Thin (≤1 mm) Melanomas of the Extremities Are Biologically Favorable Lesions Not Influenced by Regression

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Although a thickness of ≤0.76 mm has been used to define biologically favorable (thin) melanoma, there is evidence that 1 mm may be a reasonable cutoff to categorize favorable extremity melanomas. This is tempered, however, by the claim that histologic regression in thin melanomas is associated with an increased metastatic rate. We have therefore addressed the following questions: (1) Is 1 mm an appropriate cutoff point to define thin melanoma on the extremities? (2) Does regression in a thin lesion truly signify a poor prognosis? (3) Is the width of excision (narrow *vs.* wide) related to recurrence rates in these lesions? To address these issues we reviewed 48 patients with extremity melanomas, ≤1 mm in maximum thickness, treated at this institution during a 20-year period. Pathologic features included *histologic type:* superficial spreading (90%), nodular (6%), and not classified (4%); *thickness:* <0.76 mm (61%) and 0.76 to 1 mm (39%); and *Clark's level:* II (33%), III (63%), and IV (4%). A moderate or marked lymphoid infiltrate occurred in 75%, and histologic tumor regression was found in 50%. The median margin of excision, as stated by the surgeon, was 4 cm. The median margin measured by the pathologist in unfixed specimens was 3.5 cm. Although 13% had atypical melanocytic hyperplasia in the initial excisional biopsy margin, all reexcisions were clear. Of 21 patients having node dissections, none had nodal metastases. There were no recurrences or deaths due to melanoma (median follow-up: 90 months). We conclude that melanomas ≤1 mm in thickness on the extremities can be defined as biologically highly favorable, "thin" lesions. Foci of regression do not alter their behavior. Their favorable prognosis justifies conservative excision in most cases.

ALTHOUGH THERE IS general agreement about the favorable behavior of thin cutaneous melanoma (<0.76 mm thick), controversy has developed concerning the presence of regressive changes in such lesions. Gromet et al., in their review of thin melanomas from all sites, found that five of 23 (22%) partially regressed tumors metastasized in contrast to two of 98 thin lesions not showing regression.[1] Their finding of an adverse prognostic relationship with regression appeared to be substantiated by Milton et al.[2] and, more recently, by Paladugu and Yonemoto.[3] In contrast, other investigators have suggested that partial regression of primary melanomas is not of prognostic significance.[4-6]

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The foregoing controversy prompted us to review our experience with thin melanoma in order to assess the role of various prognostic factors, with particular emphasis on regression. The following questions were addressed: (1) What level of thickness constitutes a thin melanoma, *i.e.*, a biologically favorable melanoma, on the extremities? (2) What is the frequency of regression in such lesions? (3) Is there any correlation between prognosis (recurrence or survival) and regression or other histologic features in thin melanomas? (4) Is there any relationship between the extent of surgery (wide *vs.* narrow excision) and recurrence of thin melanomas? We have addressed these questions in a clinicopathologic review of a consecutive series of melanomas 1 mm or less in maximal thickness located on the extremities. We believe that our data and the apparently paradoxical observations from the literature are reconcilable and suggest that thin melanomas have an excellent prognosis. Partial regression is frequent in such lesions but does not appear to be of prognostic significance for extremity lesions. As a corollary, our observations also suggest that thin melanomas of the extremities (less than 1.0 mm) may be adequately treated by more conservative (narrower) excisions than previously believed.

Materials and Methods

We searched the McIntire Tumor Registry of the University of Virginia Medical Center for all patients with malignant melanoma of the extremities who were treated at our institution between January 1, 1960 and December 31, 1979. One hundred seventy-six patients were so identified and their clinical records reviewed. Twenty-one patients were excluded from further study because the anatomic site of their lesion was imprecisely recorded, or because their tumor involved the shoulder, scapular region, axilla, buttock, or inguinal area. The files of the Department of Pathology, University of Virginia Medical Center, were then searched for histo-

