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Clinical features and prognosis of conjunctival melanoma in Japanese patients

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ABSTRACT

Purpose To evaluate the clinical features and prognosis of conjunctival melanoma in Japanese patients.

Study design Retrospective observational case series

Methods Twenty patients (8 men and 12 women) diagnosed with conjunctival melanoma at a single-hospital between 2003 and 2017 were analyzed. Data on clinical presentation, sex, age, the affected eye, tumor location, tumor origin, tumor stage according to the American Joint Committee on Cancer staging system (eighth edition), treatment, outcomes, local recurrence, metastasis, and survival were extracted from the patients' medical records and reviewed.

Results The mean age at diagnosis was 64.2 ± 14.8 years. Tumor locations at the first examination included the bulbar conjunctiva ($n = 19$), plica ($n = 13$), and fornix ($n = 12$). The tumor stage was T1 in 5 cases (25%), T2 in 12 cases (60%), T3 in 3 cases (15%), and T4 in none. The mean follow-up duration was 91.7 ± 46.0 months. The local recurrence rates at 1, 5, and 10 years were 5.0%, 18.8%, and 31.5%, respectively, whilst the metastasis rates were 5.0%, 25.6%, and 32.4%, respectively. Four of the 6 patients who experienced metastasis

died; duration from metastasis to death was 17.5 months (range, 7–25). The 5-year survival rate for conjunctival melanoma was 78.8%. Tumor thickness was significantly associated with survival duration on univariate Cox regression analyses.

Conclusion The mortality rate for conjunctival melanoma in the Japanese population was lower and higher than that reported in the Chinese and United States populations, respectively. Tumor thickness was a prognostic factor for survival in patients with conjunctival melanoma.

Keywords Conjunctival melanoma; Metastasis; Prognosis; Survival; Tumor thickness

Introduction

Conjunctival melanoma is a rare, life-threatening ocular malignancy. It is less common in Asian individuals than in white individuals, with an annual incidence rate of 0.2 to 0.5 per million for white individuals [1] and approximately 0.15 per million for Asian individuals [2]. The frequency of conjunctival melanoma in Japan has been reported only in a written national survey conducted over 5 years (1972 to 1976) by Kaneko and colleagues. The frequency reported in that study was 0.59 cases per million people [3].

Owing to the rarity of conjunctival melanoma, no single-center study exists on its survival rates in the Japanese population. The only Japanese study on the 5-year survival rate for conjunctival melanoma was conducted by Matsumoto and colleagues [4] in 1999. The authors reviewed mostly their cases and previous reports from Japan, reporting a 5-year survival rate of 53.4%. Two other studies, including more than 10 patients with conjunctival melanoma selected from a single institution in Japan, have been published [5, 6]; however, the 5-year survival of the patients was not mentioned. In contrast, reports from the United States and Europe have indicated that the 5-year mortality rate for patients with conjunctival melanoma in these regions ranges from 7% [7] to 14.7% [8], while the 10-year mortality rate is 22.3% [9]. Hence, survival rates may vary.

Considering the paucity of studies on the features of conjunctival melanoma in Asian patients, especially Japanese patients, we analyzed Japanese patients with conjunctival melanoma who were treated at our hospital to clarify the clinical characteristics and prognoses of these patients.

Methods

Study design and ethics statements

This was a retrospective observational case series of 20 consecutive patients with conjunctival melanoma who were histologically diagnosed and treated at the Department of Ophthalmology, Kyushu University Hospital, between January 2003 and March 2017. This study was approved by the ethics committee of the university (approval number: 29-196) and conducted according to the tenets of the Declaration of Helsinki. As this was a retrospective study, an opt-out patient consent form was provided on the university's website.

