

Clinical Follow-up of Conjunctival Malignant Melanoma

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Purpose: To investigate the clinical features and course of conjunctival malignant melanoma in Korea.

Methods: The medical records of 15 patients, 5 males and 10 females, diagnosed with conjunctival malignant melanoma who had been treated at Severance Hospital from May 1991 to March 2004 were reviewed retrospectively. The clinical parameters of the patients, tumors, and treatment were analyzed for their relation to outcome measures.

Results: The mean age at the time of diagnosis was 53.4 years (± 11.7 years). In all cases, the disease was unilateral and all patients had experienced at least one recurrence. Local lymph node metastasis was found in 3 patients (20%) and the mean time to metastasis was 3.5 years. Systemic metastasis was found in 6 patients (40%) and the mean time to metastasis was 9.3 years. There were 5 cases of tumor-related death (33.3%), 4 of which were attributed to systemic metastasis. The Kaplan-Meier estimates of cumulative survival rate were 90% at 30 months and 56.6% at 70 months.

Conclusions: Although conjunctival malignant melanoma is a rare disease, it is life-threatening and complete tumor excision at an early stage is mandatory, as is additional therapy to prevent local recurrence and systemic metastasis. *Korean Journal of Ophthalmology* 19(2):91-95, 2005

Key Words: Conjunctival malignant melanoma, Metastasis, Recurrence

Conjunctival malignant melanoma is extremely rare, but when developed can be fatal. The incidence of conjunctival malignant melanoma is 1.6% of all noncutaneous melanomas.¹ In 1987, the Swedish National Cancer Registry reported 1,243 cases of new cutaneous malignant melanoma and 70 cases of uveal melanoma, but only 2 cases of new conjunctival malignant melanoma.² In Korea, several cases have been reported, but without any details of progression and treatment.³ Hence, we report here the clinical outcome of conjunctival malignant melanoma cases experienced at our hospital.

Materials and Methods

The medical records of 15 patients who were diagnosed with conjunctival malignant melanoma after biopsy from May 1991 to March 2004 at our hospital were reviewed retrospectively. The age at the time of diagnosis, gender, right eye/left eye, symptoms at the initial period, initial treatments prior to

the transfer to our hospital, visual acuity, location of lesion, treatment methods, local recurrence, distant metastasis, whether or not exenteration was performed, and death pertinent to tumor were examined. The correlation of local recurrence and distant metastasis to death related to tumor was also examined.

Results

The average age of the patients at the time of diagnosis was 53.4 years (± 11.7 years), and all patients were transferred from other hospitals. There were 5 males (33.3%), 10 females (66.7%), 6 right eyes, and 9 left eyes. As for initial symptoms, 9 patients were admitted primarily for lump (60%), which was the most prevalent symptom, and 1 patient visited a hospital for an expanding nevus. In regard to tumor location, there were 3 cases each of bulbar conjunctiva and palpebral conjunctiva (20%), 1 of conjunctival fornix, and 8 of simultaneous invasion of the bulbar conjunctiva, palpebral conjunctiva, and caruncle, etc. (53.3%), which was the most prevalent presentation. Regarding the treatments performed at other hospitals, 12 cases were treated by excisional biopsy as the first treatment (80%), which was the most prevalent, followed by 1 case of resection and cryotherapy, and 1 case of incisional biopsy. The treatments performed at our hospital after the transfer were resection in 5 cases (33.3%), wide resection and subsequent lid recon-

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Table 1. Summary of descriptive statistics on evaluated baseline study variables in 15 patients with conjunctival melanoma

