Prognostic Significance of Mitotic Rate in Localized Primary Cutaneous Melanoma: An Analysis of Patients in the Multi-Institutional American Joint Committee on Cancer Melanoma Staging Database

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ABSTRACT

Purpose

The aim of this study was to assess the independent prognostic value of primary tumor mitotic rate compared with other clinical and pathologic features of stages I and II melanoma.

Methods

From the American Joint Committee on Cancer (AJCC) melanoma staging database, information was extracted for 13,296 patients with stages I and II disease who had mitotic rate data available.

Results

Survival times declined as mitotic rate increased. Ten-year survival ranged from 93% for patients whose tumors had 0 mitoses/mm² to 48% for those with ≥ 20 /mm² ($P < .001$). Mean number of mitoses/mm² increased as the primary melanomas became thicker (1.0 for melanomas ≤ 1 mm, 3.5 for 1.01 to 2.0 mm, 7.3 for 3.01 to 4.0 mm, and 9.6 for > 8 mm). Ulceration was also associated with a higher mitotic rate; 59% of ulcerated melanomas had ≥ 5 mitoses/mm² compared with 16% of nonulcerated melanomas ($P < .001$). In a multivariate analysis of 10,233 patients, the independent predictive factors for survival in order of statistical significance were as follows: tumor thickness ($\chi^2 = 104.9$; $P < .001$), mitotic rate ($\chi^2 = 67.0$; $P < .001$), patient age ($\chi^2 = 48.2$; $P < .001$), ulceration ($\chi^2 = 46.4$; $P < .001$), anatomic site ($\chi^2 = 34.6$; $P < .001$), and patient sex ($\chi^2 = 33.9$; $P < .001$). Clark level of invasion was not an independent predictor of survival ($\chi^2 = 3.2$; $P = .37$).

Conclusion

A high mitotic rate in a primary melanoma is associated with a lower survival probability. Among the independent predictors of melanoma-specific survival, mitotic rate was the strongest prognostic factor after tumor thickness.

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INTRODUCTION

It has been known for several decades that some histologic features of a primary melanoma, notably tumor thickness and ulceration, are important determinants of prognosis. Tumor thickness and ulceration, therefore, have been used for staging patients with melanoma. More recently, cellular proliferation within the primary tumor, as reflected by its mitotic rate, has emerged as another important predictive factor for survival.¹⁻¹⁶ Indeed, Azzola et al⁴ reported that mitotic rate was a more powerful

prognostic indicator than ulceration in a 3,661-patient, single-institution series. More recently, detailed analysis of primary tumor mitotic rate data recorded in the American Joint Committee on Cancer (AJCC) Melanoma Staging Database, which contains information from multiple institutions and cancer cooperative groups, has confirmed previous reports that there is a significant correlation between increasing mitotic rate and a declining survival probability.^{15,16} On the basis of this analysis, primary melanoma mitotic rate was incorporated into the seventh edition of the AJCC Cancer Staging

Manual as a required element for melanoma staging.^{14,15} Patients with T1b melanomas are now defined as those for which the tumor thickness is ≤ 1.0 mm and for which there is at least 1 mitosis/mm² or tumor ulceration.¹⁴ In the previous (sixth) edition of the AJCC Staging Manual, Clark level of invasion or tumor ulceration was used to define T1b melanomas.²

Until now, routine histopathologic reporting of primary melanomas has infrequently included an assessment of mitotic rate. Even in a geographic area with a high melanoma incidence, such as Queensland, Australia, fewer than 50% of pathology reports on primary melanomas documented mitotic rate in a recent study assessing the completeness of histopathologic reporting of melanoma.¹⁷ Similarly, in another recently published study undertaken at the H. Lee Moffitt Cancer Center in Florida, 47% of outside pathology reports for patients with thin (≤ 1 mm) or in situ melanoma did not mention mitotic rate.¹⁸ Moreover, clinicians involved in the care of patients with primary melanomas have not generally considered mitotic rate as an important factor to be considered when discussing prognosis with patients and planning their treatment.

