation at the Leiden University Medical Center (LUMC) during the last five decades and investigated trends in patient and tumor characteristics and survival.

Methods: Data were collected from charts and pathology reports from all patients who underwent an enucleation for UM between 1973 and 2019 (n = 1212), of which 1066 were primary enucleations, and were analyzed according to five time periods: 1973-1979 (n = 209), 1980-1989 (n = 148), 1990-1999 (n = 174), 2000-2009 (n = 280) and 2010-2019 (n = 401).

Results: Over time, patients' age at the time of enucleation for UM increased from 54.9 to 64.7 years ($p < 0.001$), more showed histopathological involvement of the ciliary body ($p < 0.001$) and more tumors were classified in a high TNM/AJCC class ($p < 0.001$). Overall, the 5-year and 10-year UM-related survival rates were 0.68 and 0.59, respectively. Over time, survival showed no change in patients with tumors in AJCC stages I or III, and only recently a slightly worse survival in stage II UM ($p = 0.02$).

Conclusion: Between 1973 and 2019, we found similar rates of UM-related survival following enucleation, although we noticed a strong increase in more unfavorable tumor characteristics over time, such as an older age. The lack of improvement indicates that more research should take place to develop adjuvant treatment to prevent metastases and efficient treatment once metastases develop.

Introduction

Uveal melanoma (UM) is a rare tumor, even though it is the most common primary intraocular malignancy in adults. It originates from melanocytes in the uvea and mainly affects Caucasians, with an incidence of 5 to 7 per million in Western countries [1-5]. The mean age at diagnosis is around 60 years [6,3,4]. In most studies, women and men are affected equally, although some have reported a slightly higher incidence in males [3,4].

The 5-year survival rate of UM ranges from 60% to 82% [7-11], and the 10-year rate from 40% to 87% [7,9,11-13]. Most deaths are attributed to UM metastases [14,15,12], which involve the liver in 90% of the cases [16,17]. The mean time from primary tumor treatment to metastatic disease is 5.5 years [17], but metastases may develop even 40 years after initial diagnosis [18,19]. With respect to the effectiveness of modern treatments, UM differs greatly from cutaneous melanoma, as immunotherapy and mutation-targeting therapies are mostly ineffective in UM [20,21]. Immunotherapy [22,23] and treatment of liver metastases by isolated liver perfusion may prolong life in specific cases [24]. After detection of UM metastases, 80% of the patients die within one year [16,25,17].

Many different clinical and pathological UM parameters are associated with the development of metastases and poor prognosis. These include older age at presentation, a high largest basal diameter (LBD) of the tumor, a high percentage of epithelioid cells, high mitotic activity, ciliary body involvement, extraocular extension and the presence of an inflammatory phenotype [26,27,6,28,29]. The Tumor Node Metastasis (TNM) staging classification by the American Joint Committee on Cancer (AJCC) combines tumor size, ciliary body involvement and extraocular extension to classify patients into prognostic groups, with higher classes being associated with increased mortality [30]. Genetic factors for a poor prognosis include monosomy 3 (M3) and 8q amplification, a Class 2 gene expression profile, and loss of BRCA1 associated protein-1 (BAP1) expression [31-35].

With the development of sophisticated local treatments such as radioactive plaques and proton beam irradiation, enucleation has become a last resort approach. Furthermore, more intense follow-up and the introduction of new approaches, such as immunotherapy, isolated liver perfusion or resection and targeted chemotherapy, might have led to better survival. Our study population, which includes patients treated at the LUMC over the past 46 years, provides a large cohort, allowing the analysis of trends over time. The objective of this study is to determine whether, during this time period, changes occurred in tumor characteristics of patients selected to undergo enucleation and whether survival improved.