Intrinsically categorical variables	
Variables	
Sex	
Male	5 (33.3%)
Female	10 (66.7%)
Involved eye	
Right	6 (40%)
Left	9 (60%)
Origin	
Unknown	10 (66.7%)
De novo	1 (6.7%)
PAM	1 (6.7%)
Previous nevus	3 (20%)
Tumor location	
Bulbar	3 (20%)
Palpebral	3 (20%)
Fornix (inferior)	1 (6.7%)
Combined*	8 (53.3%)
1 st surgical technique before referral	
Incisional biopsy	1 (6.7%)
Excision	12 (80%)
Excision with cryotherapy	1 (6.7%)
No treatment	1 (6.7%)
First treatment after referral	
Excision	5 (33.3%)
Excision with lid reconstr. (Mod.Hughes)	2 (13.3%)
Excision with RTx	1 (6.7%)
Excision with Cryo/RTx	3 (20%)
RTx followed by Excision	1 (6.7%)
Inoperable case (RTx)	3 (20%)

* Combined: Bulbar and palpebral/bulbar, palpebral and caruncular involvement.

Cryo: Cryotherapy, RTx: Radiation therapy.

struction by the modified Hughes method in 2 cases, local radiation after resection in 1 case, local radiation after resection and cryotherapy in 2 cases, and conventional radiation therapy in 2 inoperable cases. Additionally, there was 1 case transferred without treatment, after biopsy, cryotherapy and radiation therapy performed. The case of infeasible complete resection had local recurrence over a wide area. In the case with tumors invading the orbit, orbital exenteration was considered. However, as the patient refused such treatment, only local radiation therapy was performed (Tables 1, 2). There were 11 cases of local recurrence prior to transfer (73.3%) and the average number of recurrences was 1.58 times. There were 7 cases of local recurrence after transfer (46.6%) and the average number of recurrences was one. In all 15 cases, local recurrence was more prevalent than once. There were 3 cases of local lymph node metastasis (20%), and the mean interval from diagnosis to the development of metastasis was 3 years and 5 months. Radical lymph node dissection was performed in 2 of these cases, and radiation therapy in one (Table 3). There were 6 cases of systemic metastasis (40%), and the average interval to metastasis was 9 years and 3 months. Regarding distant metastasis sites, there were 2 cases of metastasis to the nasal cavity through the nasolacrimal duct (Table 4). In the 6 cases with systemic metastasis, 4 patients died. In the case of local recurrence and metastasis in the nasal cavity of the same side, local resection was performed and the patient remained under follow up. In another case, metastasis in the lung was

Table 4. Locations of systemic metastasis

	Location
case 1	liver, bone
case 2	brain, lung, spine
case 3	lung
case 4,5	nasal cavity
case 6	rib

Table 2. Summary of descriptive statistics on evaluated baseline study variables in 15 patients with conjunctival melanoma

Intrinsically numerical scalar variables				
Variable	Mean	SD	Minimum	Maximum
Age at diagnosis (yr)	52.8	±11.67	34	69
Duration of follow-up (mo)	32.1	±38.76	1	141
Number of prior recurrences before referral	1.58	±1.24	0	5

SD: standard deviation.

Table 3. Clinical course of 3 patients with regional lymph node metastasis

	Involved lymph node	Treatment	Survival time from diagnosis (months)
Case 1	Preauricular Cervical	Radiation	134
Case 2	Infraauricular Parotid gland	Total parotidectomy & RND	70
Case 3	Preauricular Submandibular	Parotidectomy & RND	141

RND: Radical neck dissection

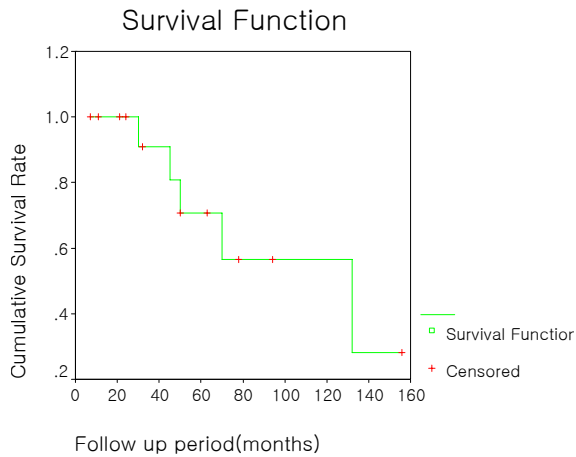


Fig. 1. Kaplan-Meier estimates of survival in 15 consecutive patients with conjunctival malignant melanoma.

