

Tumor growth rate as a prognostic factor of acral melanoma in a Korean population

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Abstract

Rapid growth of cutaneous melanoma is associated with aggressive histopathologic features and poor prognosis. However, the impact of growth rate (GR) in acral melanoma (AM) remains largely unknown.

We performed this study to identify the impact of GR on lymph node metastasis and survival in AM.

We analyzed cases of invasive AM diagnosed at our institution between 1998 and 2017. We investigated the impact of GR on the prognosis of AM.

A total of 126 cases of invasive AM were included. Log (GR) was significant associated with lymph node metastasis in the univariate logistic regression analysis ($P = .005$). The log-rank test revealed statistically significant differences in disease-free survival (DFS) and disease-specific survival (DSS) among the GR quartiles. In the Cox regression analysis, log (GR) was an independent predictor for DFS ($P = .041$), but not for DSS in multivariate analysis. In the subgroup analysis, log (GR) was an independent predictor for early-stage ($\leq 2A$) AM (DFS, $P = .002$; DSS, $P = .004$).

The limitations of this study include the retrospective design of the study and possible recall bias.

Our results suggest that GR is an important prognostic factor for DFS and DSS in AM patients and an independent predictor for early-stage AM.

Abbreviations: AM = acral melanoma, CI = confidence interval, DFS = disease-free survival, DSS = disease-specific survival, GR = growth rate, HR = hazard ratio, LN = lymph node, OR = odds ratio.

Keywords: acral lentiginous melanoma, acral melanoma, growth rate, melanoma, prognosis, recurrence, survival

1. Introduction

The misdiagnosis of acral melanoma (AM) is associated with poor prognosis. Diagnostic delay leads to the progression of

melanoma, consequently causing detection at advanced stages.^[1–4] However, paradoxically, the time to diagnosis and tumor thickness are inversely correlated in cutaneous melanoma.^[5] Moreover, a short time to diagnosis is a poor prognostic factor in patients with AM.^[6] Therefore, the time to diagnosis and biologic aggressiveness of the tumor may be essential prognostic factors.

The growth rate (GR) of cutaneous melanoma, which is defined as the ratio of the thickness of the lesion to its period of evolution, is an estimate of the speed of vertical tumor growth.^[7] A rapid GR is associated with aggressive clinicopathologic features, including thick tumor, a high mitotic rate, old age,^[8,9] and poor prognosis.^[7,10]

AM is a distinct subtype of malignant melanoma which occurs on acral skin such as the palms and soles. Its pathogenesis and biologic behavior are different from those of cutaneous melanoma on the trunk or head/neck. However, to the best of our knowledge, the impact of GR on the prognosis of AM remains largely unknown. Therefore, we conducted this study to investigate the association between tumor GR on and lymph node (LN) metastasis and survival in AM.

2. Materials and methods

2.1. Subject selection

Data were collected from Seoul National University Hospital from January 1998 to December 2017. The inclusion criteria were patients with pathologically confirmed AM who underwent surgery. AMs in situ ($n = 85$) were not included because GR could not be calculated. This study was approved by the institutional review board of our institution (H-1804-021-934).

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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2.2. Data collection

Demographic and clinical data such as sex, age, time to diagnosis, date of diagnosis, tumor location, clinical photograph, date of operation, Breslow thickness, ulceration, mitosis rate, and date of local recurrence, regional recurrence, distant metastatic recurrence, melanoma-specific death, and last follow-up were analyzed by reviewing the patients medical records and the hospitals pathologic database.

2.3. Estimation of tumor GR and statistical analysis

We calculated tumor GR as the ratio of Breslow thickness (mm) to the time to operation from disease onset (months). Breslow thickness was obtained from the pathology report of the surgical specimen. The time to operation from disease onset was determined based on information reported by the patient or their family.

GR value was converted by log scale because cancer cells increase exponentially.^[7,11] GR value satisfied the normal distribution after log conversion. Disease-free survival (DFS) and disease-specific survival (DSS) were calculated from the date of the first histopathological diagnosis to the date of recurrence or death due to melanoma progression. Patients who survived or did not experience recurrence were considered as censored on the last follow-up date before January 16, 2018. Two patients who died from causes other than melanoma were censored at the time of death.

