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Conjunctival and uveal melanoma: Survival and risk factors following orbital exenteration

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Abstract

Purpose: This study aims to analyse disease-free survival, overall survival and risk factors after orbital exenteration in patients with conjunctival and uveal melanoma.

Methods: Patients who underwent orbital exenteration due to conjunctival and uveal melanoma were included in this retrospective study (March 2000 to March 2018).

Results: A total of 76 patients were enrolled in this study: 60 patients had a conjunctival melanoma and 16 had a uveal melanoma. In conjunctival melanoma, the mean age was 68.4 years. The overall survival rate was 82% after 1 year and 52% after 5 years. Univariate analysis of overall survival found that the following parameters were predictive of a worse prognosis: gender, extent of the primary tumour, lymph node metastases, distant metastases, adjuvant chemotherapy or radiotherapy and relapse. In multivariate analysis, relapse and adjuvant radiotherapy appeared to contribute to a significantly worse prognosis. In uveal melanoma, the mean age was 63.6 years. Eleven patients died during follow-up (mean follow up 30.7 months). The overall survival and disease-free survival rates after 1 year were 62% and 57%, respectively. An analysis of risk factors was not possible due to the small number of cases.

Conclusion: Orbital exenterations in conjunctival and uveal melanoma are rarely necessary, but can be performed as an ultima ratio treatment with curative intent. Disease-free survival and overall survival are significantly lower for both groups due to the advanced stage of the disease compared to patients treated without exenteration in the literature. If a recurrence occurs after exenteration, the prognosis is poor in both groups.

Keywords

Orbital exenteration, uveal melanoma, conjunctival melanoma, disease-free survival, overall survival, risk factor

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Introduction

Conjunctival and uveal melanomas are rare tumours that arise from melanocytes. Both tumours can metastasise early and thus be life threatening, so early diagnosis, the detection of risk factors and optimisation of therapies are crucial for long-term survival.

On the one hand, conjunctival melanoma develops from primary acquired melanosis (PAM, 26%–57%), as a de novo naevus (27%–40%) or from a pre-existing naevus (4%–34%).[1,2] There is still no generally recommended therapy. In most cases, surgical excision is performed. However, surgical excision alone shows an increased recurrence rate and adjuvant or combined therapy is recommended.[3] This therapy may include cryotherapy, chemotherapy (such as mitomycin C), irradiation, brachytherapy, alcohol epitheliectomy or combinations of these treatments.[4,5] This tumour metastasises mainly to local lymph nodes; distant metastases to the liver, lungs, brain, skin or other locations occur less frequently.[6,7]

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On the other hand, uveal melanoma arises from the melanocytes of the choroid layer, ciliary body or iris. In contrast to conjunctival melanomas, this tumour usually does not spread to local lymph nodes, but mainly metastasises to distant organs, especially to the liver in about 90% of cases.[7] Several factors such as tumour size, presence or absence of metastases, visual acuity of the affected and contralateral eye, general health of the patient and location contribute to the choice of the best treatment option.[8] These include brachytherapy, charged-particle radiation therapy, photocoagulation, transpupillary thermal therapy, photodynamic therapy, transretinal or transscleral resection and enucleation.[9]

Common to both tumours, however, is that orbital exenteration remains the last resort. Basically, exenteration should be performed in cases of multifocal or recurrent disease or a dysfunctional, painful eye (conjunctival melanoma) or in cases of an extraocular tumour growth (uveal melanoma), and if there is a significant survival benefit for the patient. Therefore, this radical operation is rarely necessary and little information exists on survival and predictive factors.[5]

Thus, the aim of this study is to evaluate the effect of orbital exenteration on overall and disease-free survival in patients suffering from uveal and conjunctival melanoma. In addition, we analyse prognostic factors in these cases.

Materials and methods

Patients

Patients who underwent orbital exenteration due to malignant melanoma were identified and included in a retrospective study. The study period was March 2000 to March 2018. Patients with an enucleation were not included. In addition, patients having a follow-up period of less than 18 months and those with missing or incomplete records were also excluded. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee (University of Essen; No. 18-8406-BO) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patients did not sign informed-consent forms due to the retrospective study design. The data have been coded.

