Published in final edited form as:

J Am Coll Surg. 2013 July ; 217(1): 27–34. doi:10.1016/j.jamcollsurg.2013.03.007.

Late Recurrence in Melanoma: Clinical Implications of Lost Dormancy

Mark B Faries, MD, FACS¹, Shawn Steen, MD¹, Xing Ye, MS¹, Myung Sim, DrPH¹, and Donald L Morton, MD, FACS¹

¹John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA

Abstract

Background—For patients with melanoma, if there has been no recurrence of disease 10 years after initial treatment, additional disease is felt to be very unlikely. However, such late recurrence are known to occur. The frequency of this phenomenon and its clinical significance are not well characterized due to the difficulty in obtaining relevant data. We examined a large, mature, institutional database to evaluate late recurrence.

Study Design—The late recurrence cohort was defined as having a DFI of 10 years after potentially curative treatment and was compared to an early recurrence cohort recurring within 3 years. Actuarial late recurrence frequency and factors associated with late recurrence were examined. Post-recurrence overall and melanoma-specific survival and prognostic variables were analyzed.

Results—Among all patients, 408 exhibited late recurrence (mean DFI 15.7 years). For patients who received primary treatment at our institution with 10 years follow-up, 327/4731 (6.9%) showed late recurrence. On an actuarial basis, late recurrence rates were 6.8% and 11.3% at 15 and 20 years respectively for those with no recurrence at 10 years. Late recurrence was associated with both tumor (thin, non-ulcerated, non-head/neck, node negative) and patient (younger age, less male predominant) characteristics. Multivariate analysis confirmed younger age, thinner and node negative tumors in the late recurrence group. Late recurrences were more likely to be distant, but were associated with *better* post-recurrence survival on univariate and multivariate analyses.

Conclusions—Late melanoma recurrence is not rare. It occurs more frequently in certain clinical groups and is associated with improved post-recurrence survival.

Keywords

melanoma; late recurrence; prognosis; dormancy

The period of greatest concern for recurrence in melanoma is during the first few years after diagnosis, and survival beyond 10 years has been considered nearly synonymous with cure. However, late recurrences, defined as occurring 10 years or more after diagnosis,¹ have been

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Correspondence address: Mark B Faries, MD. 2200 Santa Monica Blvd., Santa Monica, CA 90404.

Disclosure Information: Nothing to disclose.

Presented at the Western Surgical Association 120th Scientific Session, Colorado Springs, CO, November 2012. Abstract presented at the Society of Surgical Oncology, St Louis, MO, March 2010.

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reported in a number of series. These events are difficult to study as they require a large population of patients and extensive longitudinal follow up. The established literature regarding late recurrence is quite inconsistent in estimates of frequency, predisposing factors and prognostic implications. This variability is not unexpected given the relatively small sample sizes and limited post-10 year follow up that have been available.

The late recurrence population is particularly interesting to study as it represents a group of patients exhibiting tumor dormancy. Tumor dormancy is a phenomenon that is now well described in several malignancies including melanoma and is defined as “a stage in cancer progression in which residual disease is present but remains asymptomatic.”² Study of this phenomenon may reveal both the mechanisms responsible for the indolent behavior of tumors during periods of dormancy as well as factors that lead to tumor escape and clinical presentation many years later. Tumor dormancy may also be studied by examining patients who demonstrate persistent circulating or disseminated tumor cells (CTC or DTC) after removal of all clinically evident disease.³ While such cells have now been shown to hold prognostic significance in some settings, there is incomplete correlation between their detection and recurrence.⁴

An improved understanding of tumor dormancy may have several important clinical implications. First, determination of the frequency of late recurrence and risk factors may provide a rationale for the duration of follow up in melanoma patients. Second, correlation of clinical variables with dormant behavior may suggest what mechanisms are likely to control dormancy, which may lead to strategies for capitalizing on these mechanisms. Third, an improved prognostic assessment may be made for patients who experience a late recurrence.