Herein, we report the results of detailed primary tumor mitotic rate analyses from the AJCC melanoma staging database, and we describe the effects of mitotic rate on survival in patients with localized (stages I and II) melanomas that led to its inclusion in the AJCC seventh edition Staging Manual.¹⁴ We have previously reported the effects of mitotic rate on survival in patients with stage III disease, in whom it was an independent predictor of survival in those with nodal micrometastases but not in those with nodal macrometastases.¹⁶

METHODS

The AJCC melanoma staging database was originally created in 1999 as a result of an international collaboration that combined prospective melanoma databases from 18 major cancer centers and clinical trial cooperative groups.^{1,15} It was updated in 2008, and the information that it then contained was used to revise the AJCC melanoma staging system for inclusion in the seventh edition of the AJCC Melanoma Staging Manual. This was published in 2009. For stages I, II, and III disease, information was provided for 48,322 patients with melanoma, but in only 34,896 of them (72.2%) were data available for all variables used to define stage. The actual number of mitoses per millimeter squared in the primary melanoma was recorded for 13,296 patients with stages I and II disease. More than half the patients with mitotic rate data available for analysis had at least 5 years of follow-up. Of the patients in the study group with documentation of sentinel node biopsy (SNB; yes or no) and elective lymph node dissection (ELND; yes or no), 30.4% were staged pathologically, and 69.6% were staged clinically.

Survival times were calculated from the date of initial melanoma diagnosis and were considered censored for patients who were alive at last follow-up or who died without evidence of melanoma. Standard statistical methods were used; melanoma-specific survival curves were generated by the Kaplan-Meier product-limit method and were compared using the log-rank test; multivariate analyses were based on the Cox proportional hazards model.^{1,15,19} For the Cox multivariate analyses, the relative importance of the prognostic factors was determined according to χ^2 values (with associated *df* and *P* values).¹⁹

RESULTS

In patients with stages I and II melanoma, mitotic rate correlated inversely with survival ($P < .001$) when examined as a single factor

Table 1. 5- and 10-Year Survival Rates by Mitotic Rate

Mitotic rate (per mm ²)	No. of Patients (N = 11,664)	Survival Rate*			
		5-Year		10-Year	
		%	SE	%	SE
0	3,031	97.8	0.4	93.2	0.8
0.01-0.99	281	94.5	1.4	89.2	2.1
1.00-1.99	2,117	92.0	0.7	84.2	1.2
2.00-4.99	3,254	86.9	0.7	75.4	1.2
5.00-9.99	1,781	78.2	1.2	69.3	1.5
10.00-19.99	941	71.7	1.8	58.0	2.3
≥ 20	259	59.4	3.9	47.6	5.0

Abbreviation: SE, standard error.
* $P < .001$ by log-rank test.

(Table 1; Fig 1). As the number of mitoses per millimeter squared increased, survival rates declined, with 10-year survival ranging from 93.2% for patients with a mitotic rate of 0 mitoses/mm² to 47.6% for those with a mitotic rate of ≥ 20 mitoses/mm² ($P < .001$; Table 1; Fig 1).

Mitotic rate correlated with increasing tumor thickness and decreasing survival (Table 2; Fig 2). It also correlated with increasing tumor thickness and primary tumor ulceration (Table 3). At least some mitotic activity was observed in most patients with melanomas that were greater than 2.5 mm in thickness, but activity was uncommon in those with primary tumors less than 1 mm in thickness (Table 2; Fig 2). By using two variables—tumor thickness and mitotic rate—the 10-year survival rate ranged from 97.1% for patients with a tumor thickness ≤ 0.5 mm and < 1.00 mitoses/mm² to 28.1% for those with a tumor thickness greater than 6.0 mm and greater than 10 mitoses/mm² ($P < .001$; Table 2).

When ulceration was included as a third variable, increasing mitotic rate remained highly correlated with increasing tumor thickness, particularly in patients with equal tumor thickness in the presence of ulceration ($P < .001$; Table 3). Increasing patient age also correlated strongly with a higher mean mitotic rate (2.4 mitoses/mm² for patients whose age was 20 to 29 years, 3.2 for those whose age was 50 to 59 years, and 5.7 for those whose age was 80 to 89 years; $P < .001$).

Fig 1. Survival curves by number of mitoses per millimeter squared.