Survival was compared among the GR quartiles using the Kaplan–Meier method and log-rank test. We divided the groups by GR quartiles to determine the tendency of the changes of DFS and DSS based on the GR value based on a previous study by Grob et al.^[7] Cox proportional hazards regression model was used to evaluate risks of log (GR) on DFS and DSS after adjustment for covariates. We performed subgroup analysis for Stage $\leq 2A$ and $>2A$, a boundary point for high risk for recurrence and disease dissemination.^[12] We also performed univariate and multivariate logistic regression analyses to identify the impact of GR on LN metastasis. Multivariate analysis was performed using a forward stepwise conditional method. The covariates included in the multivariate analysis were sex (male vs female), age (≤ 60 years vs > 60 years), Breslow thickness, presence of ulceration, high mitotic rate ($>5/\text{mm}^2$), and presence of LN metastasis. Breslow thickness and log (GR) were used as continuous variables. P values $<.05$ were considered statistically significant. We used SPSS 22.0 (IBM Corp., Armonk, NY, USA) for all statistical analyses.

3. Results

3.1. Clinicopathological data

We included 126 patients with AM. Their clinicopathological characteristics are shown in Table 1. The mean age of the patients was 61.8 years (range: 30–83 years). AM commonly occurred on the non-nail acral area (70.6%) or foot (79.4%). The mean time to operation from disease onset and Breslow thickness were 66.63 months and 3.06 ± 3.37 mm, respectively. The mean GR and log (GR) were 0.2402 mm/month and -1.2307 , respectively. The first, second, and third quartiles were 0.0167, 0.0556, and 0.2452 mm/month, respectively. Descriptive statistics are shown in Table 1.

3.2. Prognostic factors for LN metastasis

Log (GR) was a statistically significant prognostic factor for LN metastasis in the univariate logistic regression analysis (odds ratio

Table 1

Patient demographics and clinicopathologic data.

Parameters	Number (%)
Total	126 (100)
Sex, No. (%)	
Male	63 (50)
Female	63 (50)
Age at diagnosis, years	
≤ 60	73 (57.9)
> 60	53 (42.1)
Mean \pm SD	61.8 \pm 11.8
Median	62.5
Range	30–83
Anatomic location	
Acral, non-nail	89 (70.6)
Nail	37 (29.4)
Hand	26 (20.6)
Foot	100 (79.4)
Right	62 (49.2)
Left	64 (50.8)
Time to operation, months	
Mean \pm SD	66.63 \pm 114.49
Median	36
Range	1.00–901.00
Breslow thickness, mm	
Mean \pm SD	3.06 \pm 3.37
Median	2
Range	0.03–19.00
Pathologic T stage	
T1	46 (36.5)
T2	27 (21.4)
T3	25 (19.9)
T4	28 (22.2)
Growth rate, mm/month	
Mean \pm SD	0.2402 \pm 0.4519
Median	0.0556
Range	0.0004–2.6667
IQR	0.0167–0.2452
Log (GR)	
Mean \pm SD	(-1.2307) \pm 0.8100
Median	-1.2549
Range	(-3.3838)– 0.4260
IQR	(-1.7772)–(-0.6105)
Ulceration	
Absent	94 (74.6)
Present	32 (25.4)
High mitotic rate ($>5/\text{mm}^2$)	
Yes	53 (42.1)
No	53 (42.1)
Not available	20 (15.8)
LN metastasis	
Negative	102 (81)
Positive	24 (19)

SD = standard deviation, GR = growth rate, HPF = high power field, LN = lymph node, IQR = interquartile range.

[OR], 2.476; 95% confidence interval [CI], 1.309–4.680; $P=.005$), but did not remain in the multivariate logistic regression analysis (Table 2).

3.3. Survival analysis (DFS and DSS)

The mean and median follow-up for DFS were 44.4 and 31.5 months (range: 2–185 months), respectively, whereas those for

Table 2
Logistic regression for LN metastasis.

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Male sex	0.660 (0.269–1.624)	.366		
Age > 60 years	6.731 (1.889–23.979)	.003*	4.078 (1.063–15.637)	.040*
Breslow thickness	1.183 (1.047–1.336)	.007*		
Log (GR)	2.476 (1.309–4.680)	.005*		
Ulceration	5.163 (2.006–13.284)	.001*	3.270 (1.175–9.103)	.023*
High mitotic rate >5/10 HPF	3.103 (1.162–8.288)	.024*		

* Significantly different.

