JAMA Dermatology | Original Investigation

Association of Histologic Regression With a Favorable Outcome in Patients With Stage 1 and Stage 2 Cutaneous Melanoma

Mary-Ann El Sharouni, MD; Karina Aivazian, MBBS; Arjen J. Witkamp, MD; Vigfús Sigurdsson, MD; Carla H. van Gils, PhD; Richard A. Scolyer, MD; John F. Thompson, MD; Paul J. van Diest, MD; Serigne N. Lo, PhD

IMPORTANCE Although regression is commonly observed in cutaneous melanoma, it is uncertain whether it is associated with patient prognosis.

OBJECTIVE To determine whether histologically confirmed regression was associated with better or worse survival in patients with primary cutaneous melanoma.

DESIGN, SETTING, AND PARTICIPANTS This cohort study analyzed data from 2 large cohorts of adults (one in the Netherlands and the other in Australia) with histologically proven, stage 1 and 2 primary, invasive cutaneous melanoma with known regression status treated between 2000 and 2014, with median follow-up times of 4.5 and 11.1 years for the Dutch and Australian cohorts, respectively. For the Dutch patients, population-based data from PALGA, the Dutch Pathology Registry, were used, and follow-up data were retrieved from the Netherlands Cancer Registry. For the Australian patients, data from the database of a large, specialized melanoma treatment center were used.

MAIN OUTCOMES AND MEASURES Multivariable Cox proportional hazards analyses were performed per cohort to assess recurrence-free survival (RFS) and overall survival (OS), and subgroup analyses according to Breslow thickness category and melanoma subtype were performed.

RESULTS A total of 17 271 Dutch patients and 4980 Australian patients were included. In both cohorts, survival outcomes were better for patients with disease regression. For Dutch patients, the hazard ratio (HR) for those with disease regression was 0.55 (95% CI, 0.48-0.63; $P < .001$) for RFS and 0.87 (95% CI, 0.79-0.96; $P = .004$) for OS; for the Australian patients, the HR was 0.61 (95% CI, 0.52-0.72; $P < .001$) for RFS and 0.73 (95% CI, 0.64-0.84; $P < .001$) for OS. Subgroup analyses showed that the presence of regression improved RFS within thin and intermediate Breslow thickness melanomas in both cohorts. For patients with superficial spreading melanoma (SSM) subtype, regression improved RFS and OS in both cohorts. For Dutch patients with SSM, the HR for those with disease regression was 0.54 (95% CI, 0.46-0.63; $P < .001$) for RFS and 0.86 (95% CI, 0.76-0.96; $P = .009$) for OS; for the Australian patients with SSM, the HR was 0.67 (95% CI, 0.52-0.85; $P = .001$) for RFS and 0.72 (95% CI, 0.59-0.88; $P = .001$) for OS.

CONCLUSIONS AND RELEVANCE In 2 large patient cohorts from 2 different continents, regression was a favorable prognostic factor for patients with stage 1 and 2 melanomas, especially in those with thin and intermediate thickness tumors and those with SSM subtype.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: John F. Thompson, MD, Melanoma Institute Australia, 40 Rocklands Rd, North Sydney, NSW 2060, Australia (john.thompson@melanoma.org.au).

JAMA Dermatol. doi:10.1001/jamadermatol.2020.5032
Published online December 23, 2020.

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The phenomenon of regression in a melanoma is commonly observed. It refers to disappearance or loss of part or all of a melanoma that is thought to occur as a consequence of a host immunological response directed against the tumor cells. It can be identified both clinically (macroscopically) and histologically (microscopically). Sometimes apparent to the naked eye (**Figure 1**A), macroscopic regression can best be appreciated using a dermatoscope to examine a pigmented lesion, revealing the presence of bluish-gray or white scarlike depigmentation (of lighter color than the surrounding skin, and corresponding histopathologically to fibrosis, Figure 1B), or as "peppering" (very fine gray dots seen with a dermatoscope and histologically corresponding to the presence of pigment-laden macrophages).[1] The presence of regression is observed not only in melanoma, but also in benign nevi,[1] and it has been suggested that the decline in the number of nevi after the fifth decade of life may be partially caused by progressive regression of these nevi.[2] Despite the lack of standardized criteria for reporting histopathological regression in melanomas, it is generally characterized by a variable decrease in the number of dermal invasive melanoma cells in a tumor, accompanied by the presence of a host response consisting of dermal fibrosis, an inflammatory infiltrate, melanophages, increased vascularity, and epidermal attenuation (Figure 1C).[3] The presence of some histopathologic regression is estimated to occur in between 10% and 58%[4,5] of cutaneous melanomas. Although it is common, divergent conclusions have been drawn about the prognostic significance of regression in cutaneous melanoma. Some have suggested that its presence is associated with a worse prognosis, because it can reduce the measured Breslow thickness of the primary tumor (when the deepest melanoma cells are no longer present). Others have argued that the presence of regression implies better survival, because effective activation of the host immune system against the tumor is presumed to be the basis of regression.[6,7] When attempts have been made to determine which supposition is correct, several studies found regression to be a favorable prognostic factor,[8,9] whereas multiple others found that regression was not significantly associated with either recurrence-free survival (RFS) or overall survival (OS),[4,10-13] and 2 found that histologic regression was associated with worse OS.[14,15] These divergent results are possibly related to small study group numbers and relatively short follow-up. Hence the aim of the present study was to clarify whether histologic regression was associated with better or worse survival in patients with primary cutaneous melanomas by analyzing data from a nationwide European cohort, as well as data from the well-maintained database of a large, specialized melanoma treatment center in Australia.