Table 2. 10-Year Survival Rate by Tumor Thickness and Mitotic Rate

Table 2: 5-Year Survival Rate by Tumor Thickness and Mitotic Rate																					
Tumor Thickness (mm)	No. of Patients	Mitotic Rate (mitoses/mm ²)																			
		< 1.00			1.00-1.99			2.00-4.99			5.00-9.99			10.00-19.99			≥ 20.00			Overall	
		%	SE	No.	%	SE	No.	%	SE	No.	%	SE	No.	%	SE	No.	%	SE	No.	%	SE
0-0.50	1,521	97.1	0.9	1,194	97.1	1.7	207	93.2	3.9	89	87.7	8.6	27	4*			0*			96.7	0.8
0.51-1.0	3,340	92.5	1.1	1,472	87.4	1.8	895	86.4	2.0	775	82.2	4.6	161	36*			1*			89.3	0.8
1.01-2.0	3,367	90.9	1.8	488	83.1	2.2	703	79.4	1.7	1,351	76.5	2.6	577	70.1	4.7	205	73.8	8.7	43	80.9	1.0
2.01-3.0	1,520	77.2	6.6	78	75.8	4.2	188	65.3	3.0	555	70.8	3.1	397	58.2	4.6	241	47.7	9.8	61	67.0	1.7
3.01-6.0	1,459	78.8	8.2	58	56.7	7.8	100	57.1	4.0	381	58.5	3.2	477	55.2	3.8	333	34.3	8.7	110	56.8	1.9
> 6.00	414	11*			18*			53.0	8.7	89	52.6	6.0	135	28.1	7.6	119	42*			48.0	3.8

Abbreviation: SE, standard error.

*10-year survival rates cannot be accurately calculated in these subgroups because of small patient numbers, short follow-up duration, and/or an insufficient number of events (deaths).

For patients with a mitotic rate less than 5.00 mitoses/mm², the 5-year survival rates were almost identical for patients with clinical stages I and II disease and with pathologic stages I and II disease. However, for patients with a mitotic rate between 5.00 and 20.00 mitoses/mm², the 5-year survival rates in patients with pathologic stage I and II disease were 6% to 13% higher than in patients with clinical stage I and II disease. These differences were not surprising, because the node-positive patients (indicated by SNB or ELND) were upstaged to stage III and were not included in this data set.

The relative strength of mitotic rate as an independent prognostic factor was evaluated by performing Cox multivariate analysis. Only patients with data available on all seven prognostic variables and adequate follow-up information were included in this analysis. Most of the patients excluded had missing ulceration data ($n = 1,407$) and/or inadequate follow-up information ($n = 1,632$). To determine independent prognostic significance, if any, clinicopathologic factors were ranked in order of statistical significance on the basis of their χ^2 values and the associated df . With inclusion of mitotic rate in the model ($n = 10,233$ patients), the independent predictors of survival were as follows: tumor thickness ($\chi^2 = 104.9$; $P < .001$), mitotic rate ($\chi^2 = 67.0$; $P < .001$), patient age ($\chi^2 = 48.2$; $P < .001$), ulceration ($\chi^2 = 46.4$; $P < .001$), anatomic site ($\chi^2 = 34.6$; $P < .001$), and sex ($\chi^2 = 33.9$; $P < .001$). Thus,

mitotic rate was the second most powerful predictor of survival outcome among the seven prognostic factors examined. Clark level of invasion was no longer a statistically significant prognostic factor once mitotic rate was accounted for ($\chi^2 = 3.2$; $P = .37$). Details of this multivariate analysis are listed in Table 4.

DISCUSSION

To our knowledge, this is the first large multi-institutional study that has examined the survival impact of mitotic rate compared with other clinical and pathologic features in patients with AJCC stages I and II melanoma. Mitotic rate, a quantitative measure of melanoma proliferation, was the most important predictor of survival outcome after accounting for primary tumor thickness. The presence of many mitotic figures in any primary tumor indicates that cells are actively dividing and usually implies that such tumors are likely to grow more rapidly and may metastasize earlier than those with little or no mitotic activity. Our study confirms that, in patients with a localized primary melanoma, a high tumor mitotic rate reflects a more aggressive tumor that is associated with a worse survival outcome; conversely, a low mitotic rate is associated with a better outcome. A gradient of increasing mitotic rate with increasing tumor thickness was observed. In patients with thin melanomas (< 1.0 mm in thickness), the most common presenting stage of localized melanoma, mitotic activity was usually absent or low, whereas virtually all melanomas greater than 2.5 mm in thickness had at least some mitotic activity. From the data collected, it was apparent that there was no lower threshold for mitotic rate as a prognostic indicator. If there was evidence of any significant mitotic activity in a primary melanoma (mitotic rate $\geq 1/\text{mm}^2$), the prognosis of a patient was worse than it would have been if the mitotic rate was zero.