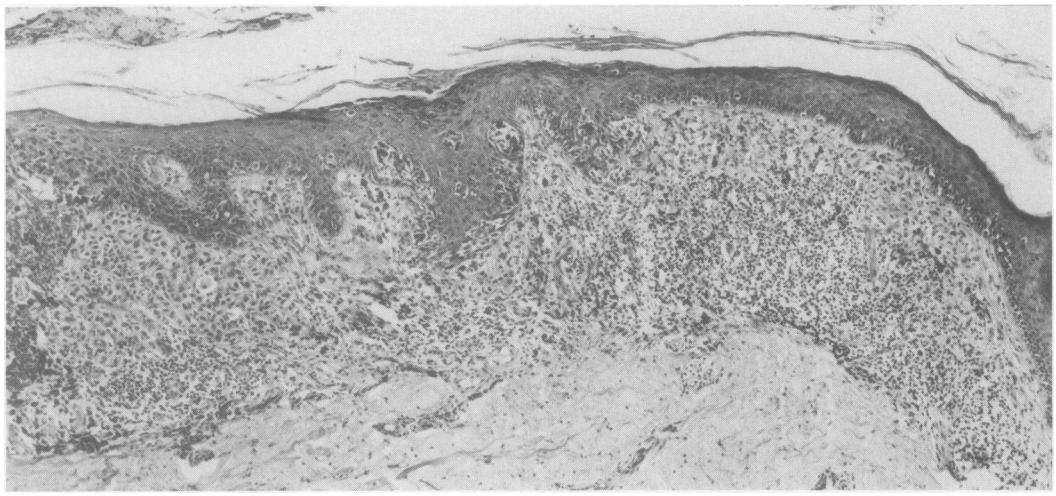

FIG. 1. Well-defined zone of regression in thin melanoma. Dermal invasion can be seen at left. Maximal thickness: 0.72 mm. Hematoxylin-eosin × 75.

logic material pertaining to the primary lesions of the remaining 155 patients. Twenty-four primary lesions had been processed at other laboratories, submitted for review, and the slides returned to contributing pathologists. Despite written request, 10 of these could no longer be retrieved. In 13 instances, the primary melanoma was not reviewed at our institution. Ten of these patients had metastases or recurrences at the time they were first admitted. The clinical records of nine patients contained no indication of histopathologic study. Most of these patients were admitted for chemotherapy. Adequate histologic material from 123 ptients with a diagnosis of malignant melanoma of the extremities was, therefore, available for evaluation. Upon review, three of the lesions were judged to be benign or atypical nevi, and two others lacked invasion of the dermis, even though the junctional proliferation of melanocytes appeared cytologically malignant. Thus there were 118 histologically verifiable malignant melanomas located on the extremities for further study.

The thickness of each lesion was measured, based on available histologic preparations, and 70 lesions exceeded 1 mm in maximal thickness. Forty-eight patients had lesions with a thickness of 1 mm or less. All available data describing the clinical characteristics, therapy, and subsequent course of these 48 patients were tabulated. Follow-up already being maintained was updated. Microscopic features recorded included histologic type of malignant melanoma, maximal thickness (mm), level of dermal invasion, maximal width in millimeters observed in available microscopic sections, the presence or absence of atypical junctional change or invasive melanoma at microscopically studied surgical margins, and the presence or absence of ulceration. In addition, the degree of mononuclear cell infiltrate was graded as 1 (sparse, scattered), 2 (patchy), or 3 (confluent or sheet-like).

For the histologic diagnosis of regression, we required the presence of one or more well-defined zones, either within the tumor or at its edge, in which there was a marked reduction or absence of invading melanoma (Fig. 1). The affected areas contained variable proportions of lymphoid infiltrate and fibrosis. Pigment incontinence and telangiectasia were often noted, and junctional change was frequently reduced or absent in the overlying epidermis. We also required that the papillary dermis in an area of regression be clearly thicker than the normal papillary dermis seen elsewhere in the sections. Lesions meeting these conservative criteria were interpreted as *definitely* showing regression for the purposes of this study. Another group of lesions were interpreted as *probably* showing regression based on more liberal criteria consisting of the presence of extensive lymphoid infiltrate and/or fibrosis that involved essentially all of the invasive component (Fig. 2). A more detailed histologic description of regression and problems encountered in its diagnosis in thin melanomas is given elsewhere.[7]