Key Points

Question Is regression associated with survival outcomes in patients with stage 1 or 2 melanoma?

Findings In this cohort study of 17 271 Dutch and 4980 Australian patients with stage 1 or 2 melanoma, patients with regression had significantly improved overall survival. Subgroup analyses showed that regression was significantly associated with improved recurence-free survival for patients with thin and intermediate Breslow thickness melanomas (≤4.0 mm), and for those with superficial spreading melanoma (SSM) subtype.

Meaning Regression was a favorable prognostic factor for patients with stage 1 or 2 melanomas, especially in those with tumors that were 4.0 mm thick, and those with SSM subtype.

Methods

Collection of Data

For the Dutch nationwide cohort, encoded and anonymous data for all patients with newly diagnosed stage 1 and 2 melanomas treated between January 2000 and December 2014 were obtained from PALGA, the Dutch Pathology Registry. PALGA has been collecting data prospectively from all pathology laboratories in the Netherlands since 1991.[16] Follow-up data were obtained from the Netherlands Cancer Registry, which gathers information on every cancer patient treated in the Netherlands. Follow-up was calculated from date of diagnosis until date of death, the date last known to be alive, or January 1, 2018, whichever occurred earlier. Ethical approval was granted by the board of PALGA, and all data were deidentified.

For the Australian institutional cohort, a search was performed of the prospectively maintained database at Melanoma Institute Australia (MIA) for all patients with stage 1 and 2 melanomas treated over the same time period. All patients had given permission for their deidentified data to be used for research purposes. Approval for use of the data was obtained from the Sydney Local Health District Ethics Committee.

Study Population

Patients with noncutaneous melanomas were excluded, as well as those with more than 1 primary melanoma. For each patient, demographics collected included date of diagnosis, age, sex, location of the melanoma, and recurrence details. Pathologic data included Breslow thickness (mm), melanoma subtype, sentinel node (SN) biopsy (performed or not performed), ulceration (present or absent), and regression (present or absent). Breslow thickness was measured to the deepest invasive tumor cell (not the base of any regression). Mitotic rate (per mm^2) was able to be included for the MIA cohort only because it was not available in the Dutch cohort. The pathology of the cases was reported by a large number of pathologists in the Netherlands (n = 750) and by MIA-affiliated pathologists (n = 17). As such, definitions of regression used by the pathologists reflected those provided in contemporary literature and textbooks.[17-22] Regression was defined as loss of part or all of a melanoma as a consequence of an immunologic response directed against the tumor and was coded as present or absent. It was broadly recognized by the presence of dermal fibrosis that was unrelated to prior trauma and usually accompanied by increased vascularity, pigment-laden macrophages, and some lymphocytes with or without epidermal thinning and loss of rete ridges (Figure 1C). In cases with residual in situ or invasive melanoma overlying the area of fibrosis, regression was

