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# Late Recurrence of Malignant Melanoma

## *Analysis of 168 Patients*

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Analysis of 7104 patients with melanoma seen at Duke University identified 168 who experienced their first recurrence 10 or more years after diagnosis, for an incidence of 2.4%. This included patients with all stages of disease. There was no sex, age, or primary site predominance. The mean disease-free interval for cutaneous melanomas was 14.3 years *versus* 22.3 years for ocular primary melanomas. The prognosis following relapse was related to the site of recurrence. Survival after local or regional node recurrence was often prolonged; survival after distant metastases was usually limited. Patients with ocular primaries had the highest incidence of distant metastases, and the shortest subsequent survival. An additional 483 patients were identified who survived 10 or more years without evidence of recurrence; of these 651 patients with long disease-free intervals, 25% (168 of 651) developed recurrent disease. This demonstrates that a 10-year disease-free interval cannot be considered a cure, and emphasizes the importance of continued annual follow-up.

**T**HE MAJORITY OF recurrences and deaths resulting from malignant melanoma occur within 10 years after treatment of the original tumor. Late recurrences, defined as those occurring 10 or more years after diagnosis and treatment, have been documented in the literature but are still considered an unusual clinical course. There have been three series reported in the literature dealing with the clinical characteristics of this small subgroup of patients. Briele<sup>1</sup> described 7 patients with late recurrences; Shaw<sup>2</sup> added the largest series of 34 patients, although pathology was only available in 21 of the 34 patients. The most recent series by Callaway<sup>3</sup> describes an additional five patients with late recurrences. The lack of information on the patient characteristics, histopathology, and clinical courses of this small subgroup of interesting patients prompted us to examine the long-term

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survivors seen at the Duke Melanoma Clinic. We report here our series of 168 patients with late recurrences.

### Patients and Methods

Since its inception in 1970, the Duke University Melanoma Clinic has registered 7104 patients. A retrospective computer-aided search identified 168 patients who had a disease-free interval of 10 or more years, with a subsequent recurrence. This yields an incidence of approximately 2.4%. Patients with multiple primaries ( $n = 4$ ) were excluded. One hundred two patients of the 168 total had pathologic records available from their original primary. The remaining 66 patients did not have complete pathologic records, but did have the diagnosis of melanoma confirmed by histologic examination of their recurrent disease. For comparison the computer-aided search also identified a total of 483 patients who had survived 10 or more years, and still had no evidence of recurrence.

In most cases the initial treatment consisted of wide local excision with primary closure or split-thickness skin graft, as indicated by the location of the primary. One exception was a patient who presented with a solitary lung nodule and an unknown primary; she was treated by resection of her isolated nodule. In addition a subset of patients underwent an elective lymph node dissection (ELND) as part of their initial management. Eleven patients had tumor-involved nodes on pathologic examination and are classified as stage II disease. An additional 17 patients with stage I disease underwent ELND; the remaining 139 patients had clinical stage I disease and did not have an ELND performed. Patients with ocular melanomas were treated by enucleation.

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**Results**

The clinical characteristics of the 168 patients are presented in Table 1. Fifty-three per cent of the patients were female and 47% were male. All patients were white. The mean age at diagnosis was the same for male (39.5 years) and female (39.6 years) patients. Ninety-three per cent of patients presented with stage I disease, with only 11% undergoing an elective lymph node dissection. Six per cent of patients presented with stage II disease, with one to three involved nodes seen on pathologic examination. Only one patient presented with stage III disease; this patient presented with a solitary lung nodule and an unknown primary lesion. The majority of primary lesions were located on the extremity in female patients (59.6% of female and 17.7% of male patients) and on the trunk in male patients (58.2% of male and 23.6% of female patients). The number of head and neck primary lesions (10.1% of female and 15.2% of male patients) and ocular primary lesions (5.6% of female and 8.9% of male patients) were similar for the two groups.

