Received: 21 October 2020 | Accepted: 17 November 2020

DOI: 10.1002/lio2.509

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Prognostic significance of regression and mitotic rate in head and neck cutaneous melanoma

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Funding information
National Center for Advancing Translational Sciences of the National Institutes of Health, Grant/Award Number: UL1-TR002494; Biostatistics and Bioinformatics Core shared resource of the Masonic Cancer Center, University of Minnesota; NIH, Grant/Award Number: P30CA077598

Abstract

Importance: While regression is a commonly reported microscopic feature of melanoma, its prognostic significance is unclear.

Objective: To examine the impact of regression on sentinel node status and the likelihood of recurrence in primary cutaneous melanoma of the head and neck.

Design: Retrospective analysis of 191 adults who underwent surgical management for primary cutaneous melanoma of the head and neck between May 2002 and March 2019.

Setting: Tertiary academic center.

Participants: Patients appropriate for the study were identified by the Academic Health Center Information Exchange using a list of current procedural terminology codes. One hundred and ninety-one cases of invasive melanoma of the head and neck were included from 830 patients identified. Clinical features assessed for each patient included age, sex, location of primary lesion, date of diagnosis, and current disease status (alive with or without disease). Histologic features assessed were histological melanoma subtype (nodular vs non-nodular), Breslow thickness, Clark level, presence/absence of ulceration, mitotic rate per square millimeter, and regression. If applicable, sentinel lymph node biopsy (SLNB) status, date of recurrence, interval treatments, and date of death related to melanoma were recorded. Exclusion criteria included melanoma outside the anatomic parameters of head and neck, ocular or choroidal melanoma, mucosal melanoma, metastatic melanoma to the head or neck with no known primary tumor, melanoma of the head or neck with no surgical intervention, and non-melanoma skin cancers of the head and neck.

Intervention/Exposure: Surgery for cutaneous melanoma of the head and neck.

Main Outcome(s) and Measure(s): The association between presence of regression and Breslow thickness, sentinel node status, and recurrence.

Results: Of the 191 patients identified, 30.9% were female and 69.1% were male with a mean age at diagnosis of 62.6 (range 20-97) years. Mean Breslow thickness was 1.2 mm in those with regression and 2.0 mm in those without regression. In patients with regression, 17.6% had a positive sentinel node, and 13.0% experienced

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a recurrence. In patients without regression, 26.5% had a positive sentinel node, and 31.4% experienced a recurrence. When adjusted for other factors above, regression was not associated with positive sentinel node (odds ratio [OR] = 0.59, 95% confidence interval [CI] = 0.13-2.00) or recurrence (OR = 0.33, CI = 0.07-1.01). Mitotic rate >2 was associated with recurrence (OR = 2.71, CI = 1.11-6.75, *P* = .03).

Conclusions and Relevance: Patients with presence of regression had thinner melanomas and trended toward decreased rates of sentinel node positivity and recurrence, suggesting regression may not be a negative prognostic indicator in patients with cutaneous melanoma of the head and neck.

1 | INTRODUCTION

Although melanoma represents only a small percentage of all skin cancers, it is responsible for a majority of skin cancer deaths.[1] As understanding of the complex biology of melanoma improves, prognostic factors of disease have been analyzed and refined.[2,3] In the seventh edition of the AJCC melanoma staging system, tumor thickness, mitotic rate, and ulceration were identified as dominant prognostic factors.[2] Changes in the eighth edition AJCC classification system included the establishment of a new T1 subcategorized tumor thickness stratum at 0.8 mm and the removal of mitotic rate as a staging criterion.[3] While mitotic rate was removed, it continues to be recognized as an important factor and its value as a prognostic indicator continues to be explored.[3,4]

The significance of other commonly reported microscopic features of melanoma such as regression remains more controversial.[5-9] Histopathologically, regression is used to describe spontaneous tumor fading and is thought to represent a partial host immune mediated response directed against tumor antigens.[10,11] Regression is found in 10% to 35% of melanomas and has been found to be more commonly associated with the radial growth phase of thin lesions.[10-12] Microscopically it appears as an infiltrate of lymphocytes mixed with pigment-laden macrophages underlying an atrophic epidermis.[10,11] Historically, after thin melanomas were reported to be capable of metastasizing especially if they showed evidence of histological regression, regression was thought to be a poor prognostic indicator.[11,13] Some authors continue to assert that regression leads to an underestimation of tumor thickness and stage resulting in a greater risk of developing nodal recurrence.[13-15] Others predict histologic regression is a favorable prognostic factor indicating an antitumor response and results in lower rates of sentinel lymph node metastasis.[16-18] While the mechanism and role of tumor regression is not fully understood, further clarification may impact future guidelines and management recommendations.