Data collection

Patient data were extracted from medical records and retrospectively reviewed. The collected data were those relating to patient demographics such as sex, age, and clinical presentation (tumor location, origin, stage). In addition, we examined the clinical characteristics of the tumors in terms of tumor thickness, treatment (tumor resection, enucleation, orbital exenteration), and adjuvant therapy. Tumor thickness was measured using a measurement tool on a virtual slide system on the tissue removed at the time of the initial resection (Fig. 1). From 2003 onward, tumors were measured with the Canon Nano Zoomer virtual slide system, whilst those from before 2003 were measured with an Olympus V110 with virtual slides created from the pathology specimen. In cases with multiple lesions, the largest value was considered. Tumor clinical staging to observe the spread of the lesions was based on the American Joint Committee on Cancer staging system (eighth edition) for conjunctival melanoma [10]. Regarding outcome measures, the duration from the initial diagnosis to the first recurrence, metastasis, or death in months was determined, and survival analyses were performed. The site of metastasis was recorded, and the time from the detection of the first metastasis to death was calculated. The date of recurrence was confirmed by means of biopsy. Follow-up was ended upon the death of a patient.

Regarding the origin of tumors, patients without pigmented lesions were interviewed to determine whether they had pigmented lesions from birth or a young age; if not, the lesion was considered de novo. Pigmented lesions were defined as those originating from a nevus or primary acquired melanosis (PAM), on the basis of the anterior ocular and histopathologic findings after surgical excision.

Statistical analysis

The Kaplan–Meier method was used to analyze recurrence, metastasis, and mortality rates. Survival analysis was performed to determine the prognostic estimates for local recurrence, metastasis, and death at 1, 5, and 10 years. The Cox proportional hazards regression model was used to assess the associations of various factors with adverse outcomes. Univariate Cox regression analysis was performed to identify the associations of each predictor with risk of death. R software (R Foundation for Statistical Computing) was used for all analyses.

Results

Patients' baseline characteristics

Twenty eyes of 20 Japanese patients were included in this study. The baseline and clinical characteristics of the patients are shown in Table 1. The patients comprised 8 men (40%) and 12 women (60%). The age of the patients at diagnosis ranged from 37 to 88 years (mean age $\pm$ standard deviation, 64.2 ± 14.8 years). Regarding the affected eye, the right eye was affected in 12 cases (60%), whereas the left eye was affected in 8 cases (40%). The main tumor locations at initial presentation were the conjunctival fornix (12 patients), caruncle (8 patients), plica (13 patients), bulbar conjunctiva (19 patients), and palpebral conjunctiva (9 patients), with some overlapping locations in some cases. The mean follow-up period was 91.7 months (range, 25–161 months). None of the patients had received treatment before

being referred to our hospital. All the patients underwent systemic examination, including contrast-enhanced computed tomography or positron emission tomography/computed tomography, at the time of diagnosis, and none of them showed metastasis to the lymph nodes or other organs. The clinical photographs of the patients' eyes are shown in Figure 2. Tumor staging, according to the eighth edition of the American Joint Committee on Cancer staging system for conjunctival melanoma, indicated that the clinical tumor stage was T1 in 5 cases (25%), T2 in 12 cases (60%), and T3 in 3 cases (15%). Only 2 of the 20 patients analyzed in this study underwent genetic analysis: case 11 was PD-L1 positive, whereas case 19 was *BRAF*-negative.

Treatment and outcomes

Tumor resection was performed in all cases. The extensive local excision method performed using the “no-touch” technique with cryotherapy (as reported by Shields and colleagues in 1997 [11, 12]) was used in all except 4 cases (Table 1; cases 6, 12, 13, and 19). All excised conjunctival transects were subjected to cryotherapy. Three of the above-mentioned 4 patients underwent enucleation, and 1 patient underwent orbital exenteration (Table 1). All the patients were administered subconjunctival injections of interferon (IFN)- β . A single subconjunctival dose of 3 million units of natural-type IFN- β , dissolved in 1 mL of 1% procaine hydrochloride, was administered on the basis of previous reports [5, 13]. The dosing interval was 1 to 2 times weekly in the perioperative period and once every 1 to 3 months after surgery. We continued treatment for as long as the patient could attend follow-up visits. IFN- β was administered until March 2023 because its use was discontinued in Japan after April 2023. Three of the patients who underwent enucleation had relatively large tumors (>2 mm in thickness) that had invaded the cornea. The patient who underwent orbital

exenteration had stage 3b disease, and the tumor was large (>2 mm in thickness) and originated from extensive PAM.