The pathologic characteristics are shown in Table 2. The majority of patients had Clark's level III and IV lesions, although there were patients with lesions in all levels. Breslow measurements were available in 67% of patients (the remaining patients had Clark's level only). The majority had lesions of intermediate (1.0 to 3.0 mm) thickness (56.7%), with a mean of 1.6 mm and a range of 0.34 mm to 6.3 mm. By histologic classification, superficial spread-

TABLE 2. *Histologic Characteristics\**

Clark's Level (number of patients; percentage)	
I	1 (1.1%)
II	11 (12.4%)
III	51 (57.3%)
IV	23 (25.8%)
V	3 (3.4%)
Breslow Thickness (number of patients; percentage)†	
<0.75 mm	11 (11.3%)
0.75 to 1.0 mm	9 (15.0%)
1.01 to 3.0 mm	34 (56.7%)
3.01 to 4.0 mm	4 (6.7%)
>4.0 mm	2 (3.3%)
Histologic Type (number of patients; percentage)§	
Superficial spreading	58 (65.2%)
Nodular	14 (15.7%)
Acral lentiginous	3 (3.4%)
Lentigo maligna	2 (2.2%)
Unclassified	12 (13.5%)

\* Ocular and unknown primary lesions excluded; available for 89 patients.

† Available for 60 patients.

§ Available for 89 patients.

ing melanoma was the most common (65.2%), with most of the remaining lesions classified as nodular (15.7%). Ulceration of the primary lesion was present in 17% of the cases.

The distribution of the 168 patients according to disease-free interval and age at relapse is shown in Table 3. The majority of patients (48.2%) recurred between 10 and 12 years after the original primary. Another 23% recurred at 13 to 15 years, and approximately 14% between 16 and

TABLE 1. *Population Characteristics*

Sex (number of patients; percentage)					
	Male	79 (47.0%)			
	Female	89 (53.0%)			
Primary (number of patients; percentage)					
Site	Trunk	Extremity	Head/neck	Unknown	Ocular
Number	67 (39.9%)	67 (39.9%)	21 (12.5%)	1 (0.6%)	12 (7.1%)
Male	46	14	12	0	7
Female	21	53	9	1	5
Age at Diagnosis (number of patients; percentage)					
	10-19 yrs.	8 (4.8%)			
	20-29 yrs.	26 (15.5%)			
	30-39 yrs.	51 (30.3%)			
	40-49 yrs.	42 (25.0%)			
	50-59 yrs.	29 (17.3%)			
	60-69 yrs.	11 (6.5%)			
	70-80 yrs.	1 (0.6%)			
Stage of Disease (number of patients; percentage)					
	Stage I	156 (92.9%)			
	ELND	17			
	No ELND	139			
	Stage II	11 (6.5%)			
	Stage III	1 (0.6%)			

TABLE 3. *Disease-free Intervals and Age at Recurrence*

Age at recurrence (number of patients; percentage)	
20-29 yrs.	3 (1.8%)
30-39 yrs.	17 (10.1%)
40-49 yrs.	40 (23.8%)
50-59 yrs.	42 (25.0%)
60-69 yrs.	50 (29.8%)
70-79 yrs.	13 (7.7%)
80-90 yrs.	3 (1.8%)
Disease-free Interval (in years; percentage of patients)	
10-12 yrs.	81 (48.2%)
13-15 yrs.	38 (22.6%)
16-19 yrs.	24 (14.3%)
20-25 yrs.	15 (8.9%)
26-30 yrs.*	5 (3.0%)
30-39 yrs.†	3 (1.8%)
40-49 yrs.§	2 (1.2%)

\* Two patients had ocular primary lesions; three patients were females with extremity primary lesions.

† One patient had an ocular primary lesion; two female patients had extremity primary lesions.

§ Both patients had ocular primary lesions.

TABLE 4. Sites of Recurrence Grouped by Location of the Primary Lesion

Primary Site	Extremity (67)	Trunk (67)	Head/neck (21)	Ocular (12)
Local skin	7 (10.4%)	7 (10.4%)	3 (14.3%)	1 (8.3%)
Regional nodes/in transit	40 (59.7%)	26 (38.8%)	5 (23.8%)	0
Distant skin	2 (3.0%)	3 (4.5%)	2 (9.5%)	0
Lung	8 (11.9%)	14 (20.9%)	4 (19.0%)	1 (8.3%)
Liver	2 (3.0%)	0	1 (4.8%)	8 (66.7%)
CNS	1 (1.5%)	4 (6.0%)	0	0
Multiple sites/other*	7 (10.4%)	13 (19.4%)	6 (28.6%)	2 (16.7%)

\* Including bone and GI metastases.