Methods

Study population

Data were collected from all patients who underwent an enucleation for UM at the Leiden University Medical Center (LUMC), The Netherlands, between 1973 and 2019 (*n* = 1212). The LUMC has been the main treatment center for UM in The Netherlands for over 50 years, and a standardized database for enucleations was set up in 1973. Data were analyzed based on five time periods, corresponding to five different decades: 1973-1979 (*n* = 209), 1980-1989 (n = 148), 1990-1999 (*n* = 174), 2000-2009 (*n* = 280) and 2010-2019 (*n* = 401). The variables assessed in this study include characteristics of the patients, histopathological tumor characteristics, chromosome status, and data on survival and the presence of metastatic disease.

Patient and histopathological characteristics

Both clinical information such as age at enucleation, gender, affected eye, ocular treatment prior to enucleation, and data on histopathological characteristics were collected from patient charts. Histopathological characteristics were determined through routine conventional analysis by ophthalmic pathologists; these included tumor location, involvement of the ciliary body, tumor thickness, largest basal diameter and cell type. Tumors were staged in accordance with the 8th edition of the AJCC Cancer Staging Manual, using the TNM model for anatomical staging [36,30].

Chromosome status

Analysis of chromosome status of UM started at our institution in 1999. Chromosome 3 status was obtained in 487 patients. This was tested by karyotyping, fluorescence in situ hybridization (FISH) or single nucleotide polymorphism (SNP) array, as previously described [37,38]. In short, karyotyping was performed following the regulations of the International System for Human Cytogenetic Nomenclature (1995), FISH was performed with DNA probes specific for the centromere of chromosome 3 and SNP array was performed with extracted DNA using the Affymetrix 250K_NSP microarray (Affymetrix, Santa Clara, CA, USA). When any of these tests revealed monosomy 3, the tumor was categorized as such [39,34,40,41].

Survival

Data about survival were obtained using both data from patients' charts and data retrieved from the Dutch National Cancer Registry. Follow-up time was last updated in August 2019 and was defined as the time between enucleation and death or last date of follow-up. The numbers of patients lost to follow-up were: 18 in total; 2 from 1973-1979; 4 from 1980-1989; 1 from 1990-1999; 8 from 2000-2009; 3 from 2010-2019.

Statistical analysis

Data were analyzed retrospectively using IBM SPSS Statistics version 25. Associations between categorical variables were assessed using Linear-By-Linear Association. Numerical variables were compared between the five groups using the one-way ANOVA test. Survival analyzes were performed using Kaplan-Meier curves and compared with a log-Rank test in SPSS. Additionally, multivariate binary logistic regression analysis and Cox univariate analysis were performed to examine time as a predictor of survival. Differences were considered statistically significant if $p < 0.05$.

Results

A total of 1212 patients underwent enucleation for UM at the LUMC in Leiden between 1973 and August 2019, of which 1066 were primary enucleations. Table 1 displays the main variables of the study cohort, compared between the five time periods.

Clinical features

From 1973 and 2019, the age at enucleation rose considerably, with a significant difference of 9.8 years in mean age between the first and last time period ($p < 0.001$). No significant changes were observed in gender distribution over the years, with an overall percentage of 55% males. The number of enucleations peaked in the last two decades. Among all time periods, enucleations were predominantly primary enucleations; however, the type of therapy given prior to secondary enucleations differed significantly between the groups. Enucleations following transpupillary thermotherapy (TTT) and sandwich therapy (a combination of ruthenium brachytherapy and TTT) were especially noticed in 3% and 9% of the cases, respectively, in the two time periods between 1990 and 2010, when this therapy was en vogue (Figure 1) [42].

Histopathology

Tumor location changed over the years, mainly due to a significant increase in involvement of the ciliary body and peripheral choroid while the number of tumors with mid-choroidal (the area between the vascular arcade and peripheral choroid), and posterior pole involvement remained stable. Both tumor thickness and diameter increased in the last two time periods. Regarding the AJCC stage of the patients, in the first three time periods, over 30% of tumors were stage I, but this was less than 25% in the last two, while stage II fluctuated around 50% and TNM stage III increased steadily over time from 11% to 25% ($p < 0.001$)(Figure 2).

Table 1. Clinical and histopathological variables of UM cases who underwent enucleation, divided over five decades.

