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Regression and Sentinel Lymph Node Status in Melanoma Progression

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Background: The purpose of this study was to assess the role of regression and other clinical and histological features for the prognosis and the progression of cutaneous melanoma.

Material/Methods: Between 2005 and 2016, 403 patients with melanoma were treated and followed at our Department of Dermatology. Of the 403 patients, 173 patients had cutaneous melanoma and underwent sentinel lymph node (SLN) biopsy and thus were included in this study.

Results: Histological regression was found in 37 cases of melanoma (21.3%). It was significantly associated with marked and moderate tumor-infiltrating lymphocyte (TIL) and with negative SLN. Progression of the disease occurred in 42 patients (24.2%). On multivariate analysis, we found that a positive lymph node and a Breslow index higher than 2 mm were independent variables associated with disease free survival (DFS). These variables together with a mild TIL were significantly correlated with overall survival (OS). The presence of regression was not associated with DFS or OS.

Conclusions: We could not demonstrate an association between regression and the outcome of patients with cutaneous melanoma. Tumor thickness greater than 2 mm and a positive SLN were associated with recurrence. Survival was influenced by a Breslow thickness >2 mm, the presence of a mild TIL and a positive SLN status.

MeSH Keywords: Melanoma • Neoplasm Regression, Spontaneous • Prognosis • Sentinel Lymph Node Biopsy

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Background

Melanoma is the most aggressive skin cancer and has unpredictable behavior. It is responsible for most of skin cancer deaths [1]. According to GLOBOCAN, there were 22,000 estimated melanoma deaths in Europe in 2012, 36% of them were reported in Central and Eastern Europe [1]. Considerable differences in melanoma mortality exist across European countries. The highest mortality rate was estimated in Norway (5.1 per 100 000) and one of the lowest was found in Romania (1.4 per 100 000) [1].

Because of its aggressiveness, new therapeutic strategies are continually being developed. There are targeted therapies that block signal transduction (e.g., BRAF inhibition) or enhance anti-tumor immune response (e.g., CTLA-4 blockade), and there have also been studies about the cytotoxic and inhibitory effect of some vitamin derivatives (e.g., retinoic acid) [2].

In order to find a feature that could predict the outcome of patients with melanoma, many biomarkers have been studied. Among the histological features recognized for their role in the survival of patients with cutaneous melanoma, Breslow thickness, ulceration, mitotic rate, and the status of sentinel lymph node (SLN) are considered the most important prognostic factors [3]. From studies of tissue biomarkers, microRNAs (miRNAs) seem to have an important role in the prognosis of cutaneous melanoma [4]. Regression is another histological feature that has been debated regarding its prognostic significance. It is found relatively frequent in cutaneous melanomas, being described in 10–35% for all thicknesses and in an even higher percent in thin tumors [5].

Regression is defined as an area inside the tumor where the malignant cells are fewer or they have disappeared and have been replaced by variable degrees of inflammatory cells, fibrosis, melanophages, neovascularization, epidermal flattening, and apoptotic melanocytes or keratinocytes [6]. The phenomenon has been extensively studied and divided in three stages: an early phase with dense lymphocytic infiltrate; an intermediate phase with tumor reduction and replacement by lymphocytes and fibrosis; and a late phase with marked reduction or absence of the tumor and its replacement by considerable fibrosis, melanophages [7].

The prognostic implication of regression in primary melanoma has been thoroughly debated over the last decades and interpreted in contradictory ways. One hypothesis suggests that the disappearance of tumor cells may determine an underestimation of the initial tumor thickness leading to a less accurate assessment of the patients and subsequently a worse prognosis [5]. Some studies have shown that the presence of regression is associated with a greater risk of developing lymph node metastases [8]. Another hypothesis supports the role of regression as an indicator of host immune response to tumor and consequently a more favorable prognosis [9,10].

Based on the discrepancy in interpretation throughout literature we elaborated a study to assess the role of regression and other clinical and histologic features for the prognosis and the progression of cutaneous melanoma.

Material and Methods

This was a retrospective, analytical, observational, longitudinal cohort study. The study population consisted of adult patients with a pathological diagnosis of cutaneous melanoma who also had a SLN biopsy. They were treated and followed at our Department of Dermatology between 2005 and 2016.

Exclusion criteria were: mucosal melanomas, absence of primary tumor, patients who refused a SLN biopsy, and patients who refused follow-up.