Overall, most studies commenting on regression include patients with cutaneous melanoma located in a variety of primary sites. This can be problematic given that head/neck melanoma may not behave the same as non-head/neck melanoma.[19,20] Patients with head/neck cutaneous melanoma carry a worse prognosis compared to their trunk and extremity counterparts.[19,20] Melanomas of the head and neck have been shown to present with thicker Breslow depth and tend to have lower rates of sentinel positivity but decreased survival.[19,20]

The objective of this study was to examine a single institution experience of the prognostic value of ancillary microscopic features in patients with primary melanoma of the head and neck. We examined the impact of mitotic rate and regression in addition to established prognostic features of Breslow depth, ulceration and histologic subtype on sentinel node status and the likelihood of recurrence. Further, we aimed to evaluate the relationship of regression with thickness of melanoma. Although head/neck melanoma has been found to present with thicker tumors than other locations, we hypothesized that patients with lesions displaying regression would have thinner melanomas than those without regression. As both head/neck site and regression have been found to be associated with decreased rates of sentinel node positivity, we also hypothesized that those with regression would have lower rates of sentinel node positivity.

2 | METHODS

This study was a single institution retrospective analysis of adult patients who underwent surgical management for primary cutaneous melanoma of the head and neck between May 2002 and March 2019. In some cases, melanoma was identified at our institution, while others were diagnosed at outside institutions and referred to our site for management. This study was approved by the University of Minnesota Research Subjects' Protection Programs Institutional Review Board: Human Subjects Committee (IRB study number 00003368), Cancer Center Protocol Review Committee (CRPC #2018NTLS081), and Fairview Research Administration. Patients appropriate for the study were identified by the Academic Health Center Information Exchange using a list of current procedural terminology codes (11640, 11640P, AS11640, 11640T, 11621, 11621P, 11621T, AS11621, 11642, 11642P, 11642T, AS11642, 11622, 11622P, 11622T, AS11622, 11641, 11641P, 11641T, AS11641, 11623, 11623T, 11623P, AS11623, 11643, AS11643, 11643T, 11643P, 11626, AS11626, 11626P, 11626T, 11624, 11624T, AS11624, 11624P, 11620, 11620T, AS11620, 11620P, 11646, AS11646, 11646P, 11646T, 11644, 11644P, 11644T, AS11644, 21012, 21012P, AS21012, 21012T, 21011, 21011P, AS21011, 21011T, 21555,

21555T, AS21555, 21555P, 21556, AS21556, 21556T, 21552, 21552P, 21552T, AS21552), and a set of patient medical record numbers was provided by the University of Minnesota integrated informatics core (Best Practices Integrated Informatics Core [BPIC]).

Individual records were reviewed to determine which fit the inclusion criteria, and parameters of interest were recorded. Clinical features assessed for each patient included age, sex, location of primary lesion, date of diagnosis, current disease status (alive with or without disease), and date of last follow-up or of death if unrelated to melanoma. Histologic features assessed were histological melanoma subtype (nodular vs non-nodular), Breslow thickness, Clark level, presence/absence of ulceration, mitotic rate per square millimeter, and regression. If applicable, sentinel lymph node biopsy (SLNB) status, date of recurrence, interval treatments, and date of death related to melanoma were recorded. Exclusion criteria included melanoma outside the anatomic parameters of head and neck, ocular or choroidal melanoma, mucosal melanoma, metastatic melanoma to the head or neck with no known primary tumor, melanoma of the head or neck with no surgical intervention, multiple head or neck melanomas on initial presentation, and nonmelanoma skin cancers of the head and neck. Recurrence was defined as regrowth of tumor following wide local excision of the primary head or neck melanoma. All collaboration between research team members was shared through a secure data shelter.