Orbital exenteration

The dimension of surgery depended on the origin, localisation and extent of the underlying disease. The procedure was performed as total (removal of all orbital contents, including the periorbital and lids), subtotal (preservation of some periocular tissue) or extended (additional removal of the bony orbit) exenteration. All the patients were presented at a multidisciplinary tumour conference to determine further therapy prior to the operation.

Follow up, survival and risk factors

The follow-up period was monthly in the first year, every 2 months in the second year and then every 6 months. Overall survival (OS) was determined along with disease-free survival (DFS). DFS was defined as the time from the operation to relapse (local recurrence, lymph node metastasis or distant metastasis) or all-cause death, whichever came first.

Recurrent diseases before exenteration were documented (relapse preoperative). These were defined as recurrent conjunctival tumour (conjunctival melanoma) or recurrent intraocular tumour with or without extraocular tumour growth (uveal melanoma). In addition, the following data were collected: gender, site, history of radiotherapy or chemotherapy before exenteration, pain at presentation, additional neck dissection, additional parotidectomy (none, primary or secondary parotidectomy), size or extent of the primary tumour (T), the presence or absence of lymph node metastases (N) or distant metastases (M), microscopically margin-negative resections (R0) or microscopically margin-positive resections (R1), invasion into lymphatic vessels (L), perineural invasion (PNI), cell type (not specified, epithelioid/mixed, spindle cell), adjuvant therapies (radiotherapy, chemotherapy), history of immunosuppression, presence of a second tumour and relapse (local recurrence, lymph node metastasis or distant metastasis). Local recurrence after exenteration was defined as a recurrent orbital tumour. Distant metastases were defined as extraorbital manifestations.

In patients with conjunctival melanoma, the focality (unifocal, multifocal) and localisation were investigated. According to Paridaens, epibulbar (cornea, limbus or bulbar conjunctiva) and non-epibulbar (caruncle, fornices and palpebral conjunctiva) locations were distinguished.[1,10] The TNM classification of malignant conjunctival and uveal melanoma was used according to the eighth edition of the TNM classification.[11]

Statistics

Statistical analysis of the data was performed using the statistical software SPSS Statistics 21 (SPSS Inc.; IBM Company, Chicago, USA) and Microsoft Office 2010 Home and Student (Redmont, USA). Descriptive statistics were used to describe categorical patient characteristics. Kaplan–Meier plots were used to represent OS and DFS. The log-rank test was used to elicit differences. Multivariate analyses were performed using a Cox proportional hazards model. The level of significance in the statistical tests was set to $p < 0.05$ and $p < 0.001$.

Results

From March 2000 to March 2018, a total of 84 patients matched the inclusion criteria. Two patients were excluded

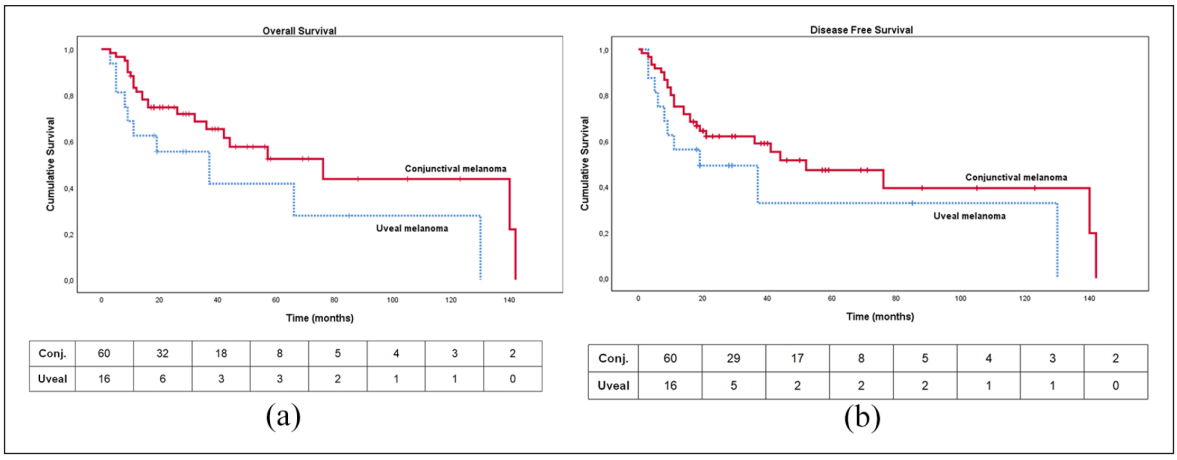

Figure 1. Kaplan–Meier plot in relation to tumour category and at-risk table: (a) Overall survival and (b) Disease-free survival.