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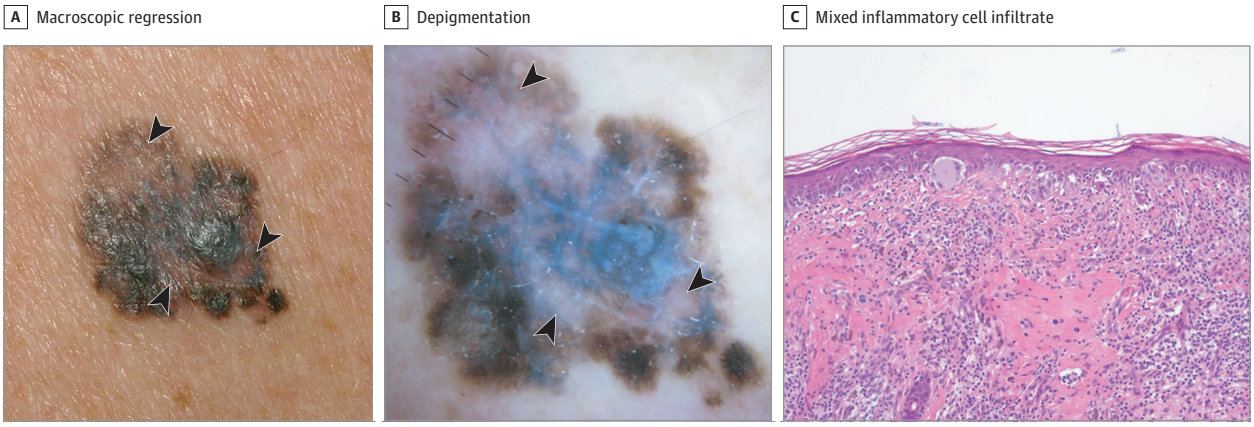
Figure 1. Clinical and Histopathologic Images



A, Macroscopic regression (black arrowheads). B, Dermatoscopic scarlike depigmentation (black arrowheads). C, Histopathologic regression characterized by immature scarlike fibrosis and a mixed inflammatory cell infiltrate including numerous lymphocytes and pigment-laden macrophages. All panels represent the same lesion.

regarded as present as long as the above criteria were fulfilled. Tumor-infiltrating lymphocytes were not considered sufficient for regression in the absence of identifiable dermal fibrosis. For both data sets, primary and secondary outcome measures were RFS and OS. Recurrence was defined as either cutaneous (local or in transit), nodal (regional), or distant metastasis. In patients with synchronous first recurrences at multiple sites, the site with the worst prognosis was recorded as first site. Patient RFS and OS were calculated from the date of diagnosis to the date of recurrence or death from any cause, respectively. Patients without recurrence were censored at either their date of death or the last date known alive or January 1, 2018 (the data collection cutoff date), whichever occurred earlier. Patients were categorized as stage 1 or stage 2 according to the *American Joint Committee on Cancer (AJCC) Staging Manual,* 8th edition.[23] When no SN biopsy was performed, it was assumed that patients had stage 1 or 2 disease.

Statistical Analysis

Data for the Dutch and MIA patients were analyzed separately. Categorical variables were summarized as numbers and percentages. Continuous variables were summarized as medians with interquartile ranges (IQR). Differences in proportions and medians were analyzed using χ^2 or Mann-Whitney U tests, respectively. Kaplan-Meier curves were generated for OS and RFS. Statistical analysis was performed using multivariable Cox proportional hazard models for both cohorts. The variables analyzed included Breslow thickness, sex, age, ulceration, regression, and SN biopsy.[9] Only patients with all these predefined variables available were selected. Age and Breslow thickness were included as continuous variables. The proportional hazards assumption was evaluated using the Schoenfeld residuals test. An additional multivariable Cox analysis was performed including mitotic rate (/mm^2) for patients in the MIA cohort. In addition, subgroup analyses were performed considering 2 stratification factors: melanoma subtype (superficial spreading and nodular, other subtypes were not analyzed owing to the small number of events observed), and Breslow thickness category (thin [≤1.0 mm], intermediate [1.1-4.0 mm], and thick [>4.0 mm]). This study adhered to the guideline for the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines, and the checklist was completed as well as a flowchart of patient selection (eTable 1 and eFigure in the Supplement, respectively).[24]

All statistical analyses were performed using R (version 3.6.1, R Core Team). A 2-sided $P<.05$ was considered statistically significant.

Results

Clinicopathological features of the patients in the Dutch and MIA cohorts with and without histologic regression are presented in **Table 1**. Of the entire cohort of 17 271 Dutch patients, 6121 (35.4%) showed regression of the primary melanoma. Of the total 4980 patients in the MIA cohort, 2198 (44.1%) showed regression. In both cohorts, similar associations were observed: presence of regression was significantly associated with male sex, lower Breslow thickness, absence of ulceration, superficial spreading melanoma subtype, and location on the trunk. There was no significant association between age and presence of regression in either of the cohorts. The median (IQR) follow-up time was 4.5 (3.1-6.5) years for the Dutch cohort and 11.1 (4.0-17.9) years for the MIA cohort.

