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ORIGINAL ARTICLE

Gene Mutation and S100 Protein can be Prognostic Predictive Factors for Mucosal Melanoma Patients

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SUMMARY

Background: **Primary mucosal melanoma is a rare tumor that is usually diagnosed at advanced stages. It is of unknown etiopathogenesis with poor prognosis due to unfavorable response to treatments.**
Methods: **The aim of this study was to analyze the clinical and laboratory characteristics of 28 cases of primary mucosal melanoma in Southwest China.**
Results: **The mean age of the patients was 57 years, and 12 patients (43%) were men. Gene mutations were detected in 25% of the study population, and patients with gene mutations had a lower risk of relapse compared to patients without mutation (HR 0.258, p = 0.048). The study population had mucosal melanoma originating from head/neck (46%), anorectum (43%), and genital tract (11%). Patients with mucosal melanoma originating from genital tract had a higher peripheral blood lymphocyte-to-monocyte ratio (6.7) and a larger number of eosinophil (0.34 x 10^9/L) when compared to patients with mucosal melanoma originating from head/neck (3.1; 0.16 x 10^9/L) or patients with mucosal melanoma originating from anorectum (4.3; 0.14 x 10^9/L). At diagnosis, 3 patients (11%) developed organ metastasis. Patients with organ metastasis had a higher level of S100 protein (0.706 ng/mL) when compared to patients without metastasis (0.095 ng/mL) or patients with lymph node metastasis (0.067 ng/mL). S100 protein could be used to predict organ metastasis (cutoff value, 0.0935 ng/mL; AUC, 0.924; sensitivity, 0.89; specificity, 0.90).**
Conclusions: **Among primary mucosal melanoma patients, gene mutations are associated with longer disease-control survival. S100 protein could help to improve the stratification process with a high risk of tumor progression.**
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KEYWORDS

mucosal melanoma, organ metastasis, S100 protein

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Table 1. Clinicopathologic features of the patient population.

Characteristic	MM (n = 28)
Age at diagnosis (median, IQR)	57 (51 - 68)
Gender	
Male	12
Female	16
Site of primary tumor	
Head/neck	13 (46%)
Anorectum	12 (43%)
Genital tract	3 (11%)
Clinical stage at diagnosis	
Local	19 (68%)
Lymph node metastasis	6 (21%)
Organ metastasis	3 (11%)
Surgery	
Yes	21 (75%)
No	7 (25%)
Radiotherapy	
Yes	17 (61%)
No	11 (39%)
Chemotherapy	
Yes	19 (68%)
No	9 (32%)
Immunotherapy	
Yes	17 (61%)
No	11 (39%)
Mutation	
Yes	7 (25%)
NRAS	1
KIT	4
BRAF	1
NRAS and KIT and BRAF	1
No	21 (75%)

INTRODUCTION

Primary mucosal melanoma (MM), usually diagnosed at advanced stages, is a rare malignancy originating from melanocytes located in the mucosae [1]. Risk factors for this rare melanoma sub-type remain poorly understood. Currently, there is no clear evidence to support the pathogenic role of UV sunlight exposure or chemical carcinogens or viruses [1,2]. Early diagnosis of this disease is difficult because of its rarity, mostly occult anatomical origin site, atypical clinical features (about half of MMs are amelanotic), and unknown risk factors [1-4].

So far, MM patients have usually had poor prognosis due to unfavorable response to treatments. Despite aggressive surgery, the occurrence of local or distant recurrences are very common, with the majority of patients ultimately dying of metastases [1]. The poor prognosis even after surgery induces the consideration of the quality of life in clinical decision-making, so that unnecessary and harmful surgical efforts can be avoided. Therefore, once MM is diagnosed, prognostic information should be obtained to help determine future treatments [1].

Unfortunately, due to the rarity of the disease, there are only a few real-word experiences investigating outcomes and prognostic factors [5-7]; therefore, it is still unclear which criteria can be used to provide prognostic information. This study aimed to analyze clinical/laboratory data and survival outcomes of MM patients diagnosed at our institute in the last two years, with emphasis on prognostic predictive factors.

MATERIALS AND METHODS

All patients with confirmed histologic diagnosis of MM at West China Hospital, Sichuan University, from December 2020 through January 2023 were included in this retrospective study. In particular, demographic characteristics, tumor histology, stage, therapy, and survival data were analyzed. Patients were followed up for 2 years. For clinical and pathological staging, three distinct types of disease progression were defined: 1) local disease, 2) regional nodal involvement, and 3) distant metastases [8].