from the study for having a follow-up period of less than 6 months, and five due to missing or incomplete records. In addition, one patient refused exenteration.

Conjunctival melanoma

The remaining cohort consisted of 31 female and 29 male patients. The mean age was 68.4 years with a range of 34–89 years. The mean follow up was 34.8 months. The mean perioperative stay was 20 days, including the staging. Of the 60 patients with conjunctival melanoma, 75% had recurrence at the time of presentation (45 cases). Thirty-one patients had a multifocal disease (52%). Five patients showed distant metastases (liver 3×, lungs 1×, brain 1×) and the indication for exenteration was a painful eye in all these patients.

A local R0-resection could be achieved in all the patients by orbital exenteration. Of these, only two patients needed a second resection to obtain a R0-resection. Additional procedures were performed in 22 patients (18 neck dissections, 17 parotidectomies). Of the 17 patients with parotidectomy, 8 had lymph node metastases. Adjuvant therapy was performed in 33 patients (radiotherapy in 4 patients, chemotherapy in 23 patients and combined radio- and chemotherapy in 6 patients). In total, 13 patients had a relapse (22%): 3 patients had a local recurrence, 9 showed lymph node metastases and 4 distant metastases (liver 2×, lung 1×, skin 1×). Of these, one patient had a lymph node metastasis with distant metastases, and one patient had a local recurrence with lymph node and distant metastases. Twenty-five of our patients with a conjunctival melanoma died (42%) during follow-up. Of these, the cause of death was tumour-related in 20 patients and unknown in 5 patients. The OS rate was 82% after 1 year and 52% after 5 years for all patients with conjunctival melanoma (Figure 1). In comparison, the DFS rate was 75% after 1 year and 47% after 5 years (Figure 1). Table 1 gives a detailed overview of patient characteristics, DFS and OS in relation to all collected parameters (Table 1).

Univariate analysis of DFS shows that the following parameters significantly predict a worse prognosis: female gender ($p=0.020$), neck dissection ($p=0.046$), parotidectomy ($p=<0.001$), lymph node metastases ($p=0.020$), adjuvant radiotherapy ($p=0.014$) and adjuvant chemotherapy ($p=0.010$). In contrast, parotidectomy ($p=<0.001$) and adjuvant chemotherapy ($p=0.028$) appear to be independent factors that result in a significantly worse prognosis in multivariate analysis. Univariate analysis of OS shows that the following parameters significantly predict a worse prognosis: female gender ($p=0.013$), T3/4 tumours ($p=0.044$), lymph node metastases ($p=0.021$), distant metastases ($p=0.024$), adjuvant radiotherapy ($p=0.001$), adjuvant chemotherapy ($p=0.043$) and relapse ($p=0.003$). Multivariate analysis of OS shows that adjuvant radiotherapy ($p=0.028$) and relapse ($p=0.026$) are independent risk factors. Table 2 shows univariate and multivariate analyses of risk factors in relation to DFS and OS (Table 2).

Uveal melanoma

A total of 16 patients had a uveal melanoma. Of these 11 were female and 5 were male. The mean age was 63.6 years with a range of 26–94 years. The mean follow up was 30.7 months. The mean perioperative stay was 18 days, including the staging. Ten of them (63%) had previously been treated with other therapies and showed a local recurrence at the time of presentation. The indication for exenteration was an extraocular tumour growth in all patients. In addition, two patients had a blind, painful eye. Eight patients had a subtotal, three had a total and five an extended exenteration. Additional procedures (neck dissections, parotidectomies) were not performed. A local R0-resection could be achieved in 12 patients. Adjuvant therapy was performed in eight cases (50%). One patient

Table 1. Patient characteristics, DFS, OS and mean survival (months).