OR = odds ratio, CI = confidence interval, GR = growth rate, LN= lymph node.

DSS were 52.27 and 40 months (range: 6–185 months), respectively. At the last follow-up, 22 patients died from melanoma, and 49 patients had recurrences. The Kaplan–Meier curves and log-rank test revealed that the higher the GR value, the shorter the DFS (*P* for trend <.001) and DSS (*P* for trend = .001) (Fig. 1). The DFS rate at 5 years based on the quartiles were 0.88, 0.52, 0.30, and 0.04. The DSS rate at 5 years based on the quartiles were 1, 0.69, 0.53, and 0.23.

Age >60 years, Breslow thickness, log (GR), ulceration, high mitotic rate (>5/mm²), and LN metastasis were significant prognostic factors for DFS in the univariate analysis (log [GR]: hazard ratio [HR]: 2.932; 95% CI: 1.867–4.603; *P* <.001). After adjustment, log (GR) (HR: 1.634; 95% CI: 1.020–2.616; *P* = 0.041), ulceration (HR: 3.399; 95% CI: 1.665–6.938; *P* < 0.001), and LN metastasis (HR: 3.037; 95% CI: 1.356–6.803; *P* = 0.009) remained independent prognostic factors for DFS (Table 3).

Breslow thickness, log (GR), ulceration, high mitotic rate (>5/mm²), and LN metastasis were significant prognostic factors for DSS in the univariate analysis. However, log (GR) was not retained after adjustment. Ulceration (HR: 3.740; 95% CI: 1.595–8.767; *P* = 0.002) and LN metastasis (HR: 9.645; 95% CI: 2.761–33.693; *P* < 0.001) remained significant prognostic factors for DSS in the multivariate Cox analysis (Table 3).

3.4. Subgroup analysis in DFS and DSS based on stage

Cox proportional hazard regression analyses for DFS in subgroups were performed (Stage ≤ 2A, Stage > A). Log (GR) was an independent prognostic factor for DFS in the early-stage group (Stage ≤ 2A) (HR: 2.909; 95% CI: 1.464–5.778; *P* = 0.002) (Table 4). In contrast, log (GR) had no statistical significance in the advanced-stage group (Stage > 2A) (*P* = 0.244) (Table 5).

Similar results were obtained for DSS. Log (GR) was an independent prognostic factor for DSS in the early-stage group (HR: 9.027; 95% CI: 1.995–40.834; *P* = 0.004). Breslow thickness was also significant in the univariate analysis; however, it did not remain after adjustment. Log (GR) was not a prognostic factor for DSS in the advanced-stage group (*P* = 0.937).

4. Discussion

In this study, we identified GR as an important prognostic factor for DFS and DSS in AM. The GR value and DFS and DSS at 5 years were clearly inversely correlated. Notably, log (GR) was an independent prognostic factor for DFS (HR: 2.909; 95% CI: 1.464–5.778; *P* = .002) and DSS (HR: 9.027; 95% CI: 1.995–40.834; *P* = .004) in the early-stage group (stage ≤ 2A).

The role of GR in malignant melanoma has been reported in previous articles. Liu et al^[8,9] elucidated that GR was associated with certain clinicopathological features of cutaneous melanoma.