METHODS

Patients with the diagnosis of clinically localized, primary melanoma, who underwent potentially curative treatment on initial diagnosis, were identified from a large, prospectively maintained institutional database. Those patients with non-cutaneous melanoma (uveal or mucosal), and those who did not undergo initial attempted curative treatment were excluded as were patients with any evidence of multiple primary melanomas. Patients with disease-free intervals (DFI) of 10 years were included in the late recurrence cohort and those with melanoma recurrence within 3 years of diagnosis were included in the early recurrence cohort.

Patient characteristics were compared using Student's t-, Chi-squared and Fisher's exact tests, and trends were examined using the Cochran-Armitage Trend test. Survival was estimated using the Kaplan-Meier method and compared using logrank. Both overall survival (OS) and melanoma-specific survival (MSS) were examined. Cox multivariate logistic regression models were constructed using a stepwise selection procedure for covariates. Due to concerns that the proportional hazard assumption may not have been valid for all variables in the analysis, an accelerated failure time analysis was also performed for survival. Tests were two-tailed and considered significant at $p < 0.05$.

Due to the potential effects of initial nodal treatment on late recurrence and MSS⁵ a more homogeneous subgroup who had undergone negative surgical nodal staging at the time of diagnosis by elective lymph node dissection or sentinel lymph node biopsy was also examined.

RESULTS

We identified 408 patients with first melanoma recurrence after 10 years. Among patients treated primarily at our institution (defined as being seen within 6 months of initial diagnosis) and more than 10 years of follow up (n=4731), 327 (6.9%) demonstrated late recurrence. On actuarial basis, among all patients with no recurrence before 10 years, recurrence rates were 6.8% at 15 years and 11.3% at 25 years. An additional 86 patients (1.8%) experienced a DFI 10 years between their first and second recurrences, but were not included in this analysis. By univariate analysis late recurrence patients were more likely to be young, be female, have thinner primary lesions, have non-head/neck primary sites, have non-ulcerated primaries, and have no known regional nodal metastases (Table 1). Age, sex, Breslow thickness, Clark level, ulceration, primary tumor site, and lymph node status were included in the multivariate model, and age (< 50 years), Breslow thickness (thinner), and lymph node status (negative) were independently associated with late recurrence.

The mean age at primary diagnosis of female late recurrence patients was 39.2 years (range 16.6–77.5) and for males was 41.5 years (range 7.7–81.5 years, p=0.097). Breslow thickness was a mean of 1.23mm (range 0.1–6.0mm). The primary tumor location was significantly associated with sex, with women having 47%:35%:18% of lesions on the extremity, trunk and head and neck respectively and men having 27%:50%:23% ratio for the same (p<0.001). The mean disease free interval was 15.7 years (women 16.3 years, men 15.3 years, p=0.077.)

Recurrences of the late recurrence group were more commonly at distant sites (n=222 [54%]) rather than locoregional (n=186 [46%]). This is in distinction to early recurrence that were predominantly locoregional (n=1942 [62%]) rather than distant (n=1185 [38%]) (Chi-squared p<0.001, Figure 1A). Distant late recurrences were M1a in 63 (28%), M1b in 52 (23%) and M1c in 107 (48%). Distant early recurrence distribution was similar to the late recurrence cohort (M1a=420 [27%], M1b=455 [30%], M1c=664 [43%]) (p=0.42, Figure 1B).

Overall survival (OS) after recurrence was significantly greater in the late recurrence cohort (logrank p=0.003, data not shown). However, due to the younger age of this group, melanoma-specific survival (MSS) was felt to be a more appropriate measure. Despite the preponderance of distant recurrences in the late recurrence group, MSS was also significantly greater (p<0.001, Figure 2A). In addition, survival was improved in late recurrence patients when analyzed within each recurrence type (OS: Stage III, p=0.009, M1a, p=0.003, M1b, p=0.047, M1c, p=0.0001) (MSS: Stage III, p=0.001, M1a, p=0.007, M1b, p=0.025, M1c, p<0.0001). The curves appear to generally overlap during the first 1–2 years during which one third to one half of recurrences occur.