	Conjunctival melanoma						Choroidal melanoma
	No.	DFS		OS		Mean survival (95% confidence interval)	No.
		1 year (%)	5 year (%)	1 year (%)	5 year (%)		
	60	75	47	82	52		16
Gender							
Female	31	65	34	77	36	28 (19.85–36.80)	11
Male	29	86	62	90	70	42 (27.15–56.15)	5
Site							
Left	30	90	44	93	51	35 (25.33–45.47)	10
Right	30	60	47	69	51	34 (20.56–47.70)	6
Localisation							
Epibulbar	10	70	NA	89	NA	30 (9.66–50.34)	NA
Non-epibulbar	50	76	48	80	50	36 (26.47–44.97)	
Focality							
Unifocal	29	76	53	83	61	35 (20.93–49.41)	NA
Multifocal	31	74	43	81	47	34 (24.87–43.90)	
Relapse preoperative							
No	15	93	NA	93	NA	29 (17.96–39.77)	6
Yes	45	69	41	78	46	37 (26.28–47.19)	10
Pain							
No	51	78	48	82	52	34 (25.52–42.00)	14
Yes	9	56	NA	78	NA	40 (5.89–75.00)	2
Type of exenteration							
Subtotal	35	77	38	85	43	33 (23.84–42.96)	8
Total	20	65	NA	70	NA	37 (18.70–55.30)	3
Extended	5	100	NA	100	NA	NA	5
Neck dissection							
No	42	79	59	83	60	37 (26.89–46.97)	16
Yes	18	67	NA	77	NA	30 (14.37–45.08)	0
Parotidectomy							
None	43	81	56	84	57	34 (25.75–42.44)	16
Primary	11	73	NA	82	NA	43 (9.46–77.08)	0
Secondary	6	33	NA	67	NA	NA	0
T							
1	12	92	NA	100	NA	53 (26.37–78.96)	0
2	23	74	NA	83	NA	35 (20.24–50.63)	3
3	15	53	NA	67	NA	23 (15.45–30.82)	0
4	10	80	NA	80	NA	29 (13.13–45.27)	13
N							
0	49	80	58	86	62	37 (27.15–46.73)	16
1	11	54	NA	64	NA	25 (14.73–35.34)	0
M							
0	55	80	50	84	54	37 (27.89–45.45)	16
1	5	20	NA	25	NA	NA	0
L							
0	57	75	49	84	54	36 (27.28–44.37)	14
1	3	NA	NA	NA	NA	NA	2
Cell type							
Epithelioid / mixed	24	83	42	83	62	32 (23.25–41.42)	4
Spindle cell	10	70	NA	100	NA	26 (12.56–38.64)	0
Not specified	26	69	50	73	51	41 (23.61–57.47)	12

(Continued)

Table 1. (Continued)

	Conjunctival melanoma						Choroidal melanoma
	No.	DFS		OS		Mean survival (95% confidence interval)	No.
		1 year (%)	5 year (%)	1 year (%)	5 year (%)		
RTx pre							
No	25	80	48	84	53	32 (20.64–42.72)	8
Yes	35	71	47	80	52	37 (24.92–49.02)	8
Adj. CTx							
No	50	78	59	84	60	37 (27.78–46.86)	15
Yes	10	60	NA	70	NA	22 (10.76–33.24)	1
Adj. RTx							
No	31	94	61	100	71	40 (28.45–51.36)	9
Yes	29	55	33	61	32	29 (17.15–41.41)	7
Relapse							
No	47	–	–	92	69	38 (27.60–47.72)	13
Yes	13			69	0	24 (13.81–34.81)	3
-Local	3						2
-Lymph node	9						1
Immuno-suppression							
No	57	77	49	79	52	36 (27.44–44.49)	16
Yes	3	NA	NA	69	NA	NA	0
Second tumour							
No	57	77	47	82	52	36 (26.98–44.41)	14
Yes	3	NA	NA	NA	NA	NA	2

T: extent of the primary tumour; N: spread to regional lymph nodes; M: presence of distant metastasis; L: invasion into lymphatic vessels; RTx pre: history of preoperative radiotherapy; Adj. RTx/CTx: adjuvant radiotherapy/chemotherapy; NA: not available.

had a local recurrence, one had a local recurrence with lymph node metastasis preauricular and one showed distant metastasis to the liver. Eleven patients died during follow-up. Table 1 gives an overview of patient characteristics. After 1 year, the OS and DFS rates were 62% and 57%, respectively (Figure 1). A calculation of the OS and DFS rates with reference to the risk factors was not performed due to the small number of cases.