19 years. A total of 25 patients relapsed after 20 years. The two longest disease-free intervals were 45 and 47 years, and both occurred in patients with ocular primaries. Of the eight patients who recurred between 26 and 40 years, three had ocular primaries and five were female patients with extremity primaries. Although the longest survivors were predominantly female (9 of 10 patients), there were approximately equal numbers of male and female patients who recurred between 20 to 25 years and between 15 to 20 years. The mean time to recurrence for all cutaneous lesions was 14.3 years; the mean time to recurrence for the 12 patients with ocular primary lesions was 22.3 years.

The patterns of recurrence were examined for each primary site and are detailed in Table 4. The actuarial survival curve for all patients, by primary site, is shown in Figure 1. The majority of recurrences associated with extremity primaries were in the local skin or regional nodes (70.1%). Of these 47 patients, 19 have died (survival time, 11 months to 6.8 years), 6 have progressive disease with a guarded prognosis (5 months to 6.9 years following relapse), and 22 are currently without evidence of disease

(follow-up, 7 months to 28 years after recurrence). More than 5 years has passed since recurrence in 10 of these 22 patients, and 5 are free of disease now for more than 10 years. Of the eight patients with pulmonary recurrences, six have died (survival time, 6 to 48 months) and two are currently without evidence of disease (3.5 and 3.8 years following recurrence). The patients with other visceral metastases, metastases at multiple sites, or distant skin metastases as the presenting site of recurrence have died (survival time, 1 to 24 months) or have evidence of progressive disease (1 to 16 months following recurrence).

For axial primaries, a local skin or regional node recurrence was still the most common presenting site (49.2%); however lung metastases were also common (20.9%). The patients with local and regional node recurrences experienced the best survival. Of these 33 patients, only six have died (survival time, 5 months to 6.3 years). Twenty-seven are alive, and 22 have no evidence of disease (8 months to 17.6 years following recurrence). Seven of these patients are free from recurrence for more than 5 years, and 3 are now disease free for more than 10 years. Of 14 patients with lung recurrences, 4 have died (survival time, 4 months to 4.1 years) and 4 have progressive disease (1 to 16 months following recurrence). The remaining six patients are currently doing well without evidence of disease (follow-up time, 6 months to 7.1 years), with 4 of 6 disease free for more than 3 years since recurrence. The patients with other distant metastases had extremely short survival times (2 to 18 months) or currently have progressive disease (1 to 14 months following recurrence).

The pattern of recurrence for the patients with head and/or neck primary lesions was similar to that seen with axial primaries, although there was a shift from local and regional recurrences to recurrences at distant sites. Only 38% of these patients presented with regional disease. Of those 8 patients, 4 have died (survival time, 22 months to 4.7 years) and 4 have no evidence of disease (4 months to 3 years following recurrence). Most patients presented with distant metastases, with limited subsequent survival. Of the 11 patients with visceral metastases, 7 have died (2 to 31 months), one has progressive disease (8 months

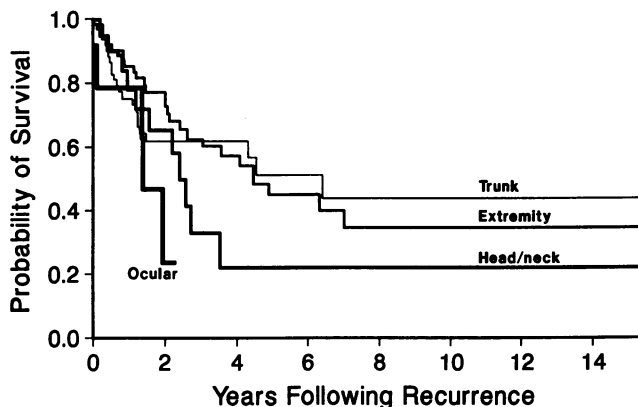


FIG. 1. Actuarial survival for all patients, by primary site. There was no statistical difference in survival between patients with extremity primaries and patients with trunk primaries. Patients with head/neck primaries tended to have a shorter survival, but this did not reach statistical significance. The shortest survival times after recurrence were in patients with ocular primary lesions ( $p < 0.05$  when compared to patients with extremity lesions).

following recurrence) and only one is currently without evidence of disease (8 months after lung recurrence).