Results

Patient Characteristics

There were 13 men and 35 women with a median age 45 years (range: 20–89). The location of the lesions is shown in Table 1. The majority were located on the lower extremity, and 30 (63%) were situated on the left side of the body. The histories recorded were variable. In 25 cases, the patient's description of the primary lesion and its duration were given. The duration was 1 to 4 months in seven patients, 6 months in three, 12 months in six, 2 to 5 years in four patients, and more than 5 years or "congenital" in five patients. An additional ten individuals had observed a mole for an unstated period of time and had sought medical advice

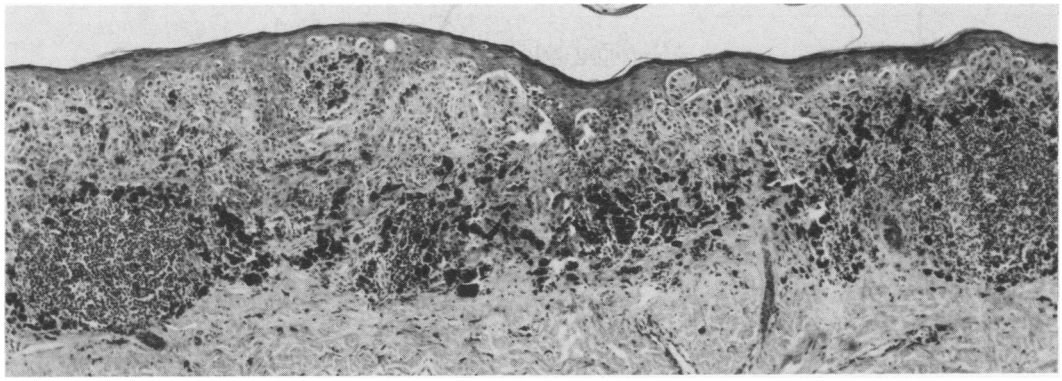

FIG. 2. Diffuse regressive changes in thin melanoma. Maximal thickness: 0.5 mm. Hematoxylin-eosin × 70.

because of observed changes or otherwise not stated concerns. In two patients the mole had become erythematous and tender, with areas showing loss of pigment. Pruritis was recorded in three; bleeding and ulceration occurred in one patient only. In nine cases no history was recorded. Subsequent or preceding second primary malignancies were recorded in 11 patients. These included basal cell cancer in six, a second primary melanoma on the flank in one patient, and cancers of the breast, colon, vulva, and jaw in one patient each.

Physical findings included clinical estimates of the size of the melanoma in 21 patients. The lesion size was estimated to be less than 0.5 cm in six patients, 0.6 to 1.0 cm in 12 patients, 1.1 to 1.5 cm in two, and 2.5 cm in diameter in one patient. All but one patient were considered to be clinical stage 1. One patient was thought to have subcutaneous nodules (satellites) 4 cm proximal to an upper arm melanoma. A node dissection revealed no metastatic disease.

Histologic Features (Table 2)

The histologic subtype was recorded in 46 cases, of which 43 were superficial spreading. The tumors invaded the dermis to level II in 33%, level III in 63%, and level IV in 4%. Only 19% were less than 0.5 mm thick, whereas 42% were between 0.51 and 0.75 mm and 39% ranged from 0.76 and 1.0 mm. Focal, incipient ulceration was noted in two lesions. Inflammatory infiltrate was grade 2 or 3 in 75% of the lesions. Definite regression was recorded in 11 lesions (23%) and probable regression in 13 (27%). Tumor free margins were obtained from the excisional biopsy alone in 41 patients (83%). One or more surgical margins were involved in six instances (13%) and in two cases the margins could not be assessed.