Discussion

We assessed conjunctival and uveal melanoma separately, since both diseases have completely different biologies.

Conjunctival melanoma: Shields et al. found in their study that exenteration due to conjunctival melanoma was necessary in 8% of the cases within a follow-up period of 5 years.[12] In fact, 75% of our patients showed a relapse after primary treatment, necessitating orbital exenteration as a curative therapy. In these cases, exenteration was the last-resort treatment for the patients. In addition, more than 50% patients had a multifocal lesion.

In another study, Shields et al. presented 20 patients with conjunctival melanoma who required exenteration due to the advanced stage of the disease.[13] Four patients died (20%) and three more (15%) developed metastases. Visual acuity of 20/200 or worse, lack of tumour pigmentation and extralimbal localisation were risk factors predictive for orbital exenteration in multivariable analysis.

Furthermore, patients should be examined for possible lymph node metastases. A neck dissection should be performed in the case of suspected isolated metastases in the neck area. Alternatively, some authors recommend a sentinel lymph node biopsy to verify affected lymph nodes.[14] In our cohort, 11 patients had a single lymph node metastasis; multiple lymph node metastases were not found in any patient. Interestingly, eight of these metastases (73%) were found in the parotid gland. This also explains why parotidectomy represents an independent prognostic factor in multivariate analysis for DFS. The same applies to adjuvant radiotherapy/chemotherapy as independent prognostic factors, as these are usually performed in advanced diseases. In this regard, another fact seems to be even more interesting: a local R0-resection could be achieved by orbital exenteration in all cases. In addition, there were only 3 local relapses out of 13 recurrences (23%). It is therefore probable that occult (micro-) metastasis already exists in advanced diseases, as in our cohort, and these seem to be crucial for the prognosis of the patient. Thus,

Table 2. Univariate/Multivariate analysis: Log-rank test (*p*-values) for potential prognostic factors in relation to relapse and death.

	Conjunctival Melanoma			
	Univariate analysis		Multivariate analysis	
	Relapse	Death	Relapse	Death
Gender	**0.020**	**0.013**	0.124	0.360
Site	0.243	0.104		
Localisation	0.615	0.397		
Focality	0.691	0.563		
Relapse preop.	0.305	0.237		
Pain	0.660	0.598		
Type of exenteration	0.452	0.156		
Neck dissection	**0.046**	0.146	0.539	
Parotidectomy	**<.001**	0.204	**<.001**	
T	0.126	**0.044**		0.449
N	**0.020**	**0.021**	0.952	0.396
M	**–**	**0.024**	**–**	0.703
L	–	–		
Cell type	0.323	0.854		
RTx pre	0.925	0.998		
Adj. RTx	**0.014**	**0.001**	0.133	**0.028**
Adj. CTx	**0.010**	**0.043**	**0.028**	
Relapse	–	**0.003**		**0.026**
Immunosuppression	–	–		
Second tumour	–	–		

T: extent of the primary tumour; N: spread to regional lymph nodes; M: presence of distant metastasis; L: invasion into lymphatic vessels; PNI: perineural invasion; R: resection-boundaries; RTx pre: history of preoperative radiotherapy; Adj. RTx/CTx: adjuvant radiotherapy/chemotherapy.
P-values <.05 are shown in bold.

relapse is the most important independent prognostic factor in multivariate analysis regarding OS. Therefore, two-thirds of the patients with a relapse survived the first year, but the estimated survival rate after 5 years was 0%.