The poor survival of patients who had primary melanomas with a high mitotic rate was first reported by Allen and Spitz in 1953.²⁰ Several other authors subsequently reached the same conclusion, but it was not until nearly 50 years later that mitotic rate began to be identified as an independent prognostic factor.^{3-13,21-23} Mitotic rate was not included in the 2002 AJCC staging system analysis because insufficient mitotic rate data were available in the AJCC melanoma staging database at that time.

Fig 2. Mitotic rates versus tumor thickness of primary melanomas.

Table 3. Correlation of Mitotic Rate With Tumor Thickness and Ulceration

Tumor Thickness (mm)	No. of Patients		Mitotic Rate (mitoses/mm ²)				% Patients with Mitotic Rate = 0	
			No Ulceration*		Ulceration*			
	No Ulceration (n = 9,586)	Ulceration (n = 2,276)	Mean	SE	Mean	SE	No Ulceration†	Ulceration†
0.01-0.50	1,786	18	0.4	0.02	0.8	0.27	79.0	55.6
0.51-1.00	3,339	161	1.3	0.03	2.3	0.20	41.5	19.9
1.01-2.00	2,660	611	3.2	0.07	5.2	0.23	12.7	6.4
2.01-3.00	957	540	5.2	0.09	8.1	0.28	4.1	1.7
3.01-4.00	414	322	6.3	0.31	9.0	0.37	5.8	0.9
4.01-6.00	281	372	6.3	0.35	10.6	0.44	5.7	0.5
6.01-8.00	96	135	6.9	0.76	11.3	0.66	5.2	0
> 8.00	53	117	7.3	0.88	10.7	0.80	7.6	0.9

Abbreviation: SE, standard error.

* $P < .001$ by Kruskal-Wallis test.† $P < .001$ by Pearson's χ^2 test.

In 2003, renewed interest in primary tumor mitotic rate as a prognostic factor was stimulated by the publication of a large retrospective series of patients who had been treated at the Sydney Melanoma Unit (SMU) between 1983 and 2002. This study by Azzola et al⁴ involved 3,661 patients for whom details of primary tumor thickness, presence or absence of primary tumor ulceration, and mitotic rate of the primary melanoma, as well as full clinical outcome data, were available. By multivariate analysis, mitotic rate was a more powerful independent prognostic indicator than ulceration and was second only to primary tumor thickness as a predictor of survival outcome. The finding that mitotic rate was an important prognostic factor was confirmed in a second large study involving a completely separate cohort of 1,317 patients who had been treated at the SMU before 1983.⁶ However, the predictive value of mitotic rate in this study was less than the rate in the SMU study from 1983 to 2002; this appears to have been a result of mitotic rate assessment using a different method.

These two SMU reports highlighted the importance of standardizing the method of histopathologic measurement of mitotic rate in a primary melanoma. In the study by Azzola et al,⁴ involving patients treated after 1982, the recommendations of the 1982 International Pathology Workshop²⁴ for assessing tumor mitotic rate were followed. This involved beginning the mitotic count in the microscope field with the greatest number of mitoses, then counting mitoses in successive fields (the hot spot method). The tumor mitotic rate was reported as the number mitoses per millimeter squared. In the study reported by Francken et al,⁶ which involved patients treated before 1982, tumor mitotic rate was assessed according to the earlier recommendations of the 1972 International Pigment Cell Conference.²⁵ This involved determination of the average number of mitoses in at least 10 high-power fields (HPFs) over the entire dermal component of the lesion (the mean method). The results were then reported as the average number of mitoses per five HPFs. Although tumor mitotic rate was found to be an important independent prognostic factor in both of the SMU studies, its influence was considerably greater when the 1982 hot spot method was used than it was when the 1972 mean method was employed. All the tumor mitotic rate measurements reported in the study by Francken et al were assessed by a single pathologist (V.J. M.) using the same microscope. However, the great variation

in microscope HPF sizes will inevitably make it unreliable to compare tumor mitotic rate measurements made by different pathologists who use a wide range of microscopes and who report their results as the average number of mitoses per five HPFs. It has been shown that mitotic rate values expressed in this way may vary by as much as 600%.²⁶