Time period	All (*n* = 1212, %)		1973-1979 (*n* = 209, %)		1980-1989 (*n* = 148, %)		1990-1999 (*n* = 174, %)		2000-2009 (*n* = 280, %)		2010-2019 (*n* = 401, %)		*P**
Gender (*n* = 1212)													0.13[1]
Female, n (%)	550	(45%)	100	(48%)	72	(49%)	80	(46%)	129	(46%)	169	(42%)	
Male, n (%)	662	(55%)	109	(52%)	76	(51%)	94	(54%)	151	(54%)	232	(60%)	
Eye (*n* = 1212)													0.31[1]
Right eye, n (%)	610	(50%)	107	(51%)	63	(43%)	88	(51%)	141	(50%)	211	(50%)	
Left eye, n (%)	602	(50%)	102	(49%)	85	(57%)	86	(49%)	139	(50%)	190	(50%)	
Age at enucleation, mean [SD] (*n*=1212)	61.2	[14.4]	54.9	[16.0]	59.5	[13.6]	61.7	[14.8]	61.8	[13.5]	64.7	[13.2]	<0.001[2]
Primary therapy (*n* = 1212)													<0.001[1]
Primary enucleation, n (%)	1066	(88%)	209	(100%)	141	(95%)	148	(85%)	222	(79%)	346	(86%)	
TTT, n (%)	11	(1%)	0	(0%)	0	(0%)	2	(1%)	9	(3%)	0	(0%)	
Ruthenium brachytherapy, n (%)	61	(5%)	0	(0%)	4	(3%)	6	(3%)	15	(5%)	36	(9%)	
Sandwich therapy, n (%)	42	(3.5%)	0	(0%)	0	(0%)	13	(7.5%)	25	(9%)	4	(1%)	
Proton beam therapy, n (%)	26	(2%)	0	(0%)	3	(2%)	5	(3%)	8	(3%)	10	(2.5%)	
Stereotactic radiotherapy, n (%)	5	(0.4%)	0	(0%)	0	(0%)	0	(0%)	1	(0.4%)	4	(1%)	
Areas with tumor involvement (*n* = 1212)													
Ciliary body, n (%)	347	(29%)	31	(15%)	13	(8.8%)	36	(21%)	93	(33%)	174	(44%)	<0.001[1]
Peripheral choroid, n (%)	611	(51%)	100	(48%)	41	(28%)	78	(43%)	152	(54%)	240	(60%)	<0.001[1]
Mid choroid, n (%)	740	(61%)	162	(78%)	90	(61%)	84	(48%)	198	(68%)	215	(54%)	<0.001[1]
Posterior pole, n (%)	499	(41%)	102	(49%)	43	(36%)	75	(43%)	120	(43%)	149	(37%)	0.05[1]
Tumor diameter, mean [SD] (*n*=1192)	11.3	[3.7]	10.9	[3.7]	11.4	[3.1]	10.6	[3.6]	12.0	[3.9]	11.3	[3.8]	0.001[2]
Tumor thickness, mean [SD] (*n*=1192)	5.7	[3.6]	5.1	[3.3]	5.4	[3.1]	5.1	[3.1]	6.4	[3.3]	6.0	[3.3]	<0.001[2]
Cell type (*n* = 1194)													<0.001[1]
Spindle, n (%)	353	(31%)	109	(52%)	44	(30%)	69	(40%)	86	(31%)	75	(18%)	