2.1 | Statistical analysis

Descriptive statistics were used to describe patient and tumor characteristics for the both the overall sample, and by regression status. The differences in the clinical and demographic measures between those with and without regression were tested using *t* test for numeric measures and chi-square for categorical measures. Missing data in the clinical factors were summarized in the patient characteristics table. Logistic regression models were used to test the association between presence of regression and the likelihood of a positive sentinel node, and also for any recurrence. These logistic regression models were repeated while adjusting for histologic subtype (nodular vs non-nodular), age at diagnosis, ulceration, and Breslow depth (>1 or ≤1), and mitoses (>2 or ≤2). Odds ratios, 95% confidence intervals, and *P* values were reported for the logistic regression analysis. R (V 3.6.0) was used for the analysis.

3 | RESULTS

One hundred and ninety-one cases of invasive melanoma of the head and neck were included from 830 patients identified—demographic and clinical summary is displayed in Table 1. 30.9% were female and 69.1% were male with a mean age at diagnosis of 62.6 (range 20-97) years. Of the pathologic data recorded for the overall sample, mean Breslow thickness was 1.9 (range 0.1-15.0) mm, mean Clark level was 3.4 (range 2-5), mean mitotic rate was 2.8 (range 0-20), and 16.3% of patients (31/190) had ulcerated melanomas. 19.4% of patients (37/191) patients had a nodular melanoma. 60.5% of patients (115/190) underwent a SLNB and 25.2% (29/115) of these patients were found to have a positive sentinel node. 29.1% of patients (53/182) experienced a recurrence.

13.1% of patients (25/191) had presence of regression. In patients with regression, mean Breslow thickness was 1.2 mm. In those without regression, mean Breslow thickness was 2.0 mm. Seventeen patients with regression had a SLNB and three patients (17.6%) were found to have a positive sentinel node. Ninety-eight patients without regression had a SLNB and 26 (26.5%) were found to have a positive sentinel node. Three patients (17.0%) with regression experienced recurrence while 50 patients (31.4%) without regression had a recurrence. Of the 53 total patients with a recurrence, 6 patients experienced a local recurrence, 8 experienced a regional recurrence, and 16 had a distant recurrence (Table 2). Twenty-three patients had a combination with one having local and regional recurrences, 7 having local and distant recurrences, 14 having regional and distant recurrences, and one having a local, regional, and distant recurrence. Of those patients with regression on initial pathology and recurrence, two had a distant recurrence and one had both regional and distant recurrences.

When not adjusting for other factors, presence of regression was not significantly associated with positive sentinel node (odds ratio [OR] = 0.59, 95% confidence interval [CI] = 0.13-2.00) (Table 3). A similar association was found after covariate adjustment (OR = 0.71, 95% CI = 0.14-2.79). Age at diagnosis was significantly negatively associated with positive sentinel node status (OR = 0.97, 95% CI = 0.95-0.99, *P* = .036). Breslow depth, mitotic rate >2, nodular melanoma, and ulceration were not significantly associated with sentinel node positivity. Still, although the respective CI's crossed 1, Breslow depth > 1 mm was associated with 2.62 times the odds of having a positive sentinel node (95% CI = 0.79-9.72) and mitotic rate >2 was associated with 2.00 times the odds of having a positive sentinel node (95% CI = 0.73-5.73).

Additionally, when not adjusting for other factors, presence of regression trended toward lower risk of recurrence (OR = 0.33, 95% CI = 0.07-1.01) (Table 3). A similar association was found after covariate adjustment (OR = 0.44, 95% CI = 0.10-1.50). A mitotic rate greater than 2 was significantly associated with recurrence (OR = 2.7, 95% CI = 1.11-6.75, *P* = .03). Breslow depth > 1 mm, nodular melanoma, age at diagnosis, and ulceration were not significantly associated with recurrence. Still, confidence intervals trended toward higher risk: patients with Breslow depth > 1 mm had 2.17 times the odds of recurrence (OR = 2.17, 95% CI = 0.84-5.55) and patients with nodular melanoma had 1.89 times the odds of recurrence (95% CI = 0.74-4.89).

4 | DISCUSSION

The microscopic features of melanoma are used to determine portions of stage and prognosis of disease. While Breslow depth and ulceration

TABLE 1 Clinicopathologic characteristics overall, in patients with evidence of regression (N = 25) and in patients without evidence of regression (N = 166)