For the above reasons, standardized assessment of tumor mitotic rate using the hot spot method is now recommended as a required component of pathology reporting by the AJCC, with results expressed as mitoses per millimeter squared.¹⁴ The recommended approach to mitotic rate measurement is detailed in the seventh edition of the AJCC Cancer Staging Manual.¹⁴ Briefly, this involves finding the so-called hot spot by identifying the area in the dermis containing the greatest concentration of mitotic figures. After counting the mitoses in the hot spot, the mitoses in adjacent fields are counted until an area corresponding to 1 mm² has been assessed. Usually, this will mean assessment of four HPFs at $\times 400$ magnification, but calibration of individual microscopes is required, because field sizes vary considerably between microscopes. If no hot spot can be identified and if mitoses are sparse and/or randomly distributed throughout the tumor, then a single mitosis is selected; beginning with the count in that field, the mitoses in adjacent fields are counted until an area of 1 mm² has been assessed. All mitotic rate results should be reported as the number of mitoses (as a whole number) per millimeter squared. When the invasive component of the tumor involves an area less than 1 mm², a 1-mm² area of dermal tissue that includes the tumor should be assessed and recorded as a number per millimeter squared. The number of mitoses should be listed as a whole number. If no mitoses are identified, then it should be recorded as 0 mitoses/mm². The use of the description of < 1 mitosis/mm² for this occurrence is not recommended. The AJCC staging committee also suggests that, as a guide, "no more than 2 slides with multiple sections be examined so that exhaustive evaluation of the lesion is not performed in an attempt to identify a single mitosis."¹⁴

Another important consideration is the reproducibility among pathologists of tumor mitotic rate assessment. A detailed study of this, involving six histopathologists with varying experience in the assessment of melanocytic tumors, all using the hot spot method, revealed excellent concordance between them (intraclass correlation coefficient, 0.76).⁵ In previous studies assessing the interobserver reproducibility

Table 4. Multivariate Cox Regression Analysis

Variable	df	χ^2 (Wald)	P	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Thickness, mm	5	104.9	< .001			
0-0.50*	—	—	—	1.00		
0.51-1.00	1	13.0	< .001	2.66	1.56	4.52
1.01-2.00	1	20.3	< .001	3.51	2.03	6.05
2.01-3.00	1	35.6	< .001	5.42	3.11	9.44
3.01-6.00	1	43.4	< .001	6.59	3.76	11.54
> 6.00	1	47.2	< .001	7.93	4.39	14.32
Mitotic rate, mitoses/mm ²	5	67.0	< .001			
0*	—	—	—	1.00		
0.01-0.99	1	3.8	.050	1.56	1.00	2.43
1.00-1.99	1	23.3	< .001	1.98	1.50	2.61
2.00-4.99	1	43.2	< .001	2.41	1.85	3.13
5.00-9.99	1	42.0	< .001	2.50	1.89	3.29
10.00-19.99	1	54.8	< .001	3.00	2.24	4.01
≥ 20.00	1	48.9	< .001	3.58	2.50	5.11
Age, years	4	48.2	< .001			
< 50*	—	—	—	1.00		
50-59	1	0.7	.396	1.07	0.92	1.25
60-69	1	6.5	.011	1.22	1.05	1.42
70-79	1	23.2	< .001	1.52	1.28	1.81
≥ 80	1	34.2	< .001	2.13	1.66	2.75
Ulceration	1	46.4	< .001			
No*	—	—	—	1.00		
Yes	1	46.4	< .001	1.55	1.37	1.76
Primary site	3	34.6	< .001			
Upper extremity*	—	—	—	1.00		
Head or neck	1	22.2	< .001	1.57	1.30	1.89
Trunk	1	26.8	< .001	1.56	1.32	1.84
Lower extremity	1	4.7	.031	1.22	1.02	1.46
Sex	1	33.9	< .001			
Male*	—	—	—	1.00		
Female	1	33.9	< .001	0.69	0.61	0.79
Clark level	3	3.2	.369			
II*	—	—	—	1.00		
III	1	0.2	.663	1.09	0.75	1.57
IV	1	1.0	.325	1.21	0.83	1.76
V	1	0.9	.336	1.23	0.81	1.88

NOTE. Total number of patients = 10,233; this number includes only patients with data available on all seven prognostic variables and adequate follow-up information. Most of the patients excluded had missing ulceration data (n = 1,407) and/or inadequate follow-up information (n = 1,632).