Time period	All (*n* = 1212, %)		1973-1979 (*n* = 209, %)		1980-1989 (*n* = 148, %)		1990-1999 (*n* = 174, %)		2000-2009 (*n* = 280, %)		2010-2019 (*n* = 401, %)		*P**
Epithelioid or mixed, n (%)	811	(68%)	97	(46%)	101	(68%)	98	(56%)	192	(69%)	323	(82%)	
Tumor pigmentation (*n* = 1170)													0.27[1]
None to mild, n (%)	617	(53%)	117	(57%)	67	(48%)	89	(52%)	158	(60%)	186	(47%)	
Moderate to heavy, n (%)	553	(47%)	90	(43%)	74	(52%)	81	(48%)	103	(40%)	205	(52%)	
Scleral ingrowth (*n* = 1197)													<0.31[1]
None to superficial, n (%)	770	(64%)	129	(62%)	79	(53%)	121	(70%)	164	(59%)	277	(70%)	
Deep, n (%)	281	(24%)	57	(28%)	49	(33%)	34	(20%)	81	(29%)	60	(15%)	
Extrascleral extension, n (%)	146	(12%)	21	(10%)	19	(13%)	17	(10%)	34	(12%)	55	(14%)	
T size in AJCC, mean [SD] (*n* = 1152)	2.0	[0.9]	1.8	[0.8]	1.9	[0.8]	1.8	[0.8]	2.2	[0.8]	2.1	[0.9]	<0.001[2]
AJCC stage (*n* = 1125)													<0.001[1]
I, n (%)	299	(27%)	73	(36%)	47	(32%)	65	(38%)	43	(16%)	71	(21%)	
IIA, n (%)	360	(32%)	73	(36%)	55	(38%)	52	(30%)	88	(33%)	92	(27%)	
IIB, n (%)	256	(23%)	33	(16%)	26	(18%)	30	(18%)	80	(30%)	87	(26%)	
IIIA, n (%)	148	(13%)	15	(7%)	13	(9%)	19	(11%)	42	(15%)	59	(17%)	
IIIB, n (%)	45	(4%)	6	(3%)	3	(2%)	4	(2%)	11	(4%)	21	(6%)	
IIIC, n (%)	15	(1%)	2	(1%)	2	(1%)	1	(0.6%)	7	(3%)	3	(1%)	
IV, n (%)	2	(0.2%)	0	(0%)	1	(0%)	0	(0%)	0	(0%)	2	(1%)	
Monosomy 3 (*n* = 487)													0.12[1]
No, n (%)	230	(47%)	ND		ND		2	(50%)	80	(47%)	148	(47)	
Yes, n (%)	257	(53%)	ND		ND		2	(50%)	89	(53%)	166	(53%)	

Variables are denoted as absolute number counted (percentage) or mean (SD).
Ω Mitotic count = n/mm2 at 40× magnification, eight high-power fields.
*Group differences were tested with:
[1] Linear-by-Linear Association
[2] One-way ANOVA
Abbreviations: ND = not determined.

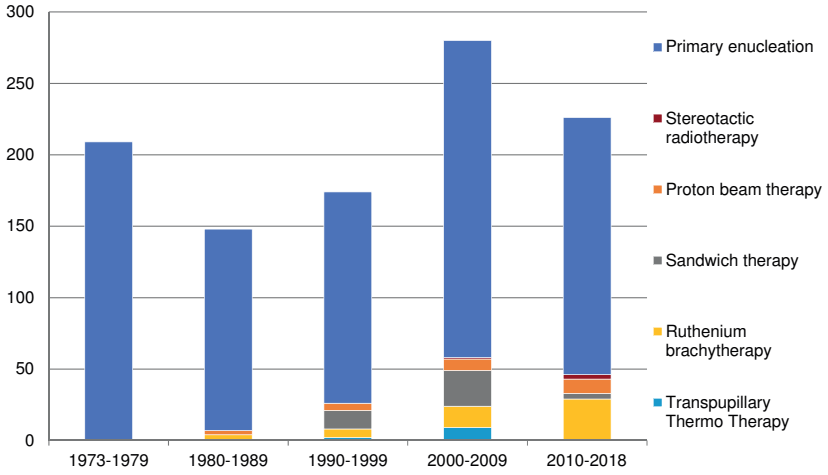


Figure 1. Prior therapy of eyes undergoing enucleation for a UM between 1973 and 2019, displayed in absolute number of patients in each time period.

In 1973-1979, 52% of the tumors showed a spindle cell type and 48% a mixed or epithelioid cell type. However, by 2010-2019, this had changed to 18% spindle cell vs. 82% mixed or epithelioid ($p < 0.001$). Tumor pigmentation and (extra)scleral tumor extension showed some fluctuations between the groups, which differences were not statistically significant. The chromosome status is mainly known in 2000-2009 and 2010-2019: in both time periods, the percentage of tested patients with monosomy 3 was 53%.

