Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 51, Number 4, 2019; 351-357
http://dx.doi.org/10.19106/JMedSci005104201909

The predictive factor for conjunctival melanoma recurrence

Agus Supartoto*, Melita Suwan Djaja, Didik Setyo Heriyanto, Endang Soetristi, Datu Respatika, Muhammad Bayu Sasongko

Reconstruction, Oculoplasty, Oncology Subdivision, Department of Ophthalmology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta

Submited: 2019-04-01
Accepted : 2019-07-02

ABSTRACT

Conjunctival melanoma potentially deadly tumor. While many cases of conjunctival melanoma appeared to be a recurrence, there is no valid data about parameters to predict the recurrence of this tumor. This study intended to evaluate whether histopathologic features can be used as a predictor for recurrence in conjunctival melanoma. This was a retrospective study, involving patients with conjunctival melanoma by the year 2013-1017 in Dr. Sardjito General Hospital and Dr. Yap Eye Hospital, Yogyakarta. Patient's characteristic was determined by age, sex, laterality, tumor size, tumor location, histopathological dominancy, MMC application, recurrence, and metastases. Sixteen cases were found: male (62.5%) and female (37.5%). Age from 5-79 years, mean was 56.19 years. Tumor location was in bulbar in 11 patients (68.7%), palpebral in 5 patients (31.3%).There was significant association between metastasis and the tumor recurrence (OR 13.0; 95% CI 1.9-85.4; p = 0.007). A favorable trend of association was also found between location and the recurrence of melanoma (OR 15.0; 95% CI 0.9-228.8; p = 0.06). In summary, our study showed that the patients that developing distant metastasis were at a greater risk for tumor recurrence.

ABSTRAK

Melanoma konjungtiva berpotensi mematikan. Sementara banyak kasus konjungtiva melanoma tampaknya berulang, ada data yang valid tentang parameter untuk memprediksi kekambuhan tumor ini. Penelitian ini dimaksudkan untuk mengevaluasi apakah gambaran histopatologis dapat digunakan sebagai prediktor untuk rekurensi pada melanoma konjungtiva. Ini adalah penelitian retrospektif, yang melibatkan pasien dengan melanoma konjungtiva pada tahun 2013-1017 di Rumah Sakit Umum Sardjito dan Rumah Sakit Mata Yap. Karakteristik pasien ditentukan oleh usia, jenis kelamin, lateralitas, ukuran tumor, lokasi tumor, dominasi histopatologis, aplikasi MMC, rekurensi, dan metastasis. Enam belas kasus ditemukan: laki-laki (62,5%) dan perempuan (37,5%). Usia dari 5-79 tahun, rata-rata adalah 56,19 tahun. Lokasi tumor berada di bulbar pada 11 pasien (68,7%), palpebral pada 5 pasien (31,3%). Ada hubungan yang signifikan antara metastasis dan rekurensi tumor (OR 13,0; 95% CI 1,9-85,4; p = 0,007). Kecenderungan hubungan yang menguntungkan juga ditemukan antara lokasi dan kekambuhan melanoma (OR 15.0; CI 95% 0,9-228,8; p = 0,06). Singkatnya, penelitian kami menunjukkan bahwa pasien yang mengembangkan metastasis jauh berada pada risiko lebih besar untuk kekambuhan tumor.

Keywords:
conjunctival melanoma
recurrence
histopathology
epithelioid- spindle
mixed

*corresponding author: agus.supartoto@ugm.ac.id

INTRODUCTION

Conjunctival melanoma was an uncommon malignancy with significant morbidity and mortality.[1] The annual incidence of conjunctival melanoma in the world was between 0.2-0.5 cases per 1.000.000 people. The earlier study in Indonesia found that the incidence of melanoma in male and female was 1:1.5.[2] Conjunctival melanoma considerably rare in children younger than 15 years.[3] Another study reported that conjunctival melanoma was a potentially deadly tumor. This previous study shown that the metastasis of the conjunctival melanoma was detected in 26% of patients, while 13% of patients were death in 10 years.[1,4] Although, the understanding of the biology mechanism that involve in conjunctival melanoma was hindered by a lack of adequate correlation between clinical and histological features of this particular neoplasm.[5]

Conjunctival melanoma typically presents as a pigmented nodular or flat conjunctival lesion, however there are cases of amelanotic tumors that may confuse the clinical picture and delay diagnosis.[3] It may arise from primary acquired melanosis with atypia or de novo. Histologically, cellular morphology in melanomas may range from spindle to epithelioid.[6] Esmaeli, *et al.* reported that the epithelioid type is correlated with higher morbidity.[1] Histopathology examination remains the gold standard for the definitive diagnosis for conjunctival melanoma.[7] The review of several studies, showed a number of histopathological features were found to be associated with increased recurrence of a malignant lesion.[8-10] Certain histologic features may also predict the prognosis of conjunctival melanoma. Purely spindle type lesion have been associated with a more favorable prognosis than mixed cell type lesion.[11-13]