*Reference.

of tumor mitotic rate,^{27,28} the exact method used to assess it had not been specified, perhaps explaining why the reported reproducibility of mitotic rate assessment had been low.

An important finding in this study was that Clark level of invasion was not an independent prognostic indicator on multivariate analysis. In the interobserver reproducibility study mentioned earlier in the Discussion section, the concordance between pathologists in assessing Clark level was poor (intraclass correlation coefficient, 0.60)⁵ and was much lower than the concordance achieved for mitotic rate assessment. On the basis of the analysis described here, the AJCC Melanoma Staging Committee has replaced Clark level of invasion with mitotic rate as one of the primary criteria for defining T1b melanomas in the seventh edition of the AJCC Staging Manual.^{14,15} T1b melanomas (approximately 40% of T1 melanomas) are now defined as those with a tumor thickness ≤ 1.0 mm that have at least 1 mitosis/mm² or tumor ulceration present. This mitotic rate threshold

was determined after statistical evaluation of multiple mitotic rate thresholds. The most significant correlation with survival was identified at a threshold of at least 1 mitosis/mm² for upstaging T1a to T1b. The process is described in more detail elsewhere.^{15,29} The influence of mitotic rate on survival and its relevance for staging in patients with T2, T3, and T4 disease and stages I and II melanomas is also discussed elsewhere.¹⁵ It must be emphasized that the new AJCC T1b category is intended to more reliably establish prognosis and does not imply that all patients with T1b disease should necessarily have a SNB. However, there are now preliminary data available from a large cohort of patients with T1 tumors demonstrating, as expected, that there is a correlation between mitotic rate and sentinel node positivity.³⁰ This will make it easier to provide factual information to patients with newly diagnosed T1b tumors when discussing with them the pros and cons of having a SNB procedure. If they know with greater precision (on the basis of mitotic rate assessment) the likelihood that they will be

sentinel node positive, the patients will be in a better position to make an informed decision in this matter.

There are some limitations of this study despite its large sample size. Mitotic rate information was not available from all collaborating melanoma centers, and there was no central pathologic review. Nevertheless, the pathologists who contributed data for this study had extensive experience with the histopathologic examination of primary melanomas and assessed mitotic rate with the hot spot method according to protocols similar to the one ultimately recommended in the seventh edition of the AJCC Cancer Staging Manual.¹⁴ Another limitation is that the cohort of patients with localized melanoma on which the analyses were based included patients with stages I and II disease determined both clinically (when they did not have either a SNB or an ELND) and pathologically (node negative on the basis of an SNB or ELND). However, although pathologic staging is clearly desirable for the purpose of studies such as ours, even minimally invasive assessment of regional nodes by SNB could not currently be justified for patients with T1a tumors, and the value of SNB has not yet been clearly established for patients with T1b tumors.

In conclusion, a powerful independent effect of mitotic rate on survival outcome in patients with melanoma was convincingly demonstrated in this study. It confirms the finding of the previous large, single-institution study by Azzola et al⁴ and other previous single-institution studies that the mitotic rate of a primary melanoma is the most important prognostic factor after tumor thickness and is of greater independent prognostic significance than tumor ulceration. With increasing mitotic rate, survival decreased progressively, regardless of whether the primary tumor was thin or thick (Table 3). Increasing mitotic rate was correlated significantly with increasing primary tumor thickness for both ulcerated and nonulcerated primary tumors. The practical implication of having accurate and reliable information about the mitotic rate of primary melanomas is that a better estimate of prognosis can be given to patients, more rational treatment planning is possible, and more accurate stratification of patients entering clinical trials can be achieved.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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