Local recurrence was detected in 4 patients (20%) during follow-up, with the average duration from treatment to initial local recurrence being 49.5 months (range, 12–108 months). Case 11 had multiple local recurrences, each time with local excision, cryocoagulation, and local injection of IFN- β . Kaplan–Meier survival analysis showed that the local recurrence rates at 1, 5, and 10 years were 5.0%, 18.8%, and 31.5%, respectively (Fig. 3). No local recurrence was observed in the patients who underwent enucleation or orbital exenteration.

Metastases were detected in 6 patients (30%); the details of those patients are shown in Table 2. The median time from initial diagnosis to first metastasis was 29.5 months (mean, 34.5 ± 23.3 months; range, 10–76 months). The first site of metastasis was the lung in 3 cases (50%), the submandibular lymph node in 2 cases (33%), and the cervical lymph node in 1 case (17%). Kaplan–Meier survival analysis showed that the metastasis rates at 1, 5, and 10 years were 5.0%, 25.6%, and 32.4%, respectively (Fig. 4).

The postmetastasis treatments administered before and after 2014, when nivolumab was approved in Japan, were different. Before 2014, 2 patients were treated with dacarbazine and CDV (dacarbazine + cyclophosphamide + vincristine) chemotherapy. After 2014, 3 patients were treated with immune checkpoint inhibitors (ICIs), such as nivolumab.

After metastasis, 4 of 6 patients (66.7%) died of tumor-related causes, and the time from metastasis to death was 17.5 months (mean, 16.8 ± 7.5 months; range, 7–25 months). Kaplan–Meier survival analysis showed that the tumor-related death rates at 1, 5, and 10 years were 0%, 21.2%, and 21.2%, respectively (Fig. 5).

Univariate Cox regression analyses (Table 3) showed that tumor thickness was significantly associated with risk of death. Other variables, including age, sex, origin, overall

tumor location, tumor stage, and treatment, were not significantly associated with risk of death.

Discussion

In this study, we analyzed the clinical characteristics and prognoses, including the 5-year survival rates, of Japanese patients with conjunctival melanoma. The results showed that tumor thickness was significantly associated with survival, whereas age, sex, tumor origin, tumor location, tumor stage, and treatment were not. To our knowledge, this is the first report describing a 5-year survival rate for a relatively large number of patients with conjunctival melanoma from a single institution in Japan.

A previous report indicated that orbital exenteration as an initial treatment has no prognostic benefit [14]. Tumor resection with safe margins and adjuvant therapy [11, 12] tends to be the mainstream treatment for conjunctival melanoma. Among the 20 patients included in this study, only one underwent orbital exenteration. However, the local recurrence rates at 1, 5, and 10 years were 5.0%, 18.8%, and 31.5%, respectively, which are lower than the 5- and 10-year recurrence rates reported for Chinese patients (5-year recurrence, 59.7%; 10-year recurrence, 66.4%) [15]. In addition, the local recurrence rates observed in this study are better than those reported in the United States (5-year recurrence: T1, 44%; T2, 78%; T3, 76%) [16] and Finland (5-year recurrence, 36%; 10-year recurrence, 38%) [17]. Notably, 95% and 37% of the patients in the above-mentioned Chinese [15] and Finnish [17] studies had stage T2 or higher disease. In the present study, 75% of patients had stage T2 or higher disease. Considering that 44% of patients with T1 disease in the American study showed recurrence and that the proportion of patients in this study with an advanced disease stage is higher than that in the Finnish study, the less frequent local recurrence in our study is unsurprising. Although it is impossible to pinpoint the reason for the low local recurrence rate

in this study, it should be noted that the continued administration of subconjunctival injections of IFN- β during the perioperative period and every 1 to 3 months after surgery in this study was not performed in previous studies. Human melanocytes and melanoma cells produce IFN- β . In addition, melanoma cells can inhibit their growth by secreting endogenous IFN- β [18]. IFN- β has antiproliferative, antiangiogenic, and immunomodulatory effects on cutaneous malignancies [19]; however, its effects on conjunctival melanoma are not well reported [5, 13].