Survival Analyses

Figure 2 shows the Kaplan-Meier OS and RFS curves for the Dutch and MIA cohorts. For both survival outcome measures and in both cohorts, patients with regression had better survival. All 17 271 Dutch patients and 4980 Australian patients were included in the Cox regression model. Multivariable analy-

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Table 1. Clinicopathological Factors of All Dutch and MIA Patients With Stage 1 and 2 Primary Cutaneous Melanoma Stratified for Regression

Characteristics	Dutch cohort			MIA cohort		
	Regression absent (n = 11150)	Regression present (n = 6121)	*P* value	Regression absent (n = 2782)	Regression present (n = 2198)	*P* value
Sex, No. (%)			<.001			<.001
Female	6444 (57.8)	2872 (46.9)		1280 (46.0)	791 (36.0)	
Male	4706 (42.2)	3249 (53.1)		1502 (54.0)	1407 (64.0)	
Age at diagnosis, median (IQR), y	58.0 (46.0-69.0)	58.0 (47.0-68.0)	.58	59.0 (45.0-71.0)	59.0 (48.0-70.0)	.24
Breslow thickness, median (IQR), mm	0.9 (0.5-1.7)	0.6 (0.5-1.0)	<.001	1.5 (0.8-3.0)	0.8 (0.5-1.4)	<.001
Breslow thickness, No. (%)			<.001			<.001
≤1.0 mm	6467 (58.0)	4857 (79.3)		991 (35.6)	1395 (63.5)	
1.1-2.0 mm	2509 (22.5)	863 (14.1)		701 (25.2)	465 (21.2)	
2.1-4.0 mm	1433 (12.9)	289 (4.7)		651 (23.4)	227 (10.3)	
>4.0 mm	741 (6.6)	112 (1.8)		439 (15.8)	111 (5.1)	
Ulceration, No. (%)			<.001			<.001
No	9696 (87.0)	5748 (93.9)		2171 (78.0)	1972 (89.7)	
Yes	1454 (13.0)	373 (6.1)		661 (22.0)	116 (10.3)	
Mitotic rate/mm^2, median (IQR)	NA	NA	NA	3.0 (1.0-6.0)	1.0 (0.0-3.0)	<.001
Primary site, No. (%)			<.001			<.001
Head and neck	1484 (13.3)	371 (6.1)		586 (21.1)	189 (8.6)	
Trunk	4582 (41.1)	3711 (60.6)		827 (29.7)	1189 (54.1)	
Upper limb	1835 (16.5)	811 (13.2)		550 (19.8)	372 (16.9)	
Lower limb	3249 (29.1)	1228 (20.1)		819 (29.4)	448 (20.4)	
Melanoma subtype, No. (%)			<.001			<.001
Superficial spreading	8518 (76.4)	5434 (88.8)		1191 (42.8)	1570 (71.4)	
Nodular	1394 (12.5)	249 (4.1)		754 (27.1)	216 (9.8)	
Lentigo maligna	497 (4.5)	160 (2.6)		106 (3.8)	90 (4.1)	
Acral lentiginous	74 (0.7)	21 (0.3)		62 (2.2)	16 (0.7)	
Other	667 (6.0)	257 (4.2)		669 (24.0)	306 (13.9)	
SN biopsy, No. (%)			<.001			<.001
No	8839 (79.3)	5501 (89.9)		1830 (65.8)	1637 (74.5)	
Yes	2311 (20.7)	620 (10.1)		952 (34.2)	561 (25.5)	
Follow-up, median (IQR), y	4.2 (2.9-5.9)	5.1 (3.4-7.6)	<.001	11.6 (4.2-19.2)	10.7 (3.8-16.7)	<.001

Abbreviations: IQR, interquartile range; MIA, Melanoma Institute Australia; NA, not applicable; SN, sentinel node.

ses showed a hazard ratio (HR) of 0.55 (95% CI, 0.48-0.63; *P* < .001) for RFS and 0.87 (95% CI, 0.79-0.96; *P* = .004) for OS associated with regression in the Dutch cohort (**Table 2**). Similarly, an HR of 0.61 (95% CI, 0.52-0.72; *P* < .001) for RFS and 0.73 (95% CI, 0.64-0.84; *P* < .001) for OS associated with regression in the MIA cohort was observed. When mitotic rate was included in the model, the HR associated with regression was 0.74 (95% CI, 0.63-0.86; *P* = .002) for RFS and 0.80 (95% CI, 0.70-0.92; *P* = .002) for OS in the MIA cohort (eTable 2 in the Supplement).