Characteristic	Total (N = 191)	Regression present (N = 25)	Regression absent (N = 166)	*P* value
Sex				.424
Female	59 (30.9%)	6 (24.0%)	53 (31.9%)	
Male	132 (69.1%)	19 (76.0%)	113 (68.1%)	
Age at Dx				.094
Mean (SD)	62.6 (17.1)	57.3 (18.7)	63.4 (16.8)	
Range	20.0-97.0	24.0-86.0	20.0-97.0	
Breslow thickness (mm)				.125
Mean (SD)	1.9 (2.3)	1.2 (1.4)	2.0 (2.4)	
Range	0.1-15.0	0.3-7.0	0.1-15.0	
Clark level				.977
N-Missing	9	2	7	
Mean (SD)	3.4 (0.9)	3.4 (0.7)	3.4 (0.9)	
Range	2.0-5.0	2.0-5.0	2.0-5.0	
Mitoses				.079
N-Missing	2	1	1	
Mean (SD)	2.8 (3.8)	1.5 (1.9)	2.9 (3.9)	
Range	0.0-20.0	0.0-6.0	0.0-20.0	
Ulceration				.085
N-Missing	1	1	0	
Yes	31 (16.3%)	1 (4.2%)	30 (18.1%)	
No	159 (83.7%)	23 (95.8%)	136 (81.9%)	
Nodular melanoma				.647
Yes	37 (19.4%)	4 (16.0%)	33 (19.9%)	
No	154 (80.6%)	21 (84.0%)	133 (80.1%)	
Sentinel lymph node biopsy				.512
N-Missing	1	0	1	
Yes	115 (60.5%)	17 (68.0%)	98 (59.4%)	
No	75 (39.5%)	8 (32.0%)	67 (40.6%)	
Positive sentinel node				.436
Yes	29 (25.2%)	3 (17.6%)	26 (26.5%)	
No	86 (74.8%)	14 (82.4%)	72 (73.5%)	
Any recurrence				.069
N-Missing	9	2	7	
Yes	53 (29.1%)	3 (13.0%)	50 (31.4%)	
No	129 (70.9%)	20 (87.0%)	109 (68.6%)	

are established prognostic indicators, the utility of other microscopic features such as mitotic rate and regression is less clear.[2-9] The current study investigated the microscopic features of head and neck melanoma in 191 patients. In accord with previous literature identifying Breslow depth as an important prognostic indicator, Breslow depth > 1 mm trended toward association with sentinel node positivity and recurrence.[2-5,19,21] While ulceration is known to be a poor prognostic indicator,[2-4,21,22] our study did not demonstrate an association between ulceration and sentinel node positivity or recurrence. While not expected, the same result has been previously reported and may be due to the relatively small number of patients with ulceration in our study.[23] Still the confidence interval for calculations made regarding ulceration do include the possibility of increased odds relating to recurrence and sentinel node positivity.

Mitotic rate >2 trended toward a higher rate of positive sentinel node status and was significantly associated with recurrence. Although mitotic rate was removed from the most recent AJCC melanoma staging system, mitotic rate ≥1 has been associated with increased incidence of positive SLNB and decreased survival.[2,4,24-26] Babajanian et al report similar findings in a cohort of patients with

melanomas of the head and neck; mitotic rate ≥1 was associated with an increased incidence of positive SLNB, higher incidence of recurrence, and negative impact on overall and disease-free survival.[27] However, variability exists regarding the most accurate prognostic mitotic rate cut-off point. Piñero-Madrona et al state the presence of two or more mitoses/mm^2 is a better predictor of overall and disease-free survival than one or more mitoses/mm^2.[28] Shen et al share that recurrences occur more frequently in patients with mitotic rates ≥5 while Roach et al suggest a mitotic rate of 6 is best to predict overall survival outcomes.[29,30] In our cohort, patients with ≥2 mitoses had increased odds of experiencing a recurrence. This may suggest that even in the presence of regression or in a thin melanoma of the head/neck patients with mitotic rate ≥2 may require more aggressive management.

Patients with regression were found to have thinner melanomas and trended toward a lower likelihood of sentinel node positivity and recurrence. Our findings are consistent with other authors' findings of regression associated with thinner melanomas; this is thought to represent the host inflammatory antitumor response which creates regression and ultimately, a thinner tumor.[8,12,17,18] Ma et al further describes the antitumor T cell response that mediates regression and its protective role against sentinel lymph node metastasis.[31] However, Gardner et al explain that it is not clear why in most cases this antitumor response leads to partial regression rather than complete eradication of the primary tumor.[12] Bastian interestingly proposes that while immune cell infiltration could destroy tumor cells it could also lead to the development of tumor cells that acquire immune escape mechanisms.[32] While the presence of regression trended toward decreased rates of recurrence in our cohort, it is notable that three patients with regression experienced a recurrence. Two had a distant recurrence and one had both regional and distant recurrences. This suggests that in rare cases regression may cause incomplete tumor removal or development of tumor cells with immune escape mechanisms which can result in delayed distant recurrence. Overall, as described in other studies, in the absence of other negative prognostic indicators, the protective regression response may decrease the need for SLNB.[10,12,17,18] While no significant relationship between regression and sentinel node status or likelihood of recurrence was established in our patient cohort, there were trends toward both decreased sentinel node positivity and decreased rates of recurrence. This suggests regression is not a negative prognostic indicator in melanoma of the head and neck.