The study was approved by the Institutional Ethics Committee of Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca. The patients signed informed consent forms, before they were included in the study.

From 403 consecutive patients with melanomas admitted to our institution, SLN biopsy was performed in 173 patients with a tumor thickness between 1 and 4 mm or <1 mm but with ulceration or mitotic rate >1/mm^2.

The clinical diagnosis of primary melanoma was confirmed by histopathological examination after an excisional biopsy, which included the entire thickness of the tumor and a narrow margin. A second intervention was performed and consisted of wide local excision, with a margin up to 1 cm or 2 cm according to the Breslow depth. The SLN biopsy was done in the same surgical session.

The clinical features recorded for each patient were: age, gender, and anatomical site of the tumor. The pathological examination of the melanoma was done by one experienced pathologist on slides stained with hematoxylin and eosin (H&E) and S100 and HMB45 immunohistochemistry. Primary tumor characteristics were recorded: histological type (superficial spreading, nodular, others: acral lentiginous melanoma, lentigo maligna melanoma), Breslow thickness, Clark level, mitotic rate (<1/mm^2 or ≥1/mm^2), TIL (absent, mild, moderate, marked), and the presence of ulceration, regression and lymphovascular invasion. SLN status was assessed on H&E slides after SLN biopsy and defined as positive or negative.

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Table 1. Clinical and pathological features associated with regression.

Variables		Absence of regression		Presence of regression		p
Age (years) – median		49.5	(39; 62)	50	(40.5; 58)	0.8
Gender	Female	66	(48.5%)	22	(59.5%)	0.3
	Male	70	(51.5%)	15	(40.5%)	
Histologic type	Superficial spreading	78	(57.4%)	24	(64.9%)	0.2
	Nodular	49	(36%)	13	(35.1%)	
	Other	9	(6.6%)	–		
Mitotic rate		129	(94.9%)	34	(91.9%)	0.7
Ulceration		69	(50.7%)	16	(43.2%)	0.5
Lymphovascular invasion		5	(3.7%)	1	(2.7%)	1
TIL	Absent	14	(10.3%)	4	(10.8%)	0.01
	Mild	43	(31.6%)	6	(16.2%)	
	Moderate	55	(40.4%)	18	(48.6%)	
	Marked	24	(17.6%)	9	(24.3%)	
Positive SLN		32	(25.8%)	5	(10.2%)	0.04
Breslow thickness (mm)		2.2	(1.8; 3)	2.3	(1.2; 3)	0.4
Breslow thickness >2 mm		79	(58.1%)	20	(54.1%)	0.8
Metastasis		33	(24.3%)	7	(18.9%)	0.6

The presence of regression was defined based on the following pathological criteria: reduction/disappearance of malignant cells within the tumor and the presence of fibrosis, melanophages, inflammatory infiltrate, neovascularization, narrowing of the epidermis [9].

Disease free survival (DFS) was defined as the period of time between excision of melanoma and first recurrence and/or disease progression (regional or distant metastases) or last follow-up. Local recurrence was defined as a recurrence up to 2 cm from the primary excision and in transit metastases as the recurrence between the scar (beyond 2 cm) and the regional lymph nodes. The diagnosis of recurrence and/or metastases was established clinically and by magnetic resonance imaging (MRI) or computed tomography (CT) and was confirmed histologically when possible. Overall Survival (OS) was determined from the excision of primary tumor to the date of death (regardless of the cause) or last follow-up.

Statistical analysis was performed using the MedCalc Statistical Software version 17.4 (MedCalc Software bvba, Ostend, Belgium; *http://www.medcalc.org*; 2017). Continuous variables were tested for the normality of distribution with Kolmogorov-Smirnov test and were expressed as median and 25–75 percentiles. Nominal variables were characterized by frequency and percent. Comparison between two groups was performed with Mann-Whitney test for quantitative variables and with chi-square test for qualitative data. Survival analysis was performed using Kaplan-Meier curve. Multivariate analysis of survival was done with Cox regression. The cutoff value for the Breslow score was chosen using the AUROC. A p value of <0.05 was considered to be statistically significant

Results

The clinical and pathological features of the 173 patients [age 50 (40; 60) years; 88 women (50.9%) and 85 men (49.1%)] were analyzed. Median follow-up time was 4.3 years. Histological regression was found in 37 melanomas (21.3%).

The association of several variables with the presence of regression can be seen in Table 1. Marked and moderate TIL were significantly associated with regression (p=0.01). Positive SLN was more frequently observed in patients without regression (p=0.04).