Subgroup Analysis by Breslow Thickness

eTable 3 in the Supplement shows the number of included patients for each Breslow thickness category and according to melanoma subtype, together with the number of events (recurrence for RFS and death for OS) for the Dutch and MIA cohorts. When stratifying the Cox analysis according to Breslow thickness, patients with thin and intermediate-thickness melanomas in both cohorts had better RFS if regression was present (eTable 4 in the Supplement). For patients with thin melanomas, the presence of regression was associated with better OS for the MIA cohort only (HR, 0.66; 95% CI, 0.50-0.88; *P* = .004). In contrast, there was no statistically significant association between regression and RFS or OS in patients with thick melanomas in either cohort; in the Dutch cohort the HRs were 0.74 (95% CI, 0.53-1.02; *P* = .06) and 1.07 (95% CI, 0.83-1.38; *P* = .62) for RFS and OS, respectively. In the MIA cohort the HRs were 0.91 (95% CI, 0.65-1.29; *P* = .60) and 0.78 (95% CI, 0.57-1.08; *P* = .14), respectively.

Subgroup Analysis by Melanoma Subtype

Analysis was conducted only for patients with superficial spreading melanoma (SSM) and nodular melanoma (NM), given the small number of events in the other melanoma subtype categories (eTable 3 in the Supplement). eTable 5 in the Supplement shows the multivariable Cox analyses for RFS and OS stratified by SSM and NM subtypes, for the Dutch and MIA cohorts. In the Dutch cohort, regression remained a significant predictor of RFS (HR, 0.54; 95% CI, 0.47-0.63; *P* < .001) and OS (HR, 0.86; 95% CI, 0.76-0.96; *P* = .009) for SSM only.

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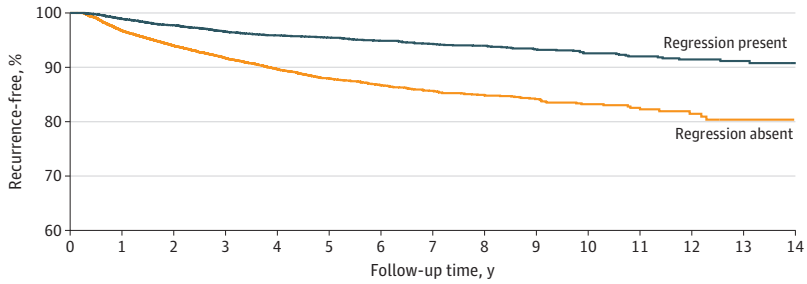
Figure 2. Kaplan-Meier Curves for Regression-Free and Overall Survival by Regression Status for Dutch and Melanoma Institute Australia Patients With Stage 1 and 2 Melanoma

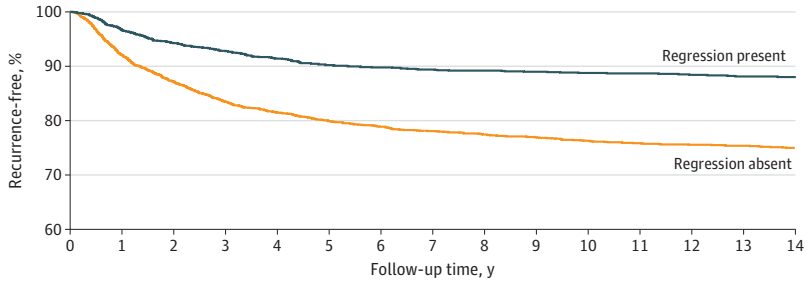
A Recurrence-free survival in Dutch cohort



No. at risk

Regression present	6121	5890	5700	4915	3906	3103	2370	1793	1390	1082	809	585	401	254	154
Regression absent	11150	10377	9809	7797	5690	3948	2567	1691	1177	824	519	306	172	104	77

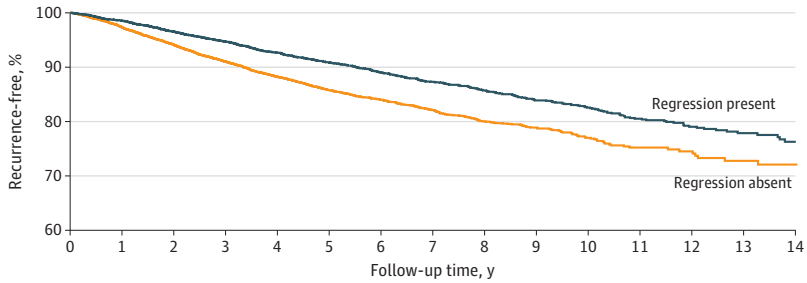
B Recurrence-free survival in Melanoma Institute Australia cohort