Surgical Management (Table 3)

Forty-four patients had reexcision of their biopsy sites; four patients had no further surgical therapy. The sizes of the excision specimens are shown in Table 4. The median radial margin to reexcision, reported by the surgeon, was 4 cm (range: 1.0 to 5.9 cm), and in five patients it was less than 3.0 cm. The median shortest dimension (excisional diameter) recorded from the unfixed specimens in the pathology laboratory was 6.5 cm. In 11 patients it was less than 6.0 cm (equivalent radius of excision less than 3.0 cm.). In only nine patients was the width of excision 8.0 cm or greater (excisional radius $\leq$ 4.0 cm), and three of these patients had an excisional diameter of 10 cm (or 5 cm radial excisions). An elective lymph node dissection was performed in 21 patients (10 axillary and 11 inguinal). There were no lymph node metastases. During the period from 1960 to 1969, seven patients had limb perfusion.

The disease-free survival at 5 years was 100% in 30 patients at risk for that period (Table 5). No tumors recurred. Overall, there were no recurrences at a median follow-up of 90 months. Two patients died of unrelated causes.

Discussion

This study confirms that thin melanomas of the extremities, with or without regression, have an excellent prognosis. Although thin melanomas have usually been defined as lesions $\leq$ 0.76 mm thick because of their

TABLE 1. *Anatomic Site of Thin Melanomas of the Extremities*

	L		R
Upper extremity			
Upper arm	5		2
Forearm	6		2
Wrist	2		
Lower extremity			
Thigh	5		4
Leg	12	(1)*	7
Foot			2
	0		
	30	(1)*	17

* Side unstated.

TABLE 2. *Histopathology of Thin Melanomas of the Extremities*

	Per cent	Per cent
Histologic type		
SSM*	43	90
NOD†	3	6
NC‡	2	4
Total	48	100
Microscopic ulceration = 2 "focal, incipient"		
Thickness		
0.31–0.5 mm	9	19
0.51–0.75 mm	20	42
0.76–1.0 mm	19	39
Total	48	100
Clark level		
II	16	33
III	30	63
IV	2	4
Total	48	100
Histologic evidence of regression		
None	19	40
Yes	24	50
Indeterminate	5	10
Total	48	100%

* Superficial spreading.
† Nodular.
‡ Not classified.

excellent prognosis,[8–14] data are accumulating which suggest that 1.0 mm may be an equally appropriate cutoff to define thin lesions of the extremities. There were no local or distant recurrences in this consecutive series of 48 patients with extremity melanomas followed for a median of 90 months. Moreover, 39% of the patients had lesions measuring 0.76 to 1.0 mm in maximal thickness. This corroborates the series of extremity melanomas from Memorial Sloan Kettering Cancer Center in which there were no deaths from melanoma at 5 years in 44 patients with lesions ≤ 1.0 mm.[11] In that group, two of 22 patients (9%) with lesions between 0.6 and 1.0 mm had regional node metastases demonstrated at elective node dissection, but both survived without evidence of further disease.[11] In the World Health Organization trial, there were no early or delayed nodal metastases in patients with extremity lesions ≤ 1.0 mm thick, and the 5-year survival, with

TABLE 3. *Surgical Management of Thin Melanomas of the Extremities*

Primary excisional biopsy only
4 patients
Reexcision
44 patients
Lymph node dissection
21 patients*
Axillary: 10
Illioinguinal: 11
Perfusion
7 patients (1960–1969)

* All specimens negative for metastases.

TABLE 4. *Thin Melanomas of the Extremities: Pathologic Status of Biopsy Margin and Size of Reexcision*

Microscopic status of biopsy margin

	#	%
Margin clear	40	83
Margin involved	6	13
Not defined	2	4
Total	48	100%

Radius of reexcision as stated by surgeon

Radius (cm)	#
1.0–1.9	1
2.0–2.9	5
3.0–3.9	9
4.0–4.9	12
5.0–5.9	9
Total	36*

Width of specimen as recorded by pathologist

Excisional Diameter (cm)	#	Radial Margins of Excision (cm)
3.0–3.9	5	1.5–1.95
4.0–4.9	1	2.0–2.45
5.0–5.9	6	2.5–2.95
6.0–6.9	13	3.0–3.45
7.0–7.9	5	3.5–3.95
8.0–8.9	6	4.0–4.45
9.0–9.9	0	4.5–4.95
10.0–10.9	3	5.0–5.45
Total	39	
Mean = 7.0 cm		Mean = 3.5 cm
Median = 6.5 cm		Median = 3.25 cm