Conjunctival melanoma originates from PAM, nevus, and de novo melanomas, which are pigmented lesions [20]. Shields and colleagues [21] reported that although melanomas may arise from preexisting nevi (7%) or from de novo melanomas (19%), the most common precursor is PAM (74%). In a Chinese study [15], 39% of cases of conjunctival melanoma originated from PAM, 21% from nevi, and 40% were de novo. In a Taiwanese study [22], 10% of cases were of PAM origin, 0% were of nevus origin, and 90% were de novo. In this study, 45% of cases were of PAM origin, 10% were of nevus origin, and 45% were de novo. These findings indicate that PAM-derived melanomas are more common in white individuals than in Asian individuals. Additionally, the frequency of PAM in Asia varies widely, indicating the necessity for further large-scale studies.

The 5- and 10-year metastasis rates in this study were 25.6% and 32.4%, respectively, whereas those in the above-mentioned Chinese study were 38.7% and 50.9%, respectively [15]. The metastasis rates observed in this study are better than those reported in the Chinese study and slightly higher than those reported in the American study (5-year metastasis rate, 16%; 10-year metastasis rate, 26%) [7]. This result may be related to the fact that 75% of the patients in this study had stage T2 or higher disease, with more patients having more advanced disease stages than those in the American study.

Univariate Cox regression analyses (Table 3) showed that tumor thickness was significantly associated with survival duration. Shields and colleagues reported that nodular melanoma is a risk factor for mortality in patients with conjunctival melanoma [21]. A Taiwanese study also showed that tumor thickness is a prognostic factor for survival in patients with conjunctival melanoma [22]. There are 4 subtypes of cutaneous melanoma: superficial spreading, lentigo maligna, nodular, and acral lentiginous, with the nodular type reported to be the most aggressive and metastatic [23]. Some conjunctival melanomas are PAM-main cases that spread thinly, whilst others are nodule-forming cases, which may be related to the disease.

Systemic therapy is typically required for metastatic conjunctival melanomas. Previously, the available therapeutic options, such as alkylating agents, dacarbazine, and IFN- α , were limited, and many patients were refractory to treatment. However, novel ICI-targeting therapies for unresectable melanoma have been extensively researched [23, 24], and nivolumab was developed as a human IgG4 monoclonal antibody against the ICI, PD-1 [25, 26, 27]. Nivolumab was approved in Japan in 2014 for the treatment of unresectable melanoma. In 2016, pembrolizumab, a PD-1 inhibitor, was approved in Japan for the treatment of unresectable melanoma. In this study, 3 patients who underwent systemic chemotherapy for metastatic melanoma after 2016 were treated using ICIs. Patient K, who was PD-L1 positive, received an ICI (nivolumab) and underwent immunotherapy (dendritic cell vaccines), thermotherapy (lung), and radiation therapy (lung) and was still alive 76 months after metastasis; however, the tumor has metastasized to the lung and is slowly growing. According to a previous report [28], the 5- and 10-year rates of metastasis-related deaths in patients with conjunctival melanoma were 87.6% and 76.3%, respectively, with most deaths occurring within 5 years. In this study, postmetastatic treatment might have led to a relatively slow postmetastasis disease course in some patients.

230 This study has certain limitations. First, it evaluated the extent of the lesion in terms
231 of clinical stage but did not consider the lesion areas. Second, our study had a small sample
232 size (20 cases). Although conjunctival melanoma is an extremely rare tumor, a multicenter
233 study would increase its statistical power. Third, only 2 of the 20 patients in this study were
234 genetically analyzed. In the future, genetic analysis of patients will be important for
235 immunotherapy for metastatic cases and prognostic analysis. Despite these limitations, the
236 strength of this study is that it is the first to report a 5-year survival rate for Japanese patients
237 with conjunctival melanoma. It is also the first report of an association between tumor
238 thickness and survival in Japanese patients with conjunctival melanoma.