The advanced tumour growth and high proportion of recurrences of our patients also explains their low rate of survival as compared to other cohorts with conjunctival melanoma in which not all patients were treated by exenteration. Most authors report a tumour-related mortality of 15%–20%.[1,4,15,16] Paridaens et al. presented 256 cases in their study.[1] The 5-year survival probability was estimated at 83%, and the 10-year survival at 70%. Tumour localisation, cell type and lymphatic invasion were significant prognostic factors in their study. Sex, age and origin of the tumour were not prognostic factors, as in our study. Nevertheless, tumour localisation and cell type play only a minor role in exenterated cases due to the radical resection. Furthermore, lymphatic invasion could not be adequately studied in our cohort.

In another study, Paridaens et al. analysed 95 patients with a conjunctival melanoma who were treated by exenteration.[17] As in our study, orbital exenteration was carried out in most patients (59/95 patients; 62%) due to the failure of other treatments. Again, the outcome in patients with lymphatic invasion was poor. Of these 16 patients, 11 had a relapse and 8 died. Interestingly, survival in patients with caruncular melanoma was also poor: ten of 18 patients died. It should be noted, however, that the study reviewed patients from 1948 until 1991. Nowadays, preoperative assessments positively influence the creation of individual treatment concepts: consequently, therapeutic and reconstructive modalities have improved in recent decades.

Our cohort, however, is not comparable to these studies, which represent cohorts without exenteration cases. Therefore, the advanced state of diseases in our cohort explains the worse OS rates. In this regard, the OS rates after 1 year ranged between 85.2% and 93% and between 44% and 64% after 5 years, in the literature.[18–21] Furthermore, there are only a few studies with DFS rates in which exenterations were performed due to melanomas. Simons et al. described a DFS rate of 35% after 5 years.[22] In this study, 7 out of 31 patients underwent exenteration due to a melanoma. In contrast, Kuo et al. described a DFS rate of 83% after 1 year and 55% after 5 years (6/38 patients).[23] Better prognoses in the studies mentioned above can thus also be explained by the different cohorts.

Uveal melanoma: Although local tumour control improved over the years, survival remained almost the same due to frequent distant metastases.[24,25] 34%–50% of all patients develop metastases within 10 years of diagnosis.[25,26] Bornfeld et al. stated that these patients already have micrometastases at the time of diagnosis, and that these are not influenced by primary treatment.[27] Thus, several clinical (e.g. older age, male gender, extraocular tumour extension), histopathological (e.g. epithelioid cell type, high mitotic activity), chromosome alterations (e.g. monosomy 3) and gene expression features (e.g. 1p loss, 6q loss) are associated with poor prognosis.[24,27–31] However, 63% of our patients had a recurrent disease at the time of presentation, so a lower age at initial diagnosis must be assumed.

All patients in our cohort showed an advanced stage of the disease with extraocular tumour growth. In contrast to conjunctival melanoma, no patient had a lymph node metastasis at the time of presentation, which shows the different biology of these tumours. On the other hand, lymph node metastases can occur more frequently after exenteration, since a connection to the lymphatic preauricular tissue then takes place. One patient in our cohort developed a preauricular lymph node metastasis during the follow-up period. Along with the high share of recurrences prior to our therapy, a significantly worse survival rate is also evident in our cohort. Of these 11 patients died,

but just 2 patients developed metastases. In contrast, the estimated OS in the literature is between 76% and 90% after 5 years.[30,32,33] Nevertheless, since the median OS is 4–20 months in metastatic uveal melanoma, it is still necessary to consider orbital exenteration in advanced diseases to prevent subsequent metastases with a worse outcome.[25, 30] An analysis of risk factors was not possible due to the small number of cases. Thus, larger multicentre studies are necessary to gain more information.

In summary, orbital exenteration in conjunctival and uveal melanoma is rarely necessary, but can be performed as an ultima ratio treatment with curative intent. The following information can be stated: (1) DFS and OS are significantly lower for both groups due to the advanced stage of the disease compared to DFS and OS in patients treated without exenteration in the literature; (2) R0-resections can usually be achieved in conjunctival melanoma; (3) lymph node metastases are found mainly in the area of the parotid gland in conjunctival melanoma, and these almost always occur as a single metastasis; and (4) if a recurrence occurs after exenteration, the prognosis is poor in both groups.

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