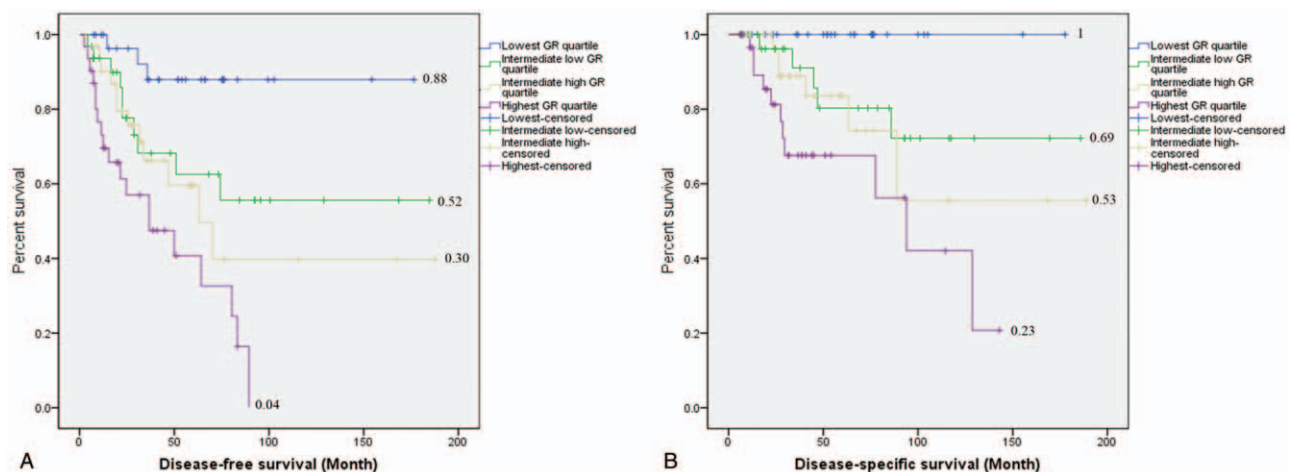


Figure 1. Kaplan–Meier curves of patients with acral melanoma: Disease-free survival (A) and disease-specific survival (B). The log-rank test revealed that patients with high growth rate had short disease-free survival and disease-specific survival. The 5-year survival rates are indicated.

Table 3
Cox proportional hazard regression model for disease-free survival and disease-specific survival (whole patients).

Outcome	Explanatory variables	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Disease-free survival					
	Male sex	1.151 (0.634–2.09)	.644		
	Age >60 years	1.891 (1.001–3.571)	.050*		
	Breslow thickness	1.117 (1.058–1.179)	<.001*		
	Log (GR)	2.932 (1.867–4.603)	<.001*	1.634 (1.020–2.616)	.041*
	Ulceration	4.494 (2.45–8.244)	<.001*	3.399 (1.665–6.938)	<.001*
	High mitotic rate >5/10 HPF	3.008 (1.529–5.919)	.001*		
	LN metastasis	6.006 (2.944–12.253)	<.001*	3.037 (1.356–6.803)	.009*
Disease-specific survival					
	Male sex	1.778 (0.753–4.198)	.189		
	Age > 60 years	1.739 (0.706–4.282)	.229		
	Breslow thickness	1.096 (1.018–1.181)	.016*		
	Log (GR)	3.328 (1.727–6.412)	<.001*		
	Ulceration	3.740 (1.595–8.767)	.002*	3.510 (1.256–9.812)	.017*
	High mitotic rate >5/10 HPF	2.743 (1.005–7.482)	.049*		
	LN metastasis	10.572 (3.736–29.919)	<.001*	9.645 (2.761–33.693)	<.001*

* Significantly different.

HR = hazard ratio, CI = confidence interval, GR = growth rate, LN = lymph node.

They revealed that rapid growth is associated with thick tumor, high mitotic rate, old age, fewer freckles, and a symmetrical appearance. These trends were also confirmed in our data. Higher log (GR) values were noted in older patients, male patients, and patients with a large Breslow thickness, high mitotic rate, or ulcers. Grob et al^[7] identified that GR is an independent predictive factor for frequent and early recurrence in cutaneous melanoma. Moreover, Tejera-Vaquero et al^[10] demonstrated that GR is an independent prognostic factor for overall survival in localized invasive cutaneous melanoma. However, the impact of GR in AM remains largely unknown. Therefore, we conducted this study and revealed the impact of GR on LN metastasis, DFS, and DSS in AM.

We calculated GR as the ratio of Breslow thickness to the time to operation from disease onset. This calculation is similar to the calculation of average speed. Average speed is defined as the rate of distance with respect to time. In our calculation, Breslow

thickness corresponds to distance, and time to operation corresponds to time. Thus, the GR value refers to the distance of vertical invasion during the unit time and indicates the aggressiveness of the tumor. Tumors with a rapid GR are thought to become thicker and metastasize earlier than tumors with slow GR.^[8,10,13]

Clark et al^[14] suggested that melanomas grow through the radial and vertical growth phases. Based on this progression model, how early a melanoma transitions from the radial to the vertical growth phase and how quickly it can invade the surrounding dermal stroma may affect its GR. However, the precise biochemical mechanisms underlying this transition have not been fully elucidated. Akt, vascular endothelial growth factor, matrix metalloproteinase, the small G protein RhoC, integrins such as $\alpha_v\beta_3$ and $\alpha_v\beta_5$, PI3K signaling pathways, and nuclear factor-kappa B signaling pathways have been suggested to be involved in this transition.^[15] We hypothesize that tumors

Table 4
Cox proportional hazard regression model for disease-free survival and disease-specific survival (Stage $\leq 2A$).