No. at risk

Regression present	2198	1886	1772	1664	1559	1487	1420	1376	1316	1234	1148	1036	949	872	795
Regression absent	2782	2385	2186	2013	1910	1790	1693	1616	1562	1483	1396	1320	1247	1189	1123

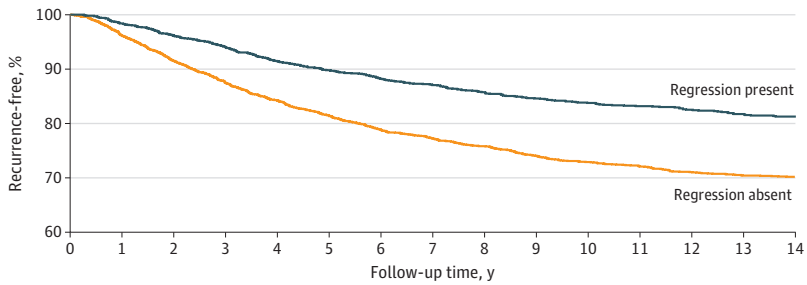
C Overall survival in Dutch cohort



No. at risk

Regression present	6121	5950	5794	5013	3979	3163	2423	1834	1415	1103	827	601	415	263	161
Regression absent	11150	10665	10236	8209	6026	4182	2717	1798	1246	880	565	333	188	116	86

D Overall survival in Melanoma Institute Australia cohort



No. at risk

Regression present	2198	1931	1840	1734	1633	1553	1475	1430	1357	1270	1184	1068	976	897	815
Regression absent	2782	2548	2390	2231	2111	1988	1866	1782	1715	1614	1528	1443	1358	1286	1223

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Table 2. Multivariable Cox Regression for Regression-Free and Overall Survival for All Dutch and MIA Patients With Stage 1 and 2 Melanoma Not Adjusted for Mitotic Index

		Recurrence-free survival				Overall survival			
		Dutch (1522 events)		MIA (836 events)		Dutch (2231 events)		MIA (1078 events)	
Variable	Class	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Regression	Present vs absent	0.55 (0.48-0.63)	<.001	0.61 (0.52-0.72)	<.001	0.87 (0.79-0.96)	.004	0.73 (0.64-0.84)	<.001
Ulceration	Yes vs no	2.30 (2.03-2.61)	<.001	2.00 (1.70-2.34)	<.001	1.82 (1.64-2.02)	<.001	1.84 (1.61-2.12)	<.001
SN biopsy	Yes vs no	1.09 (0.97-1.22)	.15	1.00 (0.87-1.16)	.97	0.72 (0.63-0.82)	<.001	0.83 (0.73-0.95)	.006
Breslow thickness	Per mm	1.41 (1.38-1.44)	<.001	1.25 (1.22-1.29)	<.001	1.28 (1.26-1.31)	<.001	1.21 (1.18-1.24)	<.001
Sex	Male vs female	1.41 (1.27-1.56)	<.001	1.26 (1.09-1.45)	.002	1.49 (1.37-1.62)	<.001	1.46 (1.28-1.66)	<.001
Age	Per year	1.01 (1.00-1.01)	<.001	1.01 (1.01-1.01)	<.001	1.06 (1.06-1.07)	<.001	1.04 (1.04-1.05)	<.001

Abbreviations: HR, hazard ratio; MIA, Melanoma Institute Australia; SN, sentinel node.

In the MIA cohort, the presence of regression was a significant predictor of better RFS and OS for both these melanoma subtypes: for SSM, the HR was 0.67 (95% CI, 0.52-0.85; *P* = .001) for RFS and 0.72 (95% CI, 0.59-0.88; *P* = .001) for OS. For NM, the HR was 0.71 (95% CI, 0.53-0.95; *P* = .02) for RFS and 0.73 (95% CI, 0.55-0.97; *P* = .03) for OS. There was no statistically significant difference in the percentage of melanomas that were of nodular subtype in each Breslow thickness category in the 2 cohorts (*P* = .30, eTable 6 in the Supplement).

Discussion

This study, to our knowledge the largest examination of regression in melanoma patients performed to date, showed in cohorts from 2 continents that the presence of regression was a favorable prognostic factor for patients with stage 1 and 2 melanomas, especially those with thin and intermediate-thickness tumors (Breslow thickness ≤4.0 mm) and those with SSM subtype.