The majority of patients with ocular primary lesions experience recurrence in the liver (67%). These patients have either died or have progressive disease (range, 1 to 24 months). The other three patients with distant recurrences also have progressive disease (1 to 2 months after recurrence) or have died (survival time, 1 month). Only one patient is currently disease free (for 28 months) after having a local recurrence.

The single patient with an unknown primary lesion experience recurrence 12 years after diagnosis, with a recurrence in the lung and distant skin. This patient died from metastatic melanoma 6 months after recurrence.

The patients with stage II disease at the time of presentation tended to experience recurrence earlier than the stage I patients. These 11 patients included 5 trunk primaries (4 male, 1 female), 5 extremity primaries (2 male, 3 female), and one male patient with a head and/or neck primary. These patients recurred at a mean of 12 years *versus* 14.3 years for cutaneous stage I patients, and experienced more distant recurrences. The sites of relapse included regional nodes or local skin (2), lung (2), distant skin (1), central nervous system (2), or multiple sites (4). Seven of these patients have died (survival time, 1, 2, 2, 6, 12, 24, and 42 months) and three have progressive disease (1 to 15 months following recurrence). Only one patient (nodal recurrence) is disease free 4 years after recurrence.

The 17 patients who had ELND experienced recurrence at a mean of 13.9 years, which is similar to the mean time to recurrence for all cutaneous stage I patients. Ten of these patients had extremity lesions, and the majority still recurred locally or in the regional nodes (60%). Four patients had trunk primaries, and recurrences were divided between local skin (50%) and distant sites (50%). Three patients had head and/or neck primaries and all lesions recurred at distant sites.

Although the menstrual status of the women in the series was not specifically known, 23 of the 89 female patients were older than 50 years, and thus were presumably postmenopausal. An additional 8 patients were between 45 and 50 years old, and also likely to be perimenopausal. A total of 45 patients were less than 39 years, and therefore were likely to be premenopausal. Only one patient was pregnant at the time of diagnosis.

### Discussion

Late recurrences from malignant melanoma occur infrequently;<sup>1-7</sup> the present study presents the clinical and pathologic characteristics of 168 patients with this unusual clinical course. Briele<sup>1</sup> reported a 6.7% incidence in his series of 105 patients; Shaw<sup>2</sup> reported a lower incidence at 2.7% in his series of 1283 patients; and Callaway<sup>3</sup> reported a 0.98% incidence in a series of 536 patients. In

our series of more than 7000 patients, the incidence was 2.4%. Of note, the database also contains 483 patients who have lived 10 or more years without a subsequent recurrence. This means that for all patients who had a disease free interval of 10 or more years (651 patients), 25% had a subsequent recurrence. This significant percentage demonstrates that a 10-year disease-free interval can not be considered a cure.

There remains a considerable degree of controversy in the literature regarding factors related to a long disease-free interval. Day<sup>8</sup> suggested that deaths from melanoma occurring after 5 years in patients without previous evidence of bony or visceral metastases occurred exclusively in patients with lesions measuring 1.70 to 3.64 mm in thickness. In the present series, mean tumor thickness was 1.6 mm, with a range of 0.34 to 6.3 mm. This is similar to the results of Callaway<sup>3</sup> (mean, 1.8 mm; range, 0.81 to 3.1 mm) and Shaw<sup>2</sup> (mean, 2.0 mm; range, 0.2 to 7.4 mm), which suggests that tumor thickness is not an absolute predictor of a long disease-free interval. Not unexpectedly the majority of lesions in this series were Clark's III and IV, and very few patients had thick (more than 4 mm) lesions. Essentially all patients with deeper primary lesions would be expected to recur within 10 years.

The influence of gonadal hormones on the disease-free interval is also an area of controversy. Briele<sup>1</sup> and Raderman<sup>4</sup> concluded from their series and literature review that premenopausal women constitute the majority of patients with late recurrences, and suggested that the endocrine system played a role in the long disease-free interval. In contrast, Shaw<sup>2</sup> and Callaway<sup>3</sup> concluded from their series that menstrual status at the time of diagnosis was not important in predicting a long disease-free interval. The present series also fails to demonstrate any advantage for premenopausal women. Although menopausal status was not specifically known for all women, nearly 30% of patients were older than 50 years, and were presumably postmenopausal. In addition approximately one half of the late recurrences occurred in men.