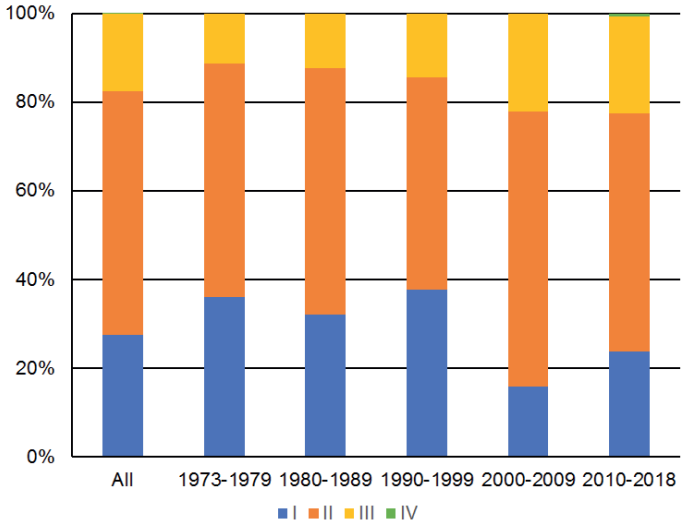
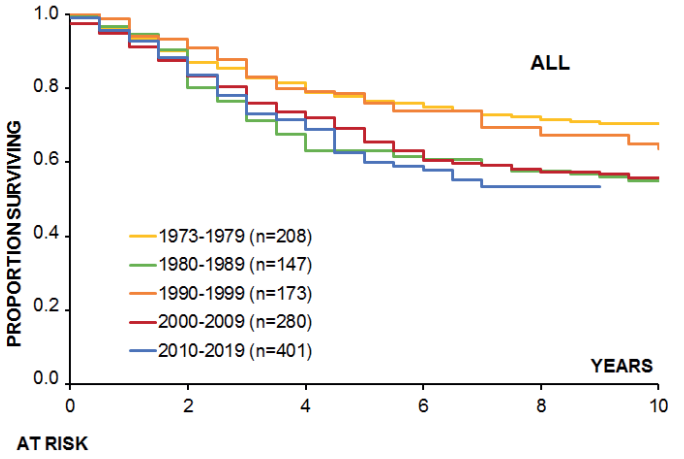
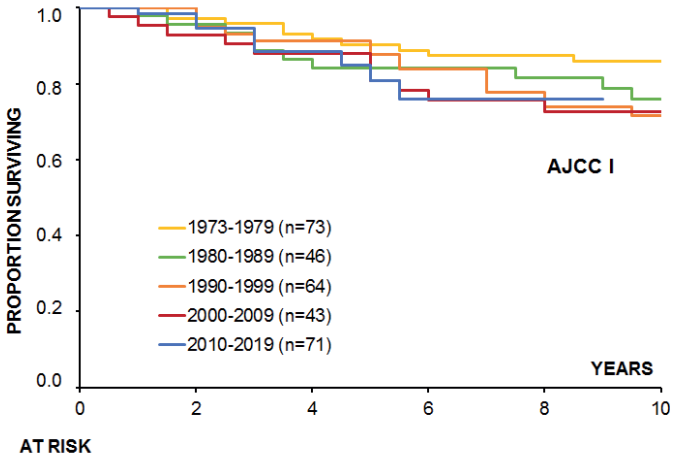


Figure 2. TNM stage of UM in eyes that have been enucleated between 1973 and 2019.