239 In conclusion, this study showed that the 5-year survival rate for Japanese patients
240 with conjunctival melanoma was 78.8%. In addition, tumor thickness was found to be a
241 prognostic factor for survival in patients with conjunctival melanoma. In the future, analysis
242 of patients with conjunctival melanoma, including analysis of tumor characteristics and
243 behavior, may advance into the field of genetics. Although only 2 of the 20 patients in this
244 study underwent genetic analysis, we believe that further genetic testing and analysis of the
245 collated data will allow for the development of mutation-specific cancer genome medicine for
246 conjunctival melanoma.

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Figure legends

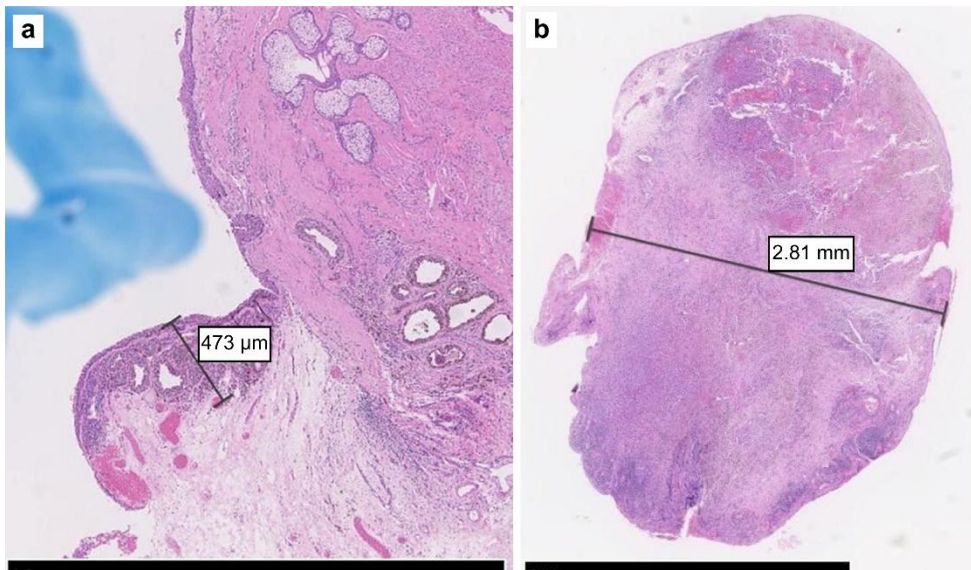


Fig. 1 Tumor thickness measurement method. Tissue thickness was measured using the function on the Virtual Slide System as shown in the figure. Bar = 2.5 mm. **a** case 17, **b** case