* No reexcision was done in four patients.
Excision data not available for eight patients.

or without lymph node dissection, was 94% for upper and lower extremity melanomas measuring ≤ 1.0 mm.[15,16] In the Melanoma Cooperative Group (New York University and Massachusetts General Hospital) series of patients with melanomas of all sites invasive to 0.85 mm, the 8-year survival was 99%,[17] and in a study that focused on melanomas 0.76 to 1.69 mm thick,[18]

TABLE 5. *Survival and Recurrence Rates of Thin Melanomas of the Extremities*

Time	Pts. Followed	Developed Recurrence	Survival Disease-Free	Deaths from Disease	Other Causes
3 yrs	46*	0	46/46 (100%)	0	0
4 yrs	38	0	38/38 (100%)	0	0
5 yrs	30	0	30/30 (100%)	0	0
7 yrs	20	0	18/18 (100%)	0	2
10 yrs	13	0	11/11 (100%)	0	0

Median follow-up = 90 months.
* One patient was followed for only 22 months. One was lost to follow-up.

the failure rate in the 0.76 to 1.25 mm group was nine of 141 (6%). All but one of these had lesions in the high risk BANS area (upper back, posterior arm, posterior neck, posterior scalp). Only one failure occurred in 136 non-BANS lesions that were 0.76 to 1.25 mm thick. The survival data for 81 lesions ≤ 1.75 mm thick on the thigh or leg was 99% at 5 years.[19] Of 84 patients with upper extremity melanoma ≤ 2.25 mm thick and without ulceration, the 5-year survival was 98.7%.[20] It would thus appear, from a review of these series, that lesions ≤ 1.0 mm thick (and possibly thicker) on the extremities are highly favorable.

The prognostic influence of partial regression in thin melanoma has been controversial. Indeed, the histologic criteria for regression in thin melanomas have not been rigorously defined,[7] and the diagnosis of regression in many melanoma studies has not been bolstered by adequate detail. Nevertheless, this feature has been stated to have an adverse effect on prognosis by some authors,[1-3] whereas others have claimed it had no significant prognostic effect.[4-6] Gromet et al. found that 22% of thin melanomas with regression metastasized.[1] Several of these were large lesions, ranging between 1.3 cm and 2.5 cm in diameter, and three occurred on the trunk, one on the face, and one on the arm. The latter patient presented with axillary metastases, and the facial lesion had recurred twice, after an initial resection, before metastasizing to neck nodes. Three of the patients had distant metastases and two had regional node involvement, attesting to the virulence of these lesions. Paladugu and Yonemoto found that five of 11 (45.5%) thin melanomas with regression metastasized compared with three of 25 (12%) thin melanomas without regression.[3] Although the focus was on lesions with regression, the patients with nonregressing thin melanomas also had a high frequency of metastases, making this series difficult to interpret. Milton et al. also believed that partial regression in thin melanomas conferred a tendency to metastasize.[2] In their series, partial regression was present in 89% of recurring thin lesions compared with 50% of all thin lesions. In contrast, McGovern et al., from a different perspective of the same data base, found that in superficial spreading melanoma there was a better prognosis (though not significant) in patients whose lesions had partial regression.[4]

Trau et al. reported that regression was present in 27% of superficial spreading melanoma (SSM) and zero per cent of nodular melanoma.[5] The frequency of regression varied with thickness and was 36% for lesions ≤ 0.76 mm, 29% for lesions 0.76 to 1.69 mm, and 19% for lesions thicker than 1.70 mm. Although there was an apparent better survival in patients with lesions showing regression (92% *vs.* 84% of lesions lacking regression), when the data were analyzed by multivariate analysis, regression was not a significant independent prognostic factor. Only thickness was prognostically significant. The frequency of regression correlated inversely with thickness but did not correlate independently with prognosis. McLean et al. reviewed a series of superficial spreading melanomas in which white depressed areas (regression) were apparent in photographs.[6] Although there was a correlation between white depressed areas and size (area) of the melanoma, there was no relationship to recurrence rate or patient survival.