AT RISK

1973-1979	178	157	142	125	117
1980-1989	127	91	82	69	64
1990-1999	150	122	106	96	86
2000-2009	233	187	148	108	65
2010-2019	251	127	55	18	



AT RISK

1973-1979	70	67	62	57	54
1980-1989	44	37	36	31	28
1990-1999	58	52	44	39	33
2000-2009	39	36	31	27	21
2010-2019	54	33	15	6	

Figure 3A. Kaplan-Meier curves showing UM-related survival of patients who underwent an enucleation for UM in five different time groups, respectively for all patients ($p < 0.001$) and AJCC stage I ($p = 0.37$)

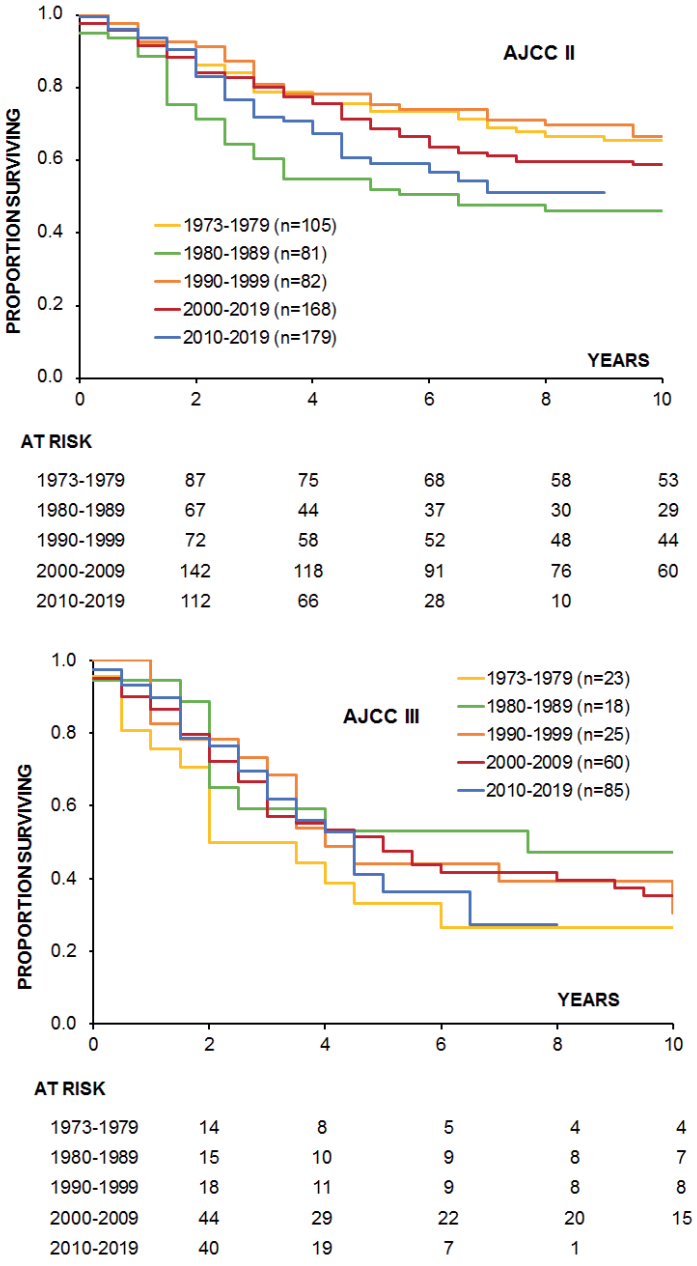


Figure 3B. Kaplan-Meier curves showing UM-related survival of patients who underwent an enucleation for UM in five different time groups, respectively for AJCC stage II (p = 0.02) and AJCC III (p = 0.64)