Two previous studies have also found regression to be a favorable prognostic factor,[8,9] but others have reported that regression was not significantly associated with either RFS or OS[4,10-13] (eTable 7 in the Supplement), and 2 found that histologic regression was associated with worse OS.[14,15] A systematic review and meta-analysis published by Gualano et al[25] in 2018 included 10 studies comprising 8557 patients, and indicated that histological regression is associated with improved survival. However, the studies that were included were very heterogeneous in melanoma subtype, used differing definitions of regression, and most had limited samples sizes, so that HRs for RFS ranged from 0.62 (95% CI, 0.43-0.90) in 1 study,[9] to 1.62 (95% CI, 0.58-4.54) in another study[12] that included only acral lentiginous melanomas. Three additional studies have been published since that review, with differing conclusions: Maurichi et al[14] developed a nomogram to predict 12-year OS in 2243 patients with thin (≤1.0 mm) melanomas and reported that regression was an independent predictor for worse survival (in addition to age, mitotic rate, ulceration, lymphovascular invasion, and SN status). Zugna et al[8] reported better survival associated with regression when analyzing 264 patients with stage 3 SN-positive disease, and Ribero et al[10] assessed 954 patients with melanomas smaller than 1 mm in thickness and determined its predictive value for SN status, RFS and melanoma-specific survival. In the latter study,[10] regression was not found to be an independent prognostic factor for survival, but was associated with a lower incidence of SN-positivity. The lack of agreement in the literature may be partially explained by an absence of standardized criteria for defining disease regression. In the earliest study examining its prognostic utility, Clark et al[15] required a complete absence of tumor overlying or deep to the area of regression. In contrast, other studies only required an area of dermal regressive fibrosis to be present.[9,10] This less restrictive definition may have resulted in significantly more tumors being classified as having regression, potentially altering the calculated associations with outcomes. In our experience, histologically unambiguous regression is often associated with residual in situ or invasive melanoma. It is possible that this difference in definition is, at least in part, the reason for discordant findings between our study and that of Clark et al.[15]

Only 2 previous studies have focused exclusively on patients with stage 1 and 2 disease; 1 showed no survival benefit when regression was present,[11] whereas the other did show a benefit.[9] Nagore et al[11] studied the histology of 823 stage 1 and 2 patients, with 10.3% showing regression. On univariable analysis for RFS and OS they found no significant benefit for regression (assessed by calculating HRs), and therefore did not include it in their final prognostic model that comprised Breslow thickness, primary tumor site, sex, vascular invasion, mitoses, and ulceration. Ribero et al[9] studied 1693 patients with stage 1 and 2 cancer from a single center in Italy; 20.6% showed regression, and they reported an HR of 0.62 (95% CI, 0.43-0.90) for RFS and an HR of 0.43 (95% CI, 0.23-0.80) for OS in the overall group. These results are similar to ours, even though the percentages of patients with regression in the current cohorts were

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substantially higher (6121 Dutch patients [35.4%] showed regression and 2198 MIA patients [44.1%]). In addition, we found that regression was only a statistically significant prognostic indicator in patients with thin or intermediate thickness melanomas. In those with thick melanomas, the presence of regression was less common (112 [13.1%] and 111 [20.2%] in the Dutch and MIA cohorts, respectively). A statistical consequence of this may be that regression lost its relative prognostic significance compared with other prognostic predictors in thick melanomas.

For patients with the SSM subtype, regression was associated with improved RFS and OS in both cohorts. However, for NM, the 2 cohorts showed mixed results. For RFS, the HRs in both cohorts were less than 1, indicating consistent results between the 2 cohorts, even though this was only statistically significant in the MIA cohort. For OS, the HR was 1.11 (95% CI, 0.88-1.40; $P = .37$) in the Dutch cohort, and 0.73 (95% CI, 0.55-0.97; $P = .03$) in the MIA cohort. This likely reflects the known stronger influence of other prognosis factors in patients with nodular melanomas.[26]