The foregoing would suggest a lack of correlation between regression *per se* and prognosis in the vast majority of thin melanomas. Nevertheless, the observations of Gromet et al.[1] and Paladugu and Yonemoto[3] indicate that, in rare instances, regression may invalidate microstaging of thin melanomas. The case reports supplied by Gromet et al. also suggest, however, that several of their thin regressing melanomas that metastasized were atypical, in one or more ways, in comparison with thin melanomas in general. The clinical data supplied by Paladugu and Yonemoto are insufficient to draw similar conclusions.

There appears to be a continuum of host response in thin melanomas. The large majority, represented in our series and in most other series, have an inflammatory reaction and, in some cases, more convincing foci of regression. Such lesions may be at a relatively early stage of evolution as evidenced by their frequent small size and relatively short clinical duration. These thin melanomas have an excellent prognosis, unaffected by microscopic regression. The opposite end of the continuum may be represented by cases such as those of Smith and Stehlin, wherein patients presenting with regional lymph node metastases were found to have clinical and pathologic evidence of completely regressed melanomas.[21] It could be speculated that some (perhaps most) of the reported examples of regressing thin melanoma that metastasized occupied a position in the continuum of evolution closer to these latter cases. This is suggested by their larger size, longer clinical duration, and clinically evident regression.[1] Indeed, Gromet et al. noted that the regression in their thin metastasizing melanomas was also readily apparent microscopically but, unfortunately, this term was not defined further. It could also be speculated that, over time and in the face of regression, the biologic potential of the surviving melanoma changes. Possibly such lesions become intrinsically more aggressive, with an increased capability of producing metastases prior to the attainment of substantial microscopic thickness or invasion of the reticular dermis. It is also possible that some thin regressing melanomas were thick, high-risk lesions prior to undergoing regression.

As a corollary to the demonstration of an excellent prognosis in thin melanomas, with or without regression,

it is important to examine the issue of the width of excision. The width of excision was surprisingly narrow in a substantial number of cases in this series. By the surgeon's account, 36% had a radial excision of less than 4 cm, and only 32% were stated to have had the classic 5-cm radial excision commonly postulated as adequate during the time period of this study. The measurements in the pathology laboratory of unfixed specimens suggested that over half the patients (64%) had an excisional diameter less than 7 cm (equivalent to a radial excision less than 3.5 cm). None of the patients had local recurrence, corroborating the retrospective analyses by several groups that narrower excisions are reasonable for thin lesions.[22-27] Although our series is too small to adequately address the issue of narrower excisions, *i.e.*, 3 cm or less for thin melanomas, this would appear to be a reasonable approach for thin melanomas. In a recent report by Cosimi et al., a conservative reexcision was prospectively done in 49 patients with primary melanomas.[26] The procedure was defined as the maximum excision that would allow for primary closure. The width of excision ranged between 0.7 to 4 cm. There were no local recurrences during a 2.5 to 7-year period, but two patients developed local or regional recurrence and subsequent distant metastases and died. These authors concluded that wide excision and skin grafting were unnecessary for thin lesions.[26] A recent study by Urist et al. of a collective series of 3445 patients from the Universities of Alabama and Sidney, Australia, reported local recurrence rates of 2.1% for lesions 0.76 to 1.49 mm, 6.4% for melanomas 1.5 to 3.99 mm, and 13.1% for lesions thicker than 4 mm.[27] Among 936 patients with melanomas $\leqslant$ 1.0 mm, there were no local recurrences. Sixty-two per cent had excisional margins of 2 cm or less. It was suggested that a 1- to 2-cm margin would suffice for thin melanomas.

Although the definition of what constitutes a safe, conservative margin of excision has not been rigorously defined by clinical trial, it would appear that a radial excision of 2 to 3 cm is certainly adequate and that possibly a narrower margin of excision would suffice. It should be remembered, however, that thin melanomas on rare occasions may metastasize to lymph nodes or to distant sites. This may be an expression of the unique biology of those particular lesions rather than a consequence of the surgical technique (width of excision) or because of the presence of regression.

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