Categorical and continuous variables were compared with the chi-squared and the *t*-test, respectively. The survival probabilities of postoperative relapse were calculated with the Kaplan-Meier method. The risk of recurrence (hazard ratios, HR) was estimated using multivariable Cox regression. The cutoff value was determined by the receiver operating characteristic curve (ROC) curve. p-value < 0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics 29.

RESULTS

Over a period of 2 years, 28 patients with MM were diagnosed at our institute. The clinicopathologic features of the patient population are shown in Table 1.

Disease-control survival (DCS) was defined as time from surgery until the first disease progression of any type or loss of follow-up. The median DCS across all of the surgery patients was 9.5 months. At univariate analysis, only mutation was statistically significant [HR = 0.258 (0.067 - 0.987), p = 0.048] (Table 2). Patients with gene mutations had a lower risk of relapse compared to patients without mutation.

The median DCS was 20 months for patients with mutations, and the median DCS was 7 months for patients without mutation. Kaplan-Meier estimates were slightly more favorable for mutations compared to without mu-

Table 2. Exploratory analysis of effects of prognostic factors on disease-control survival.

Factor	Univariate	p
	HR (95%, CI)	
Clinical stage at diagnosis	0.890 (0.240 - 3.301)	0.861
Radiotherapy	0.841 (0.250 - 2.824)	0.799
Chemotherapy	2.126 (0.284 - 17.301)	0.448
Immunotherapy	1.833 (0.494 - 6.801)	0.365
Mutations	0.258 (0.067 - 0.987)	0.048

Table 3. Laboratory parameters at disease diagnosis.

	Geometric means (95% CI)						
	PDW	LMR	NMR	NLR	Eosinophil (x 109/L)	LDH (U/L)	S100 (ng/mL)
Site of primary tumor							
Anorectum	15.6 (12.8, 18.4)	4.3 (3.2, 5.4)	11.4 (7.1, 15.6)	2.9 (1.6, 4.1)	0.14 (0.09, 0.19) *	197.9 (137.5, 258.4)	0.23 (-0.10, 0.56)
Head/neck	13.7 (11.8, 15.6)	3.1 (2.0, 4.2)	8.8 (6.8, 10.8)	5.5 (0.4, 10.7)	0.16 (0.10, 0.22) *	169.2 (144.5, 193.9)	0.11 (-0.01, 0.23)
Genital tract	14.9 (9.7, 20)	6.7 (1.1, 12.2)	7.5 (-0.9, 15.9)	1.1 (0.8, 1.4)	0.34 (-0.35, 1.03)	245.7 (-99.1, 590.4)	0.05 (0.02, 0.08)
p-value	0.454	0.014	0.349	0.394	0.035	0.307	0.631
Clinical stage at diagnosis							
Local	14.4 (12.8, 16.1)	3.9 (2.7, 5.0)	9.3 (7.3, 11.2)	4.6 (1.1, 8.1)	0.18 (0.11, 0.25)	178.6 (146.9, 210.2)	0.095 (0.02, 0.17) ##
Lymph node metastasis	16.6 (12.1, 21.2)	4.0 (2.6, 5.4)	9.2 (5.7, 12.8)	2.4 (1.5, 3.4)	0.16 (0.07, 0.24)	239.1 (109.4, 368.9)	0.067 (0.04, 0.10) ##
Organ metastasis	11.9 (8.6, 15.2)	4.8 (1.5, 8.0)	13.9 (-16.8, 44.8)	2.8 (-2.2, 7.9)	0.12 (-0.14, 0.38)	161.3 (146.1, 176.5)	0.706 (-1.8, 3.23)
p-value	0.176	0.805	0.339	0.724	0.681	0.227	0.015
Postoperative recurrence							
No	14.5 (12.5, 16.4)	4.4 (3.2, 5.6)	10.1 (6.4, 13.9)	2.8 (1.6, 4.0)	0.19 (0.10, 0.28)	185.5 (142.5, 228.5)	0.19 (-0.09, 0.47)
Yes	14.8 (12.4, 17.2)	3.6 (2.4, 4.8)	9.4 (7.3, 11.5)	5.0 (0.23, 9.9)	0.15 (0.10, 0.20)	193.9 (142.9, 244.9)	0.12 (0.01, 0.23)
p-value	0.886	0.314	0.719	0.338	0.445	0.787	0.624
Mutation							
No	14.4 (12.8, 16.1)	4.2 (3.2, 5.3)	10.8 (8.2, 13.3)	4.4 (1.3, 5.8)	0.16 (0.10, 0.23)	194.9 (153.4, 236.4)	0.15 (-0.03, 0.33)
Yes	15.3 (11.4, 19.2)	3.3 (2.4, 4.2)	6.8 (5.8, 7.8)	2.4 (1.1, 3.7)	0.20 (0.12, 0.27)	174.1 (147.0, 201.3)	0.17 (-0.06, 0.41)
p-value	0.616	0.295	0.076	0.45	0.555	0.563	0.901