Progression of the disease occurred in 42 patients (24.2%): three cases with local recurrence, seven with in-transit metastases,

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Table 2. Univariate analysis of variables associated with DFS and OS.

Variables		DFS	OS
Age (years) – median		0.2	0.8
Male gender		0.7	0.1
Histologic type	Superficial spreading	0.02	0.06
	Nodular		
	Other		
Mitotic rate		0.06	0.09
Ulceration		0.01	0.05
Regression		0.2	0.04
Lymphovascular invasion		0.6	0.4
TIL	Absent	0.008	0.03
	Mild		
	Moderate		
	Marked		
Positive SLN		<0.001	<0.001
Breslow thickness (mm)		<0.001	0.02
Breslow Thickness >2 mm		<0.001	<0.001

six with regional lymph node involvement (four with previously negative SLN), and 42 with distant metastases. The presence of metastases was associated with nodular type of melanoma, the presence of ulceration, positive SLN, and a Breslow score higher than 2 mm. Regression was not statistically correlated with the occurrence of metastases (p=0.6), or when stratified for SLN status (p>0.05).

The survival was influenced by the histological type, ulceration, TIL, positive SLN and a Breslow score higher than 2 mm (AUC 0.685; 95% CI 0.610–0.754; p<0.001; Se 85.29%; 95% CI 68.9–95.0; Sp 49.64%; 95% CI 41.1–58.2). The presence of regression was more frequent in the group of patients who were still alive at the end of the follow-up period (33 out of 139 (23.7%) versus 4 out of 34 (11.8%), but this finding was not statistically significant (p=0.1). When calculated according to SLN status, survival was not influenced by the presence of regression in patients with negative or positive SLN (p>0.05).

Regarding the correlation of regression with DFS and OS, we obtained the following result: regression was associated with survival, but not with the recurrence of the disease, in univariate analysis (Table 2).

For the evaluation of the independent factors that predicted recurrence in our study, with the Cox regression (Table 3), the most stable prediction model included the following variables: histological type, TIL, positive SLN, a Breslow score higher than 2 mm. Only the positive SLN and a Breslow score higher than 2 mm were independent variables associated with the recurrence.

For evaluation of the independent factors that predicted the mortality in our study, we introduced the variables that achieved a level of significance below 0.1 (Table 4). The most stable prediction model included the following variables: gender, regression, histological type, TIL, positive SLN, and a Breslow score higher than 2 mm. Only the mild TIL (HR, 3.92; p=0.04), positive SLN (HR, 3.3; p=0.003) and a Breslow score higher than 2 mm (HR, 3; p=0.0 retained the independent status for mortality prediction. The regression was not associated with OS (p=0.2).

Discussion

The purpose of the present study was to determine the role of histological regression and other features for the prognosis and the progression of cutaneous melanoma.

In our study, histological regression accounted for 21.3% of patients, and was similar to the results reported by other authors [12–14]. The absence of regression was correlated with positive SLN on univariate analysis. Our results are comparable to those obtained by Han et al. [13]. They analyzed 1,250 patients who underwent SLN biopsy and reviewed the

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Table 3. Multivariate analysis of variables associated with DFS.

Variables		B	P	HR	95% CI for HR	
					Min	Max
Histologic type	Other		0.5			
	Superficial spreading	–0.58	0.3	0.55	0.17	1.75
	Nodular	–0.59	0.2	0.55	0.18	1.67
TIL	Absent		0.3			
	Mild	0.23	0.6	1.26	0.46	3.40
	Moderate	–0.12	0.8	0.88	0.32	2.40
	Marked	–1.03	0.2	0.35	0.06	1.83
Positive SLN		1.35	<0.001	3.88	1.98	7.59
Breslow thickness >2 mm		1.50	0.003	4.50	1.68	12.02

Table 4. Multivariate analysis of variables associated with OS.