Other features examined included nodular histologic subtype and age at diagnosis. In our cohort, nodular histologic subtype was not associated with increased rates of sentinel node positivity but trended toward association with increased odds of recurrence. Interestingly this may be related to the findings of Faut et al and O'Connell et al in which the nodular melanoma subtype was linked to increased incidence of melanoma recurrence in those patients with a negative SLNB.[33,34] Though no association between age at diagnosis and recurrence was found, age at diagnosis was significantly negatively associated with positive sentinel node status. This aligns with previous studies using the National Cancer Database which identified an inverse relationship between age at diagnosis and likelihood of sentinel node positivity.[26,35]

In our single institution retrospective review, limitations include small sample size as well as incomplete patient data sets with a variety of missing elements. Insufficient information was available to calculate the role of adjuvant therapy in patients with and without regression

TABLE 2 Analysis of recurrences in patients with evidence of regression (N = 3) and in patients without evidence of regression (N = 50)

Recurrence	Regression	No regression	Total
Local	0	6	6
Regional	0	8	8
Distant	2	14	16
Local + regional	0	1	1
Local + distant	0	7	7
Regional + distant	1	13	14
Local + regional + distant	0	1	1
Total	3	50	53

TABLE 3 Simple and multiple logistic regression analysis of histologic characteristics associated with positive sentinel node and recurrence in patients with a nonmissing regression

	Positive sentinel node		Recurrence	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Without covariate adjustment				
Presence of regression	0.59 (0.13-2.00)	.44	0.33 (0.07-1.01)	.082
With covariate adjustment				
Presence of regression	0.71 (0.14-2.79)	.645	0.44 (0.1-1.5)	.234
Breslow >1 mm	2.62 (0.79-9.72)	.126	2.17 (0.84-5.55)	.106
Mitoses >2	2.00 (0.73-5.73)	.182	2.71 (1.11-6.75)	.03
Nodular melanoma	0.63 (0.29-1.89)	.42	1.89 (0.74-4.89)	.187
Age at Dx	0.97 (0.95-0.99)	.036	1.00 (0.97-1.02)	.661
Ulceration	0.74 (0.21-2.37)	.625	0.82 (0.3-2.16)	.688

Note: N = 115 (n = 113 for multiple regression) for the positive sentinel node model. N = 182 (n = 180) for the recurrence model.

as well as disease specific or overall survival. As some patients were referred to our institution from outside institutions, patient selection bias toward patients with worse prognosis may have occurred. Additionally, regression is interpreted as a pattern of characteristics and its true definition is still discussed such that the assignment of the regression may not be consistent across pathologists. This may lead to variable reporting of this feature. Further, the inability to distinguish regression as one feature of thinner melanomas or as directly associated with lower incidence of sentinel positivity is a weakness of our study.

5 | CONCLUSION

This study examining the microscopic features in primary cutaneous head and neck melanoma demonstrates no clear evidence that regression is a negative prognostic indicator. Indeed, it may be a favorable finding. No association was identified between regression and percentage of sentinel node positivity, but trends suggest lower rates of recurrence. As primary cutaneous melanoma of the head and neck represents a unique subset of melanoma, further analysis to evaluate these findings as well as to continue to investigate the association between other microscopic features of melanoma and patient prognosis is needed.

ACKNOWLEDGMENTS

Research reported in this publication was supported by NIH grant P30CA077598 utilizing the Biostatistics and Bioinformatics Core shared resource of the Masonic Cancer Center, University of Minnesota and by the National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1-TR002494. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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How to cite this article: Kim E, Obermeyer I, Rubin N, Khariwala SS. Prognostic significance of regression and mitotic rate in head and neck cutaneous melanoma. *Laryngoscope Investigative Otolaryngology*. 2021;6:109–115. https://doi.org/10.1002/lio2.509