PDW - platelet distribution width, LMR - lymphocyte-monocyte ratio, NMR - neutrophil-lymphocyte ratio, NLR - neutrophil-lymphocyte ratio, LDH - lactate dehydrogenase. * - Compared to genital tract, $p < 0.05$, ## - compared to organ metastasis, $p < 0.01$.

tation ($p = 0.035$, Figure 1).

At diagnosis (Table 3), patients with mucosal melanoma originating from genital tract had a higher peripheral blood lymphocyte-to-monocyte ratio (6.7 vs. 3.1) and a larger number of eosinophils (0.34 vs. 0.16 x 10^9/L) when compared to patients with mucosal melanoma

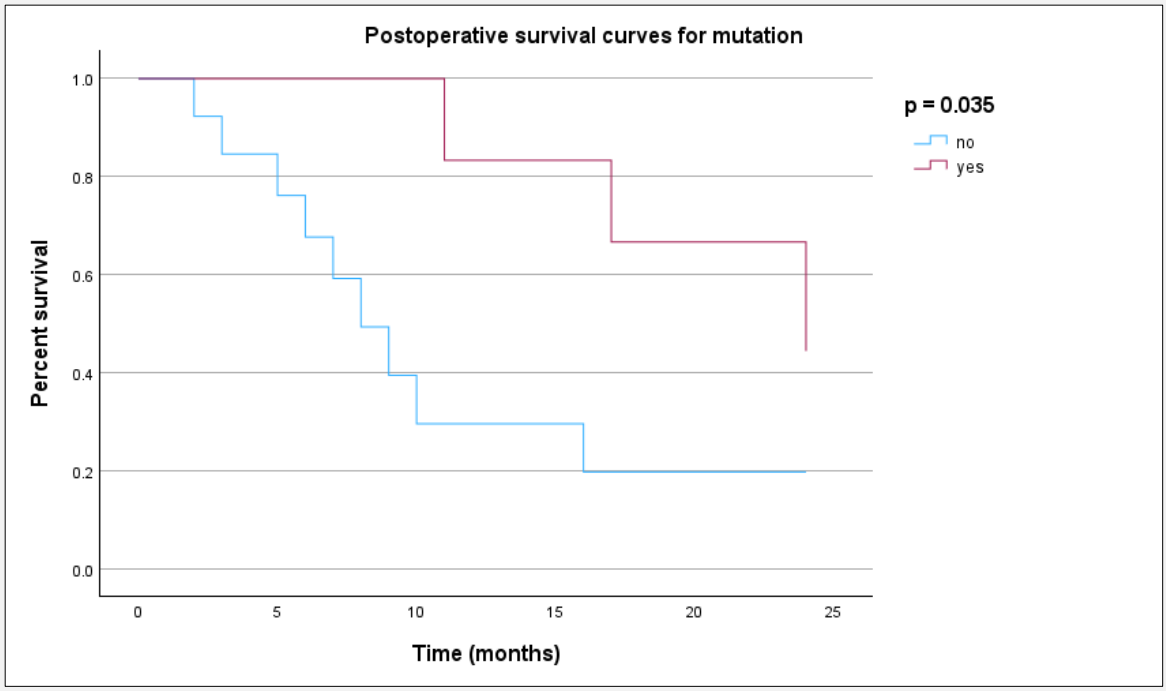

Figure 1. Kaplan-Meier estimates for disease-control survival.