confirmed by positron emission tomography (PET) test and the patient remained under follow up. There were 5 deaths related to tumor (33.3%), and 4 cases of systemic metastasis. The survival rate related to tumors as predicted by Kaplan-Meier estimate was 90% survival after 30 months, and 56.6% survival after 70 months (Fig. 1). During the course, exenteration was performed in 2 cases, one of which developed systemic metastasis and the other patient stopped the treatment voluntarily after local recurrence and subsequently died. Due to the small sample size, it was not possible to examine the statistical significance of the prognostic factors for recurrence and metastasis such as clinical patterns (patient age, gender, tumor origin, location, limbus invasion, tumor size and thickness), initial treatment methods, presence of local recurrence, etc.

Discussion

Conjunctival malignant melanoma is extremely rare, but may be fatal. Most malignant melanomas are developed in sun-exposed skin, although it also develops rarely in other tissues. Conjunctival malignant melanoma is developed de novo, from an existing nevus or a primary acquired melanosis. The reported incidence has varied widely. The development from primary acquired melanosis has been reported as 9% by Werschnik and Lommatzsch,⁶ 57.4% by Paridaens et al,⁷ 53% by Shields CL et al,⁸ and 42.1% by Anastassiou et al.⁹ The range of reported incidence for the development from existing nevi is 4~39.1%.^{4,9} The reported incidence for the absence of precancerous lesions ranges from 15.9~47%.^{4,9} In our study, the incidence was higher in females (10 cases) than males (5 cases). Conjunctival malignant melanoma occurs primarily in the bulbar conjunctiva. Shields et al⁸ have reported that among 150 cases of conjunctival malignant melanoma patients, 92% (138 cases) had the lesion on the bulbar conjunctiva, 3% in the

conjunctival fornix, 4% in the palpebral conjunctiva, and 0.67% (1 case) each in the plica semilunaris and the caruncle. Werschnik and Lommatzsch⁶ classified the lesion sites as favorable locations (bulbar conjunctiva and limbus) and unfavorable locations (caruncle, fornix, corneal parenchyma, and palpebral conjunctiva). In 85 patients, the lesion occurred in the favorable location for 56.5% and in the unfavorable location for 43.5%. In our study, the cases invading the bulbar conjunctiva, tarsal conjunctiva and caruncle were the most prevalent (8 cases, 53.3%). Although the prognosis according to location could not be assessed, the survival rate was high in the 3 cases with the lesion limited to the bulbar conjunctiva. However, among these 3 cases, in the 2 cases with local metastasis and systemic metastasis, it appeared that appropriate treatments were performed to increase the survival (Table 3).

The recurrence rate reported in other studies has ranged from 20~50%.^{6,8,9} In our study, local recurrence was 100% (all 15 cases) because local recurrence was developed prior to the transfer in most patients (14 cases out of 15 cases).

Histopathological factors pertinent to fatal metastasis have been reported to be tumor thickness and width, epithelioid cells, from presence of atypical melanin cells in case of development from primary acquired melanosis, pagetoid invasion, in situ growth pattern, development in the caruncle and palpebral conjunctiva, reduced small polygonal cells, and mild inflammation and abundant mitoses.^{4,10}