There are several clinical features that reported related to the melanoma recurrence. The association between metastasis and melanoma recurrence were reported in previous study.[14,15] Other studies also mentioned the association of melanoma recurrence with the location of the tumor.[16,17] Several studies also showed that the male gender was more affected and associated with tumor recurrence.[18-20] While many cases of conjunctival melanoma appeared to be recurrence, there is valid data about parameters to predict the recurrence of this tumor. To date, there is limited study that analyzed the correlation between clinical features of conjunctival melanoma and its recurrences in Indonesia. Our study aimed to evaluate the correlation between the clinical features of conjunctival melanoma and its recurrences in Indonesia.

MATERIALS AND METHODS

Study design and population

This cross-sectional retrospective study involved 16 cases conjunctival melanoma presented between 2013 2017 at Dr. Sardjito General Hospital and Dr. Yap Eye Hospital, Yogyakarta. All the patients underwent a surgery and the entire surgical specimen were sent to pathology department for further examination. The tumor specimens were examined with minimum of five high-power fields. Prior specimens from our institution were reviewed in the patients submitted with recurrent lesions. All specimens were defined as conjunctival melanoma according to WHO classification that confirmed with pathological examination reviewed by at least 2 pathologists.[21] All the patients that found to be diagnosed with conjunctival melanoma were enrolled, while choroidal and uveal melanoma cases were excluded from this study. Current study reviews the age, sex, laterality, tumor size, tumor location, mitomycin-C (MMC) application, recurrence, and metastases data that taken from medical

records. Predominant histopathological features (epithelioid vs spindle) of conjunctival melanoma were also reviewed according to previous study.[1]

Ethical approval

This study was approved by The Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta and followed the basic principles of the Declaration of Helsinki (2008).

Statistical analyses

The pooled data were then analyzed using SPSS 24 for descriptive quantitative results and correlation using Spearman correlation test. p value less than 0.05 was considered statistically significant. Data were presented as frequencies or mean ± standard deviation (SD).

RESULTS

Demographic data for all patients enrolled in this study were summarized in TABLE 1. Among patients enrolled in this study, 37.5% were female and 62.5% were male. The mean age of the patients was 56.2 (SD±23.34) years. We found 11 (68.7%) patients showed a bulbar conjunctiva tumor, while 5 (31.3%) patients were exhibit tumor in palpebral conjunctiva. The predominant histopathology features that found 9 (56.3%) patients were mixed type which include both of spindel and epithelial cell. Meanwhile, the spindle type melanoma was found in 6 (37.5%) patients and the epithelioid type in 1 (6.3%) patient. In this study, we found 4 (25%) patients that presented with a recurrence lesion. The distant metastases were also found in 3 (18.8%) patients.

TABLE 1. Patient's characteristic

Parameter	Frequency	Percentage (%)
Gender		
• Female	6	37.5
• Male	10	62.5
Age		
• < 50 years	5	31.3
• ≥ 50 years	11	68.7
Tumor size (cm3)		
• < 1	7	43.7
• ≥ 1	9	56.3
Predominant histopathologic features		
• Spindle	6	37.4
• Epithelioid	1	6.3
• Mixed	9	56.3
MMC		
• Yes	11	68.7
• No	5	31.3
Laterality		
• Right eye	8	50
• Left eye	8	50
Location		
• Bulbar	11	68.7
• Palpebral	5	31.3
Metastases		
• Yes	3	18.8
• No	13	71.2

TABLE 2. Association of several factors with the recurrence of melanoma

Characteristic	Total	Recurrence (%) n = 4	Non-recurrence (%) n=12	p	OR (95% CI)
Gender					
• Female	6	3 (75)	3 (25)		
• Male	10	1 (25)	9 (75)	0.11	9.0 (0.6-122.7)
Age group					
• < 50 years	5	1 (25)	4 (33.3)		
• ≥ 50 years	11	3 (75)	8 (66.7)	1.00	0.6 (0.1-19.4)
Location					
• Bulbar	11	1 (25)	10 (83.3)		
• Palpebra	5	3 (75)	2 (16.7)	0.06	15.0 (0.9-228.8)
Tumor size					
• < 1 cm^3	7	1 (25)	6 (50)		
• ≥ 1 cm^3	9	3 (75)	6 (50)	0.58	3.0 (0.2-37.6)
MMC Application					
• No	5	2 (50)	3 (25)		
• Yes	11	2 (50)	9 (75)	0.55	0.3 (0.03-3.5)
Histology					
• Spindel	6	2 (50)	4 (33.3)		
• Epithelioid	1	0 (0)	1 (8.3)		
• Mixed	9	2 (50)	7 (58.3)	0.744	
Metastasis					
• No	26	1 (25)	12 (100)		
• Yes	11	3 (75)	0 (0)	0.007	13.0 (1.9-85.4)