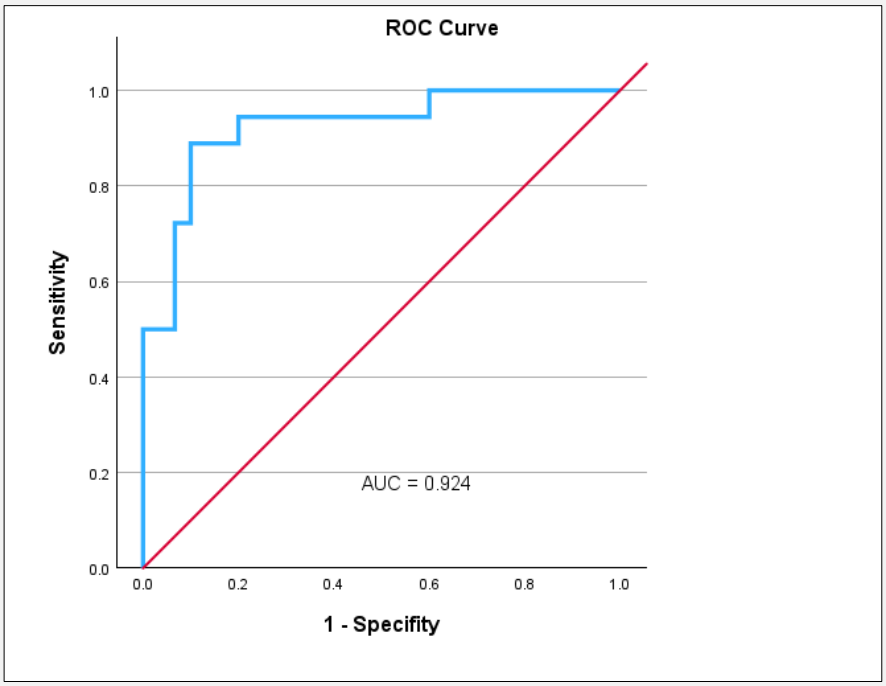

Figure 2. Optimized cutoff was determined for S100.

originating from head/neck or patients with mucosal melanoma originating from anorectum (6.7 vs. 4.3, 0.34 vs. 0.14 x 10^9/L). Patients with organ metastasis had a higher level of S100 protein when compared to patients without metastasis (0.706 vs. 0.095 ng/mL) or patients with lymph node metastasis (0.706 vs. 0.067 ng/mL). A ROC curve was plotted to verify the optimal cutoff value for S100, which was 0.0935 (Figure 2). It demonstrated that S100 could predict cancer prognosis (to organ metastasis) with a sensitivity of 88.9% and a specificity of 90% (AUC = 0.924, 95% CI: 0.884 - 1.004, $p < 0.0001$).

DISCUSSION

In our study, patients with gene mutations had a lower risk of relapse compared to patients without mutation (median DCS was 20 months vs. 7 months), probably because their burden of gene mutations could make them more responsive to immunotherapy treatments. This is similar to the fact that the life expectancy of patients with cutaneous melanoma remains longer than that of patients with MM, since cutaneous melanoma patients have a heavier burden of point mutations and a wider number of structural chromosomal variants, making them more responsive to immunotherapy treatments [1]. This reminds us that genetic testing can be helpful in providing prognostic information for MM patients. Another important finding of this study is that serum S100 protein could be used to predict organ metastasis. In fact, S100 protein has been one of the most investigated and useful biomarkers in cutaneous melanoma [9-12]. However, there is few research about S100 protein in MM, probably due to the rarity of the disease. Even though the sample size of our study was small, the correlation between S100 protein and the prognosis of MM we found here could still help to implement and to increase the efficacy of melanoma management. More specifically, serum S100 protein could help to decide whether MM patients need to take further examinations, such as magnetic resonance imaging or computed tomography, to find out if the disease is disseminated or not. If the S100 protein level is elevated, the patients should have further examinations. If it is not elevated, the chance of disease dissemination is small, the patients might choose not to take further examinations; this is especially useful for patients who cannot afford expensive examinations in developing countries.

Lastly, although peripheral blood lymphocyte-to-monocyte ratio has been associated with prognosis in many malignancies including metastatic melanoma [13,14], we did not find any correlation between lymphocyte-to-monocyte ratio and prognosis in MM patients in this study. Similarly, while some studies find that eosinophilia is a prognostic marker in patients with metastatic melanoma, probably because eosinophils are pleiotropic effector cells of the innate immune system [15,16], we did not find any correlation between eosinophil counts and prognosis in MM patients. Nevertheless, in this study, we found that patients with mucosal melanoma originating from genital tract had a higher peripheral blood lymphocyte-to-monocyte ratio and a larger number of eosinophil than other types of MM patients. Whether this finding is meaningful needs to be validated in a larger study in the future.

In conclusion, the ability to diagnose MM early, to stage it easily, and to predict it properly is important for effective and rapid intervention and treatment of affected individuals. In our study, S100 protein could help to improve the stratification process with a high risk of tumor progression, and genetic testing could help to provide prognostic information. The limitation of this study is its retrospective nature and its small sample size, but the perspective results could help to implement and increase the efficacy of MM management.

Data Availability Statement:
All data of the clinical case are included in this article. Further inquiries can be directed to the corresponding authors.

Consent for Publication:
Informed consent for publication of data was obtained from the patient.

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Declaration of Interest:
All authors declare absence of any real or potential conflicts of interest related to this work.

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