19

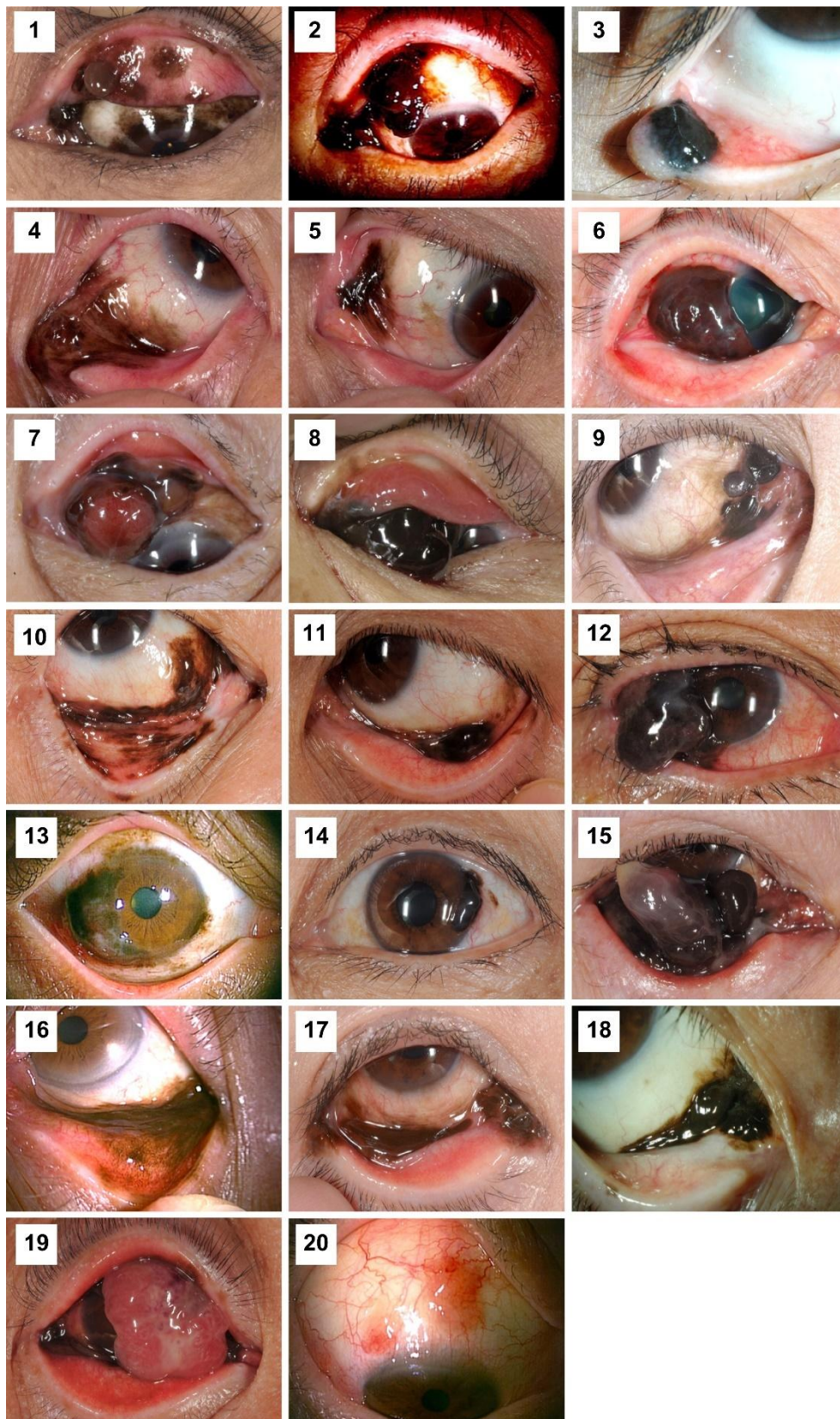


Fig. 2 Clinical photographs of Japanese patients with conjunctival melanoma

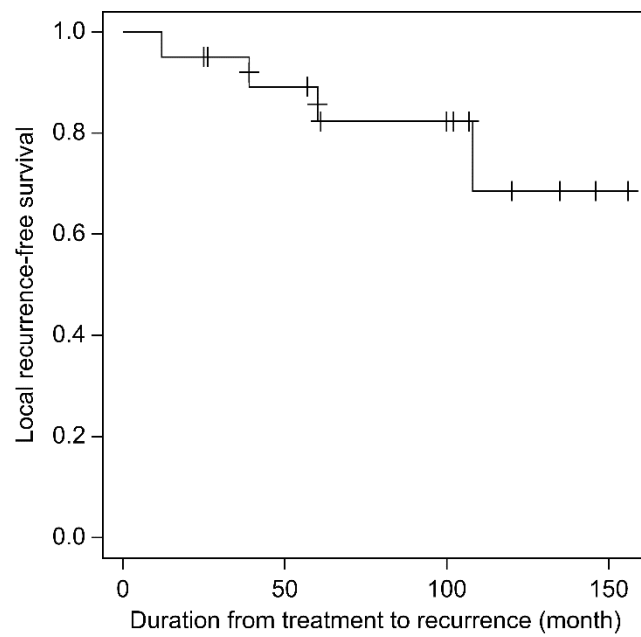


Fig. 3 Local recurrence-free survival rates for conjunctival melanoma

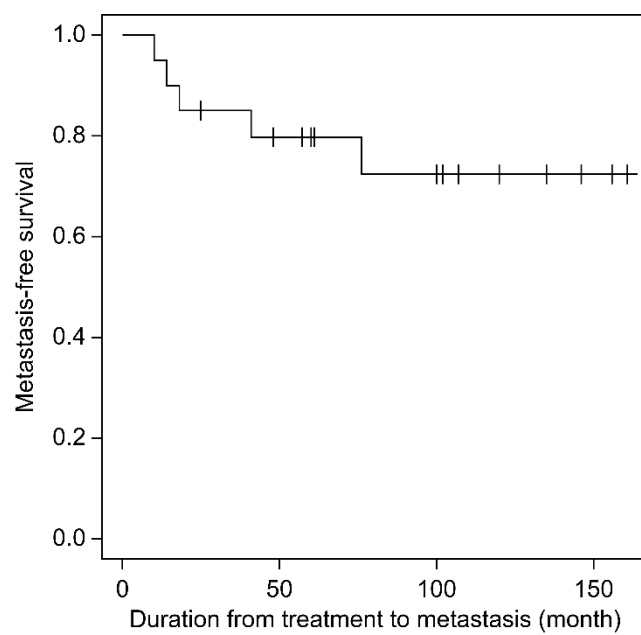


Fig. 4 Metastasis-free rates for conjunctival melanoma

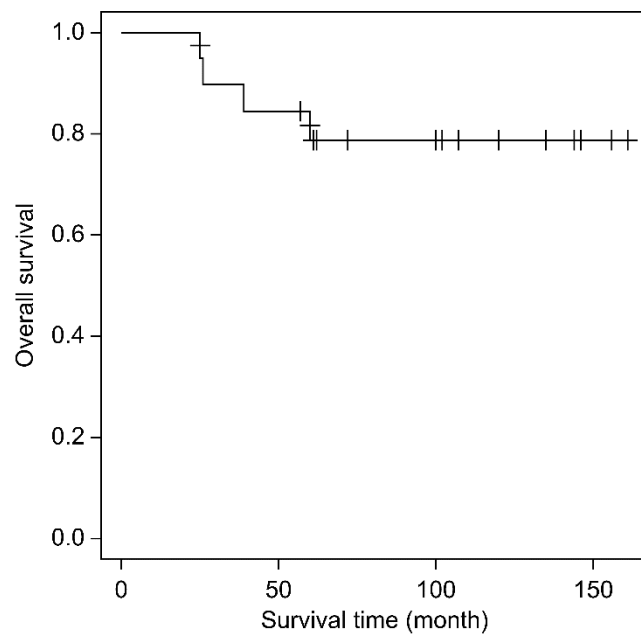


Fig. 5 Tumor-related survival rate with conjunctival melanoma

Table 1 Baseline and clinical characteristics of the Japanese patients with conjunctival melanoma

case	Age(years)	Gender	Right/Left	Tumor Origin	Treatments other than tumor resection	tumor thickness (mm)	Clinical staging (cT)	Total follow-up duration (M)	Local Recurrence	Local Recurrence Time (M)	Metastasis (see Table.2)	Death	Death Time (M)
1	47	F	L	PAM	NA	1.5	2d	57	NA	57	NA	NA	57
2	76	M	L	PAM	NA	8.8	3d	161	+	108	NA	NA	161
3	37	F	R	Nevus	NA	2.1	2a	156	NA	156	NA	NA	156
4	80	F	L	PAM	NA	1	2b	25	NA	25	NA	NA	25
5	64	F	L	PAM	NA	1.6	1b	100	NA	100	NA	NA	100
6	63	M	R	De novo	Enucleation	5.4	1c	26	NA	26	+	+	26
7	86	F	L	De novo	NA	4.7	2d	60	NA	60	NA	NA	60
8	55	F	L	De novo	NA	15.1	2d	25	NA	25	+	+	25
9	53	F	R	De novo	NA	3.8	2d	107	NA	107	NA	NA	107
10	57	M	R	PAM	NA	1.9	2d	146	NA	146	NA	NA	146
11	57	F	L	PAM	NA	2.4	2b	144	+	60	+	NA	144
12	78	M	R	De novo	Enucleation	7.6	1c	61	NA	61	NA	NA	61
13	47	M	R	De novo	Enucleation	2.5	1c	135	NA	135	NA	NA	135