There was significant association between metastasis and the recurrence of melanoma (OR 13.0; 95% CI 1.9-85.4; p = 0.007). A favorable trend of association was also found between location and the recurrence of melanoma (OR 15.0; 95% CI 0.9-228.8; p = 0.06). The association between melanoma recurrences with gender, age group, tumor size, MMC application and predominant histopathological were analyzed, but none of them showed a significant association.

DISCUSSIONS

A proper clinical examination with slit lamp biomicroscopy that includes the size, color, focality, laterality, borders, elevation, feeder vessels and location of the lesion with drawings for documentation is essential for diagnosing ocular melanoma, although a tissue biopsy is required for a definite diagnosis.[22] Our study revealed that there was significant association between metastasis and the recurrence

of melanoma and also a favorable trend of association between location and the recurrence of melanoma. A metastasis was reported as the most common form (40%) of melanoma recurrence.[14] Other study also has shown that the only parameter significantly associated metastasis of melanoma was tumor recurrence.[15] Thus, the patients that exhibit metastasis have higher risk of tumor recurrence.

Interestingly, our study also showed a marginally significance in the association of tumor location with the melanoma recurrence. A study of 150 subjects showed that the location of the tumor was a predictive factor for tumor recurrence.[16] A similar study also showed that non-limbal location of the primary tumor was a predictive factor for local recurrence.[17] In agreement with the previous study, the tumor location might be attributable to the recurrence of melanoma.

We found no correlation between gender and the recurrence of melanoma. In our study we found male were more affected than female, but this has no correlation with disease recurrence. Other various studies also showed no predilection for either gender, while some had shown greater association with male gender.[18,19] A study that enrolled 1.156 adults diagnosed with melanoma, reported that females has more advantage prognostic factors in melanoma. This study was used amitotic rate of melanomaas the prognostic factor for recurrence, although the results only showed marginally significance data.[20] Therefore, the gender might not relate to the recurrence of melanoma.

Next, we look for a correlation between predominant histopathological features with the recurrence of melanoma. Our study showed that there was no correlation between predominant histopathological features and conjunctival melanoma recurrence. There was also no correlation found between predominant histopathological features and metastases of conjunctival melanoma. There was no other study specifically mentioned the correlation between predominant histopathological features with neither recurrence and metastases of conjunctival melanoma. A study managed to report the correlation between predominant histopathological features and metastases of conjunctival melanoma. In that study, the predominant epithelioid cells features on histopathological examination was tend to have higher rate of metastases.[12] The variation of the results between current study with the previous study could be affected from the race and the risk factor for melanoma in different region.

MMC application used as an adjuvant therapy to reduce the likelihood of disease recurrence.[23] Our study showed that MMC application has no correlation with tumor recurrence and distant metastases. Limitations of this study were the small sample size and unequal follow up time for each patient. Further study in conjunctival melanoma is needed to find other factors that may lead to the prediction of disease recurrence and distant metastases.

CONCLUSION

In this study, our results showed that the patients with a history of distant metastasis were at the greater risk for tumor recurrence. Thus, the distant metastasis might be a strong predictor for the recurrence of the diseases.

ACKNOWLEDGEMENTS

We would like to thank all the parties from both contributed hospitals (Dr. Sardjito General Hospital and Dr. Yap Eye Hospital, Yogyakarta) for the assistant trough this study.