Outcome	Explanatory variables	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Disease-free survival					
	Male sex	0.883 (0.340–2.291)	.798		
	Age > 60 years	1.842 (0.714–4.756)	.207		
	Breslow thickness	1.627 (1.124–2.355)	.010*		
	Log (GR)	3.092 (1.540–6.208)	.001*	2.909 (1.464–5.778)	.002*
	Ulceration	3.476 (0.767–15.755)	.106	6.849 (1.287–36.465)	.024*
	High mitotic rate >5/10 HPF	2.348 (0.842–6.543)	.103		
Disease-specific survival					
	Male sex	2.183 (0.581–8.207)	.248		
	Age > 60 years	1.272 (0.34–4.756)	.721		
	Breslow thickness	2.416 (1.373–4.25)	.002*		
	Log (GR)	10.603 (2.846–39.505)	<.001*	9.027 (1.995–40.834)	.004*
	Ulceration	4.729 (0.49–45.659)	.179		
	High mitotic rate >5/10 HPF	0.793 (0.142–4.411)	.791		

* Significantly different.

HR = hazard ratio, CI = confidence interval, GR = growth rate.

Table 5
Cox proportional hazard regression model for disease-free survival and disease-specific survival (Stage >2A).

Outcome	Explanatory variables	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Disease-free survival	Male sex	0.946 (0.432–2.072)	.889		
	Age >60 years	1.079 (0.45–2.591)	.864		
	Breslow thickness	1.025 (0.945–1.112)	.553		
	Log (GR)	1.595 (0.727–3.499)	.244		
	Ulceration	2.453 (1.061–5.672)	.036*	3.872 (1.492–10.048)	.005*
	High mitotic rate >5/10 HPF	3.551 (1.262–9.988)	.016*		
Disease-specific survival	LN metastasis	3.339 (1.373–8.117)	.008*	3.474 (1.3–9.281)	.013*
	Male sex	0.971 (0.317–2.977)	.959		
	Age >60 years	1.727 (0.469–6.366)	.411		
	Breslow thickness	1.001 (0.892–1.122)	.988		
	Log (GR)	1.042 (0.373–2.909)	.937		
	Ulceration	2.22 (0.677–7.282)	.188		
	High mitotic rate >5/10 HPF	4.44 (0.950–20.758)	.058		
	LN metastasis	8.06 (1.987–32.704)	.003*	7.502 (1.534–36.7)	.013*

* Significantly different.

HR = hazard ratio, CI = confidence interval, GR = growth rate, LN = lymph node.

which transition from the radial to the vertical phase early are aggressive and have high GR values. Therefore, it is plausible that the higher the GR of a tumor, the worse the prognosis.

The staging system for cutaneous melanoma, which includes Breslow thickness, ulceration, mitosis rate, LN metastasis, and distant metastasis, has some limitations.^[16,17] There is a significant difference of survival rates among patients even at the same stage,^[18] and 30% of deaths due to cutaneous melanoma occurred in patients with thin melanomas (Breslow thickness ≤ 1 mm), which are generally considered to have a good prognosis.^[19] Therefore, our results have clinical importance. This study can help physicians identify high-risk patients for recurrence or death in AM below stage 2A, which was generally considered to be a low-risk group for recurrence and disease dissemination.^[12] Thus, GR can contribute to the prognostic factor that can complement the limitation of the current staging system in early-stage AM.

This study has some limitations. First, the results of this study are limited by its small sample size and retrospective design. However, this is the first study to investigate the effects of GR on AM with relatively large samples with 126 cases of AM. Second, this study did not include the impact of treatment methods such as additional chemotherapy, immunotherapy, or targeted therapy or the extent of surgical resection margins on AM prognosis. Lastly, there was recall bias. However, this method is thought to be relatively accurate and feasible because melanoma occurs on the skin, which is a visible organ, and previous studies using the same method showed consistent results.^[7–10,13,20] A prospective study in patients with AM is not feasible because melanoma should be treated as early as possible.

In conclusion, our study reveals that GR is an important prognostic factor in AM. Rapid GR is associated with shorter DFS and DSS in patients with early stages of AM.

Author contributions

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