14	47	F	L	De novo	NA	1.7	1a	135	NA	135	NA	NA	135
15	81	F	R	Nevus	NA	4.9	3b	60	+	39	+	+	60
16	88	M	R	PAM	NA	1.1	2d	120	NA	120	NA	NA	120
17	55	F	R	PAM	NA	0.47	2d	102	NA	102	NA	NA	62
18	78	F	R	De novo	NA	2.1	2b	102	NA	102	NA	NA	102
19	56	M	R	PAM	orbital exenteration	2.8	3b	39	NA	39	+	+	39
20	78	M	R	De novo	NA	2.1	2d	72	+	12	+	NA	72

M = male; F = female; R =right; L = light; Local Recurrence Time = duration from treatment to recurrence; Death Time = duration from treatment to death; PAM = primary acquired melanosis; NA = not applicable

Table 2 Clinical details of patients with metastasis

Case	Duration of metastasis (M)	Metastatic lesion (listed in chronological order of occurrence)	Post-metastatic treatment (Numbers in parentheses indicate year treated)	Duration from metastasis to death (M)
6	10	Cervical lymph node, liver	Chemotherapy (DTIC, CDV) (2011)	16
8	18	Lung, liver, spleen, bone	Chemotherapy (DTIC) (2012)	7
11	76	Lung, preauricular lymph nodes	ICI (nivolumab) (2018) Immunotherapy (dendritic cell vaccines) Thermotherapy (lung) RT (lung)	Alive (64 months after metastasis)
15	41		ICI (nivolumab) (2016)	19
19	14	Lung	ICI (pembrolizumab) (2017) RT (cervical, nasal, and ribs) Chemotherapy (DTIC, CBDCA) (2018)	25
20	48	Submandibular lymph node, lacrimal sac, multiple bones (upper arm, ribs), pharynx	Surgery (cervical dissection only)	Alive (25 months after metastasis)
		Submandibular lymph node		

M = months; ICI = immune checkpoint inhibitor; RT = radiotherapy; DTIC = dacarbazine; CDV = dacarbazine+cyclophosphamide+vincristine; CBDCA = carboplatin.

Table 3 Univariate Cox regression analysis for predictors of survival time

Characteristic	Hazard ratio	95% CI	p-value
Age (years)	0.99	0.94-1.06	0.94
Sex			
Male	1.42	0.20-10.06	0.73
Female	Reference	Reference	Reference
Side			
Right	1.65	0.17-15.94	0.66
Left	Reference	Reference	Reference
Location			
Palpebral, yes vs. no	3.81	0.40-36.73	0.25
Fornix, yes vs. no	1.88	0.20-18.13	0.58
Caruncle, yes vs. no	2.27	0.24-21.92	0.48
Plica, yes vs. no	1.79	0.19-17.20	0.62
Treatment			
Enucleation, yes vs. no	2.02	0.21-19.51	0.54
Orbital Exenteration, yes vs. no	8.64	0.78-95.38	0.08
Tumor origin			
De novo	Reference	Reference	Reference

Nevus	1.92	0.17-21.23	0.59
PAM	0.51	0.045-5.54	0.57
Clinical stage			
Stage 1	Reference	Reference	Reference
Stage 2	0.44	0.03-7.03	0.56
Stage 3	3.31	0.29-36.59	0.33
Thickness (mm)	1.39	1.05-1.84	0.02*

HR = hazard ratio; CI = confidence interval; PAM = primary acquired melanosis

*Statistically significant <0.05