Survival

UM-related survival Kaplan-Meier curves differed significantly between the time periods, however, no specific trend or pattern could be identified (Log-Rank test, p = 0.001). Table 2 displays UM-related survival and overall survival proportions in all groups. Combining all cases, UM-related survival was 0.68 after 5 years and 0.59 after 10 years. The 5-year and 10-year UM-related survival rates were, respectively, 0.77 and 0.70 in 1973-1990, 0.63 and 0.55 in 1980-1989, 0.76 and 0.64 in 1990-1999, 0.66 and 0.56 in 2000-2009, with a 5-year survival for 2010-2019 of 0.60. However, comparing the first and last UM-related survival curve within the different AJCC stages, the survival did not significantly change in stage I (p = 0.37) and stage III (p = 0.64), but did in stage II (p = 0.02), where a worse survival was seen for the most recent time period (Figure 3). A multivariate analysis with time periods as a predictor of mortality was performed, correcting for age at enucleation and AJCC stage. The adjusted odds ratio (AOR) with period 1973-1979 as reference were 0.70 (0.45 – 1.10 95%CI) for 1980-1989; 1.01 (0.65 – 1.57 95% CI) for 1990-1999; 1.01 (0.73 – 1.61 95% CI) for 2000-2009; 2.38 (1.94 – 3.57 95%CI) for 2010-2019.

Table 2. UM-related and overall survival in patients who underwent enucleation for UM divided according to decade.

	All (n = 1209)	1973-1979 (n = 208)	1980-1989 (n = 147)	1990-1999 (n = 173)	2000-2009 (n = 280)	2010-2019 (n = 401)
5-year UM-related survival	0.68	0.77	0.63	0.76	0.66	0.60
(95% CI)	(0.66 – 0.70)	(0.71 – 0.83)	(0.55 – 0.71)	(0.70 – 0.82)	(0.60 – 0.72)	(0.52 – 0.68)
10-year UM-related survival	0.59	0.70	0.55	0.64	0.56	ND*
(95% CI)	(0.55 – 0.63)	(0.64 – 0.76)	(0.47 – 0.63)	(0.56 – 0.72)	(0.50 – 0.63)	
5-year overall survival	0.59	0.69	0.58	0.64	0.58	0.49
(95% CI)	(0.55-0.63)	(0.63-0.75)	(0.50-0.66)	(0.56-0.72)	(0.52-0.64)	(0.43-0.55)
10-year overall survival	0.45	0.56	0.45	0.49	0.40	ND*
(95% CI)	(0.41-0.49)	(0.50-0.62)	(0.37-0.53)	(0.41-0.57)	(0.34-0.46)	

Data are presented as proportion (95% CI).
Abbreviations: ND = not determined.
* Value could not yet be calculated at the time of the study.

Discussion/Conclusion

When comparing five decades of our cohort of 1212 UM patients who underwent enucleation at the LUMC between 1973 and 2019, we found no improvement in UM-related survival over time after correction for TNM/AJCC stage. Stage II even showed a slightly worse 5-year survival during the last decade than during the first period.

Also, the AOR for mortality was the highest in the period between 2000 and 2019. We noticed changes over time regarding tumor characteristics, including an increase in age, an increased involvement of the tumor in the ciliary body and a higher prevalence of AJCC stage III at the expense of AJCC stage I.

Even though, in general, the treatment for UM has changed from enucleation to eye-preserving treatments, and new approaches have become available to treat metastases (e.g. hepatic perfusion, liver surgery, chemotherapy and immunotherapy), we did not see an improvement in survival over time. When looking at the tumor characteristics, we observed a shift to higher risk categories (AJCC stage, ciliary body involvement). This means that the included cases in our cohort have changed to patients with more aggressive tumors over time. We think this trend is the result of selection of cases that require enucleation, as this now has become the treatment of last resort in often elderly patients who cannot be treated by radio-active plaque or proton beam therapy: the significant increment of age at enucleation over the years may be due to alternative treatments being offered to younger, more resilient individuals, leaving the older patients in the study cohort. The fact that not only tumor TNM/AJCC stage but also other parameters such as age play a role is demonstrated by the decreased UM-related survival in the last decade compared to the first for AJCC stage II.