Callaway<sup>3</sup> also concluded from his series that women who present with primary lesions on their extremities seem to be at higher risk of developing late recurrences. Again the present study does not support this conclusion. There were approximately equal numbers of men with axial primaries to women with extremity primaries in this series. In addition, if one looks at patients with a 15- to 25-year disease-free interval, the number of female patients with primary lesions of the extremities (15) is still approximately equal to the number of men with axial primary lesions (13). Only in the group of patients with cutaneous primary lesions and extremely long disease-free intervals (more than 25 years) was there an absolute dominance of female patients with extremity lesions.

The clinical course after recurrence is variable but is

most closely related to the site of recurrence, rather than to the primary site. In our series most recurrences from extremity lesions were either local skin, in transit, or regional nodes (70.1%), and these patients had the best survival. Distant metastases were much less common and were associated with extremely short survival times. In contrast, trunk and head and/or neck primary lesions were associated with locoregional metastases in approximately 50% and 38% of cases, respectively; these patients had a higher incidence of distant metastases, which was often associated with limited survival after recurrence. Our data suggests that the survival subsequent to recurrence is related to the site of the recurrence rather than to the primary site or sex of the patient. Clearly those patients with local and regional metastases have the best survival after relapse; these patients are often women with extremity lesions. There was a higher incidence of distant metastases associated with trunk and head and/or neck primaries, with often limited survival. These patients were frequently male, due to the higher incidence of axial primaries in men.

Ocular primary lesions have been associated with an extremely high incidence of liver metastases,<sup>9</sup> and this was confirmed in our group of 12 late recurrences. The vast majority of these patients had distant metastases at the time of recurrence (92%), the majority of them hepatic (67%). These patients had extremely short survival times after relapse. Ocular primary lesions also have been associated with long disease-free intervals, and in our series five of the longest latent periods were in this patient group (47, 45, 30, 28, and 27 years). However, because most of the recurrences are hepatic, these patients have an extremely limited survival time after relapse.

The influence of ELND on the subsequent survival of patients with late recurrences has not been clearly defined. In the series by Briele,<sup>1</sup> Koh,<sup>6</sup> and Callaway,<sup>3</sup> all recurrences were either local or in the regional nodes, and none of these patients had undergone an ELND at the time of primary diagnosis and treatment. However, in these series, 12 of the 14 patients had extremity primaries, and thus would be expected to experience regional recurrence. Shaw<sup>2</sup> attributed the greater degree of distant metastases in his series to the high incidence of ELND (10 of 34 patients), concluding that patients with ELND tended to recur at distant sites, with the attendant short survival time subsequent to recurrence. The incidence of ELND in this series was extremely low (11%). Approximately 60% of patients with extremity lesions who underwent ELND still had an in transit or regional nodal

recurrence. Two patients with ELND and trunk primaries also had local recurrences (50%). This distribution of recurrence is similar to that seen for all stage I patients, and again suggests the site of recurrence is influenced by the site of the primary, and not by the presence or absence of an elective lymph node dissection.

This series also reports late recurrences in stage II patients, which has not been documented in the literature. These patients had a shorter mean disease-free interval (12.0 *versus* 14.3 years), with 9 of 11 recurring at distant sites. The one patient with prolonged survival experienced a regional node recurrence, again demonstrating the influence of the site of recurrence rather than the primary lesion. We also report one case of a stage III patient who survived 12 years before recurrence; the relapse was at a distant site (lung) and associated with only 6 months subsequent survival.

The significant percentage of patients with a disease-free interval of 10 or more years who subsequently recur (25%) emphasizes the fact that a 10-year survival interval does not represent a cure. We recommend annual follow-up examinations for all melanoma patients. Examinations should include evaluation of the primary site and regional nodes; we also recommend annual chest x-ray and liver function studies because of the significant rate of recurrence in these areas. An aggressive approach is warranted because many patients do have prolonged survival times following treatment of their recurrent disease.

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