REFERENCES

1. Esmaeli B, Roberts D, Ross M, Fellman M, Cruz H, Kim SK, et al. Histologic features of conjunctival melanoma predictive of metastasis and death (an American Ophthalmological thesis). Trans Am Ophthalmol Soc 2012; 110:64.
2. Wiraguna AWA. Incidence of nevus pigmentosus and malignant melanoma at the Department of Anatomical Pathology, Faculty of Medicine Gadjah Mada University. Journal of the Medical Sciences (Berkala ilmu Kedokteran) 1994; 26(01): 37-44.
3. Vora GK, Demirci H, Marr B, Mruthyunjaya P. Advances in the management of conjunctival melanoma. Surv Ophthalmol 2017;62(1):26-42. https://doi.org/10.1016/j.survophthal.2016.06.001
4. McInnes CW, Bellan L. Conjunctival melanoma. N Engl J Med 2015; 372(19):1844. https://doi.org/10.1056/NEJMicm1405612
5. Kenawy N, Lake S, Coupland S, Damato B. Conjunctival melanoma and melanocytic intra-epithelial neoplasia. Eye 2013; 27(2):142-52. https://doi.org/10.1038/eye.2012.254
6. Rosa RH. Ophthalmic pathology and intraocular tumors. Am Acad Ophthalmol 2018.
7. Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. Int J Clin Exp Pathol 2013; 6(7):1230.
8. Coury JR, Davis BN, Koumas CP, Manzano GS, Dehdashti AR. Histopathological and molecular predictors of growth patterns and recurrence in craniopharyngiomas: a systematic review. Neurosurg Rev 2018; 1-8. https://doi.org/10.1007/s10143-018-0978-5
9. Marciscano AE, Stemmer-Rachamimov AO, Niemierko A, Larvie M, Curry WT, Barker FG, *et al.* Benign meningiomas (WHO Grade I) with atypical histological features: correlation of histopathological features with clinical outcomes. J Neurosurg 2016; 124(1):106-14. https://doi.org/10.3171/2015.1.JNS142228
10. Cottom HE, Bshena FI, Speight PM, Craig GT, Jones AV. Histopathological features that predict the recurrence of odontogenic keratocysts. J Oral Pathol Med 2012; 41(5):408-14. https://doi.org/10.1111/j.1600-0714.2011.01113.x
11. Wong JR, Nanji AA, Galor A, Karp CL. Management of conjunctival malignant melanoma: a review and update. Expert review of ophthalmology 2014; 9(3):185-204. https://doi.org/10.1586/17469899.2014.921119
12. Tuomaala S, Toivonen P, Al-Jamal R, Kivelä T. Prognostic Significance of Histopathology of Primary Conjunctival Melanoma in Caucasians. Curr Eye Res 2007; 32(11):939-52. https://doi.org/10.1080/02713680701648019
13. Anastassiou G, Heiligenhaus A, Bechrakis N, Bader E, Bornfeld N, Steuhl K-P. Prognostic value of clinical and histopathological parameters in conjunctival melanomas: a retrospective study. Br J Ophthalmol 2002; 86(2):163-7. https://doi.org/10.1136/bjo.86.2.163
14. O'Connell EP, O'Leary DP, Fogarty K, Khan ZJ, Redmond HP. Predictors and patterns of melanoma recurrence following a negative sentinel lymph node biopsy. Melanoma Res 2016;26(1):66-70. https://doi.org/10.1097/CMR.0000000000000211
15. De Potter P, Shields CL, Shields JA, Menduke H. Clinical predictive factors for development of recurrence and metastasis in

conjunctival melanoma: a review of 68 cases. Br J Ophthalmol 1993; 77(10):624-30. https://doi.org/10.1136/bjo.77.10.624
16. Shields CL, Shields JA, Gündüz K, Cater J, Mercado GV, Gross N, et al. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. Arch Ophthalmol 2000; 118(11):1497-507. https://doi.org/10.1001/archopht.118.11.1497
17. Tuomaala S, Eskelin S, Tarkkanen A, Kivela T. Population-based assessment of clinical characteristics predicting outcome of conjunctival melanoma in whites. Invest Ophthalmol Vis Sci 2002; 43(11):3399-408.
18. Scoggins CR, Ross MI, Reintgen DS, Noyes RD, Goydos JS, Beitsch PD, *et al.* Gender-related differences in outcome for melanoma patients. Ann Surg 2006; 243(5):693. https://doi.org/10.1097/01.sla.0000216771.81362.6b
19. Morgese F, Berardi R, Sampaolesi C, Torniai M, Marcantognini G, Giacchetti A, *et al.* Gender differences and outcome of melanoma patients. J Transl Med 2015; 13(1):P13. https://doi.org/10.1186/1479-5876-13-S1-P13
20. Farahi JM, Fazzari M, Braunberger T, Caravaglio JV, Kretowicz A, Wells K, *et al.* Gender differences in melanoma prognostic factors. Dermatol Online J 2018; 24(4).
21. Campbell RJ. Histological typing of tumours of the eye and its adnexa. Berlin Heidelberg: Springer Science & Business Media; 2012.
22. Karcioglu ZA. Orbital tumors: diagnosis and treatment. New York: Springer; 2014. https://doi.org/10.1007/978-1-4939-1510-1
23. Kurli M, Finger PT. Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: 12 years' experience. Graefes Arch Clin Exp Ophthalmol 2005; 243(11):1108-14. https://doi.org/10.1007/s00417-004-1080-y