A few studies have investigated UM mortality over time. Aronow et al. compared 5-year relative survival rates in a cohort of 4999 patients, in 3-year time intervals from 1973 to 2013, which remained stable around 81% over time [5]. Bergman and Seregard calculated a crude survival rate of 60% at 5 years and 43% at 10 years, and a relative survival of 70% at 5 years and 59% at 10 years, from 2997 cases with UM between 1960 and 1998 [43]. Kujala and Kivela investigated the very long term prognosis of UM in Finland and found a 5-year melanoma-related mortality of 31%, and a 35-year rate of 52% [9]. They followed a cohort of 289 patients included between 1962 and 1981 but did not compare their data to a more recent cohort. Their report does not state if the frequency of poor prognostic histopathological factors increased or decreased over time. Other investigations on UM-related survival only report average survival rates, without comparison between cohorts from varying time periods. Our 5 and 10-year UM-related mortalities are comparable to the rates in the other mentioned studies [7-9,27,10,11]. However, reports differ and depend on the type of primary UM that are included (e.g. primary tumor size and location). Therefore, to observe trends in survival, it must be measured in cohorts that are comparable regarding epidemiological factors. A study by Shao et al. reviewed 49 studies to investigate reasons for different survival outcome in UM patients with a bad prognosis. They conclude that both study methods and outcome methods have to be standardized in order to generate comparable survival

data [44]. By and large, our findings are consistent with the limited available data regarding UM survival trends over time.

A recent paper concerning metastatic UM stated that different treatment modalities of metastases have not made a difference in mortality [45,46]. In The Netherlands, a registry has been set up that includes UM patients with metastases. Jochems et al. studied this cohort consisting of 227 patients added between 2012 and 2018, of which 175 patients had complete data. Cases that were eligible for local treatment of metastases (e.g. surgical resection, isolated hepatic perfusion with melphalan, radiotherapy, radiofrequency ablation) showed the best survival, with a 1-year survival of 82%, versus 49% for systemic therapy and 28% for supportive care [47]. These data indicate that especially young patients with a good WHO performance score and few metastatic sites are good candidates for local therapy. Although we do not know how many of the patients in Jochems' study were included in our cohort, it is likely that there is overlap.

This investigation has several limitations. First, we only had access to the data of enucleated patients. We think that the cases that were included in our analysis typically concern the larger and more aggressive tumors. In the latest decades, smaller tumors did not require enucleation and were consequently poorly represented in our cohort. Our results are therefore more reliable for larger than smaller tumors. Another limitation is that, while some advocate the use of time to metastases as a measure of tumor malignancy, we did not have reliable data on the onset of metastatic disease.

However, over the last five decades, we notice that enucleation takes place in elder patients with more high risk tumor characteristics, as patients with low risk tumors are eligible for treatments other than enucleation. Despite the development of more specialized treatment of primary tumors, our results do not show improvement in survival rates, but the increased age of the groups (from a mean of 54.9 to 64.7 years) may play a role here. When using the risk assessment algorithm LUMPO III,[48] this becomes obvious: when assessing survival of a male patient with a UM with a largest basal diameter of 15 mm, thickness of 5 mm, and monosomy 3, 10-year survival in a 54-year old would be predicted to be 47%, but in a 64-year old 35%. The focus of engagement in UM research should be on adjuvant treatment to prevent metastases and treatment of metastatic disease. The results of treating metastatic UM with combinations of immune checkpoint inhibitors and the application of new therapies such as tebentafusp (formerly IMCgp100) are eagerly awaited, generating potential for the future [22,49,23].

Additionally, for future studies investigating UM survival trends, we recommend studying all UM patients, not only those who underwent enucleation. To monitor disease, evaluate treatment and survival, and guide our research efforts into the right direction, it is very important to conduct epidemiological studies on UM patient groups.

Statements

Acknowledgements

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The project was approved in August 2019 by the Biobank and Medical Ethics Committee of the LUMC (number: Uveamelanoomlab-2019-9). The research adhered to Dutch law and the tenets of the Declaration of Helsinki (World Medical Association of Declaration 2013; ethical principles for medical research involving human subjects).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.D.M. Roelofsen, A.P.A. Wierenga and M.J. Jager designed and conducted the study including analysis and interpretation of the data and manuscript preparation. Sjoerd van Duinen, Robert M. Verdijk, Jaco Bleeker, Marina Marinkovic and Gregorius P.M. Luyten were involved in data collection and manuscript review.

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