Surgical resection is the therapy of choice for conjunctival malignant melanoma. Shields et al¹¹ have reported a complete resection technique by no-touch technique. No-touch technique involves minimal tumor manipulation and partial lamellar scleroconjunctivectomy, to remove the tumor without touching the affected areas. After tumor resection, cryotherapy on the surrounding bulbar conjunctiva is performed. Additional cryotherapy has been reported to prevent recurrence. DePotter et al¹² have reported that the only clinical factor associated with distant metastasis is local recurrence, and that local recurrence, in turn, is related to surgical methods. In our study, among 15 cases, resection and cryotherapy were performed in parallel in 1 case (6.6%) prior to the transfer and in 2 cases (13.3%) after the transfer. Werschnik and Lommatzsch⁶ have reported two issues demanding attention in the local resection of conjunctival malignant melanoma. First, during tumor removal, even under the microscope, the tumor boundary is not clear. Shields et al¹¹ have reported that tumors could be removed completely by drawing a picture showing the shape and boundary of the tumor with a slit lamp examination prior to surgery and then performing surgery based on the picture. Second, for surgery on the sclera and cornea, tumor cells may be leaked to the globe. To prevent this, they recommended the elimination of tumor cells by treating with alcohol or formalin prior to the surgery and alternatively, the administration of mitomycin eye drops immediately after

operation.¹¹ For cases of difficult primary suture due to wide resection, coverage of the removed area using amniotic membrane was recommended.¹³ The advantages of using amniotic membrane are that, in addition to the rapid wound healing effect, recurrence could be detected readily as the amniotic membrane is transparent. Espana et al¹⁴ have reported that for resections larger than 20 mm, treatment with amniotic membrane ensured rapid wound healing and few complications.

It has been reported that even the orbital exenteration of conjunctival malignant melanoma at its early stage did not increase the long-term survival rate.¹⁰ Hence, orbital exenteration should be considered only when the tumor has invaded the orbit or local recurrence has occurred over a wide area.⁸ In our study, none of the patients were initially treated by orbital exenteration, although in 2 patients, both of whom died, it was performed during the follow up period. Additional known adjuvant therapies are the previously described cryotherapy, radiation therapy, and local treatment with mitomycin eye drops.^{11,15,16}

Conjunctival malignant melanoma metastasizes in the preauricular lymph, parotid lymph, and submandibular lymph nodes, dependent on the location of the lesion in the conjunctiva. Esmaeli et al¹⁷ have reported the detection of microscopic metastasis of the sentinel lymph node and its appropriate treatment. Amato M et al¹⁸ were able to detect more than 1 sentinel lymph node metastasis by the test using Technetium Tc-99m sulfur colloid pre- and post-surgery. Park et al¹⁹ also confirmed the sentinel lymph node metastasis by performing lymphoscintigraphy after surgery in conjunctival malignant melanoma patients. Seppo and Tero²⁰ have reported that due to the longer survival period of patients with metastasis only in the lymph nodes at the early period than of patients with systemic metastasis, it was important to prevent systemic metastasis by treating the patients with lymph node metastasis. In the cases of metastasis in the sentinel lymph nodes, radical lymphadenectomy was performed, followed by adjuvant therapies. Adjuvant therapies are local radiation therapy in the vicinity of the lymph nodes, systemic administration of interferon, chemotherapy, and combination therapies. Although the studies on cutaneous malignant melanoma are ongoing, its effectiveness has not been elucidated yet.²¹⁻²³

Lommatzsch et al²⁴ have reported a 10-year local recurrence rate of 24% and a 10-year fatality rate of 23% for metastasis. They also reported that local recurrence and metastasis rates increased with larger tumors. Shields et al⁸ have reported that metastasis was developed in 14~27% of patients, and that 30 % of patients died of metastasis after 10 years. In our study, systemic metastasis was developed in 6 cases (40%), with a death rate related to tumors of 33.3%.

On regard to survival analysis, our results showed higher mortality rate than that of previous reports, which may be related to small number of patients and the severe conditions of the lesions when transferred to our hospital.

The shortcomings of our study were the small study population, and the insufficiently detailed information on tumor clinical patterns. Nevertheless, the study demonstrated that the treatment for conjunctival malignant melanoma has not been clearly established. Conjunctival malignant melanoma is extremely rare, but potentially fatal. Hence, it is believed that its survival rate may be improved by the prevention of recurrence and metastasis through complete resection, the early application of adjuvant therapies and the early detection of metastasis in the sentinel lymph node. Future research examining the effect of each clinical pattern on the prognosis with a large study population is required.

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