Strengths and Limitations

Strengths of our study include the large size of the patient cohorts from 2 continents who were studied, the relatively long follow-up in both cohorts, and the use of nationwide data as well as data from a large, well-maintained institutional database. Another strength is that patients with stage 1 and 2 cancer were stratified according to Breslow thickness category and melanoma subtype. A limitation is that there are no established guidelines for histologic assessment and reporting of regression; it was interpreted subjectively by pathologists on the basis of the presence of a widely accepted pattern of characteristics.[20] Even though a recent study[27] showed a high concordance between pathologists (95.0%) for the reporting of regression, others have reported lower concordance rates (74.2%).[28] It is possible that variation in the reporting of regression could account, at least in part, for the inconsistent results of some previous, smaller studies. However, given the large numbers that were included in the present study, and the fact that the data were derived from 2 independent cohorts, the assessment of histopathologic regression was not limited to the interpretation of a few pathologists, but reflects how regression is interpreted in current clinical practice by a large number of pathologists, increasing the generalizability of our results. Another limitation is that when no SN biopsy was performed, it was assumed that patients had stage 1 or 2 disease. Although this is a plausible assumption because most patients had a Breslow thickness of 1.0 mm or smaller, we cannot exclude the possibility that some patients might have been upstaged to stage 3 if SN biopsy had been performed. Another limitation is that we had no information regarding treatment with immunotherapy. The time frame of enrollment overlapped with the advent of effective immunotherapy for patients with stage 4 disease (from 2012), which might have had a different efficacy in the presence or absence of regression. However, the stronger association with improved RFS than with OS suggests that this was not a dominant factor. A final limitation is that mitotic rate data were not available for the Dutch cohort; however, when mitotic rate was included in the multivariable analysis using MIA data our findings remained unchanged.

Conclusions

Consistent with several previous reports, the results of this study, by far the largest reported to date, indicate that regression can be considered a favorable prognostic factor for patients with stage 1 and stage 2 melanomas. Those with thin and intermediate-thickness tumors (Breslow thickness ≤4.0 mm) and those with SSM subtype are most likely to have an improved prognosis when regression is present.

ARTICLE INFORMATION

Accepted for Publication: November 4, 2020.

Published Online: December 23, 2020. doi:10.1001/jamadermatol.2020.5032

Author Affiliations: Melanoma Institute Australia, The University of Sydney, Sydney, New South Wales, Australia (El Sharouni, Aivazian, Scolyer, Thompson, Lo); Department of Dermatology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (El Sharouni, Sigurdsson); Department of Tissue Oncology and Diagnostic Pathology, Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, New South Wales, Australia (Aivazian, Scolyer, Thompson); Department of Surgery, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (Witkamp); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, University Utrecht, Utrecht, the Netherlands (van Gils); Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia (Scolyer, Lo); Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia (Thompson); Department of Pathology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (van Diest).

Author Contributions: Dr Thompson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: el Sharouni, Scolyer, Thompson, van Diest, Lo.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: el Sharouni, Sigurdsson, Scolyer, Thompson, van Diest, Lo.
Critical revision of the manuscript for important intellectual content: el Sharouni, Aivazian, Witkamp, Sigurdsson, van Gils, Scolyer, Thompson, Lo.
Statistical analysis: el Sharouni, van Gils, Lo.
Obtained funding: Scolyer.
Administrative, technical, or material support: el Sharouni, Scolyer, Thompson, van Diest, Lo.
Supervision: Witkamp, Sigurdsson, van Gils, Scolyer, Thompson, van Diest, Lo.

Conflict of Interest Disclosures: Dr Scolyer has received fees for professional services from Qbiotics, MSD Sharp & Dohme, GlaxoSmithKline, Bristol Myers Squibb, Novartis, Myriad, NeraCare and Amgen. Dr Thompson has received honoraria from Merck Sharpe Dohme Australia and Bristol Myers Squibb Australia, GlaxoSmithKline and Provectus, and travel expenses from GSK and Provectus. No other conflicts are reported.

Funding/Support: Dr El Sharouni was supported by a Research Fellowship Grant from the European Association of Dermatology and Venereology (EADV). Dr Aivazian is supported by the Deborah and John McMurtrie Melanoma Pathology Fellowship through Melanoma Institute Australia. Drs Scolyer and Thompson are recipients of an Australian National Health and Medical Research Council Program Grant. Dr Scolyer is supported by the Australian National Health and Medical Research Council Fellowship program. This research was also supported by research program grants from Cancer Institute New South Wales and the Australian National Health and Medical Research Council. Dr Lo is supported by Melanoma Institute Australia. Support from the Cameron Family and the Ainsworth Foundation is also acknowledged. The authors gratefully acknowledge support from colleagues at their respective institutions.

Role of the Funder/Sponsor: The funding institutions had no role in the design and conduct of the study; collection, management, analysis, and

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interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Rinus Voorham, PhD (PALGA, the Dutch Pathology Registry), and Hazel Burke, BAppSc (MIA), for their assistance with data extraction, and the team at the Netherlands Comprehensive Cancer Organisation (IKNL) for providing survival data from the Netherlands Cancer Registry.

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