Variables		B	P	HR	95.0% CI for HR	
					Min	Max
Male gender		0.33	0.3	1.40	0.67	2.92
Histologic type	Other		0.4			
	Superficial spreading	–0.29	0.6	0.74	0.19	2.82
	Nodular	0.21	0.7	1.23	0.33	4.52
Regression		–0.61	0.2	0.54	0.17	1.68
TIL	Absent		0.1			
	Mild	1.36	0.04	3.92	1.04	14.67
	Moderate	0.69	0.3	2.00	0.52	7.65
	Marked	0.56	0.4	1.75	0.37	8.31
Positive SLN		1.20	0.003	3.33	1.51	7.35
Breslow thickness >2 mm		1.11	0.02	3.06	1.12	8.34

clinicopathologic characteristics associated with SLN metastasis. In their cohort, on univariate analysis, absence of regression was significantly associated with positive SLN, but on multivariate analysis, absence of regression did not retain its independent status (p=0.2) [13]. Liszkay et al. evaluated the relationship between the regression of primary melanomas and the status of SLN in 269 patients and showed that a lower number of patients with regressed melanoma had nodal metastasis compared with the ones without regression (8% versus 19.1%, p=0.026), but this result was not maintained on multivariate analysis [12]. A meta-analysis about the association of histologic regression and sentinel lymph node status was performed and showed that the risk of positive SLN was significantly lower in patients with histologic regression [15].

We found that regression was associated with the moderate and marked TIL. The same result was found by Tas et al. [16]. They investigated the significance of histological regression in 664 patients with melanoma and identified that it was correlated with male gender, axial localization of the tumor, superficial spreading histologic type, thin tumor thickness (<2 mm), and presence of TIL. Regression was not significant correlated with SLN status in their study [16].

The prognostic role of regression has been studied for many years and the results are controversial. The first studies showed that regression was an indicator of poor prognosis [5,17,18], as it was more frequently found in patients who developed metastasis. This was discovered especially in thinner tumors. It

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was considered that it may destroy the vertical growth phase and determine an underestimation of the initial tumor thickness, in a tumor that could have already metastasized [18]. Shaw et al. suggested that the presence of regression might be the answer of the immune system, which was stimulated by the metastatic melanoma found in the regional lymph nodes [19]. Based on these theories, the presence of regression in thin melanomas was used in the decision of performing SLN biopsy. More recent studies showed that regression could be a protective factor, being associated with a negative SLN and a better outcome [9,20–22]. Ribero et al. conducted a study on 1,693 melanoma patients with stage I-II and showed that regression was associated with a significant lower risk of disease progression (9.5% regressed melanomas developed metastatic disease versus 23.4% non-regressed melanomas, $p<0.001$) and with a better DFS and OS [22].

These conflicting results demonstrate that the pathogenic role of regression is not well understood. Melanoma regression could be a host immunological response directed against the tumor and its presence may contribute to a favorable prognosis, reflecting the strength of the immunological system [22]. Weide et al. showed that patients with melanoma with an unknown primary site and positive lymph nodes have a better outcome than those with known primary tumors with lymph node involvement [23]. This could be explained by the favorable role of regression: the unknown primary results from an initially unidentified tumor which regresses over time through immunological elimination [23]. Rubinstein et al. suggested that the association of regression with a lower chance of positive SLN could be explained by the same immunological response both in the primary tumor and in the lymph nodes. They affirmed that when regression is present, the detection of lymph node metastasis is problematic, because the immunological response that causes regression in the primary tumor can also induce regression of the metastatic cells from the lymph nodes [24].

In our study the presence of recurrent or metastatic disease was associated with the nodular histologic subtype, Breslow thickness >2 mm, presence of ulceration, mild TIL, and a positive SLN. Also, the patients with these features had a worse OS. Multivariate analysis revealed that regression was not an independent prognostic factor for the outcome of patients with melanoma; just Breslow index >2 mm, positive SLN, and mild TIL were statistically linked to the survival of melanoma patients. These findings are similar to those reported in the literature [25]. Azimi et al. conducted a study on 1,865 melanoma patients and studied the role of TIL grade on the SLN status and survival. They recorded a worse survival for the cases with no or mild TIL [25].

The most important limitations of our study were the small number of melanoma patients and the relatively uneven follow-up period. The small sample size of patients could explain our results, which do not support the role of regression as a protective factor and were not consistent with previous studies. Another explanation for the difference in data reported in the literature regarding the role of regression could be the absence of a standardized definition for this histologic feature. Also, other reported studies included patients with melanoma with dissimilarities of tumor thickness. Further studies are required for an improved understanding of this phenomenon.

Conclusions

In conclusion, we could not demonstrate an association between regression and the outcome of patients with cutaneous melanoma. Tumor thickness greater then 2 mm and a positive SLN were associated with recurrence. Survival was influenced by a Breslow thickness >2 mm, the presence of a mild TIL, and a positive SLN status.

Conflict of interest

None.

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