Cox multivariate regression was used to evaluate independent prognostic variables for post-recurrence survival. This analysis showed Breslow thickness (HR 1.03, p=0.002), primary site (extremity > trunk: HR 0.81, p=0.011), head/neck > trunk, HR 0.78, p=0.007), lymph node status (positive: HR 1.27, p=0.001), and stage of recurrence (vs. Stage III, M1a HR 1.58, p<0.001, M1b HR 2.04, p<0.001, M1c HR 4.07, p<0.001), and late vs. early recurrence (HR =0.61, p=0.002). However, due to concerns that the proportional hazard assumption may not be valid for some covariates, an accelerated failure time model was also examined. This analysis showed independent adverse effect on melanoma-specific survival of male gender (p=0.002), increasing Breslow thickness (p=0.032), lymph node metastasis (p<0.001), increased recurrence stage (p<0.001), and early recurrence (p=0.002).

Prior data from our institution demonstrated decreased late recurrences and improved survival among patients who underwent elective lymph node dissection.⁵ A lack of nodal staging may account for some of the excess regional recurrences in the early recurrence

group and could confound our analysis. We therefore identified a more homogeneous group of surgically-staged, node negative patients with Stage I/II melanoma (n=3,332). Late recurrence occurred in 58 (1.7%) patients or 3.3% of patients with 10 years follow up (n=1,740). There were 297 early recurrence patients representing 8.9% of the narrowly-defined cohort. Univariate analysis showed an association between late recurrence and younger age, thinner tumors, and less ulceration (Table 2). Sex was not significantly differently distributed between the groups (late recurrence 29% female vs. early recurrence 33% female), but the male predominance seen in the larger cohorts was even more exaggerated in both of these nodally-staged groups. A similar multivariate analysis was performed to identify factors associated with late recurrence, and younger age and thinner Breslow thickness were significant independent variables. Comparison of recurrence type showed significantly more distant recurrences in the late recurrence group (78%) than the early recurrence group (55%) (p=0.001, Figure 1A).

There were fewer melanoma deaths in the homogeneous late recurrence group overall and when compared within each recurrence stage. However, these differences did not reach statistical significance. On Cox regression, late recurrence was associated with significantly improved melanoma-specific survival (HR 0.65, p=0.042), as was a lack of ulceration, non-trunk primary site and lower recurrence stage. However, on accelerated failure time modeling, only Breslow thickness, ulceration and recurrence stage were significant.

DISCUSSION

Late recurrence is an important phenomenon in melanoma, and the presence of undetected, persistent tumor in patients has implication not only for clinical management but also for our understanding of tumor biology, particularly dormancy. When can a patient be considered “cured”? It appears the risk of melanoma recurrence is never completely gone. While late recurrence risk is probably low enough to preclude the need for invasive or expensive monitoring beyond 10 years, patients should be aware of the chance that new symptoms or physical findings could be related to their earlier melanoma diagnosis. This awareness and evaluation of new findings will be facilitated if follow up is maintained with their melanoma or primary care physician. Late recurrence risk may also impact the safety of organ donation by those with a history of melanoma, even many years earlier.⁶ Our understanding of tumor dormancy is also shaped by patients with late recurrence. Clinical characteristics associated with late recurrence may suggest mechanisms by which dormancy is maintained, and post-recurrence survival may elucidate the nature of tumor progression during the dormant period.

How common is late recurrence? As evidenced by the wide range of frequencies reported in prior series (0.41% to 25% (Table 3))^{1,7-22}, determination of the precise number is challenging. The variability may result from small sample size, inadequate long-term follow up, or referral bias. The current series provides a much larger cohort than has been previously examined and fairly extensive follow up beyond 10 years. In addition, we utilized an actuarial analysis of late recurrence which helps to control for the effect of length of follow up. By this measure the risk for LR at 15 and 25 years for those free of disease through 10 years is 6.8% and 11.3% respectively. Also, while patients with known multiple primary melanomas were excluded from this study, it is impossible to completely rule out the possibility of an occult second melanoma as the source of a late recurrence.

What clinical variables are associated with late recurrence? Most previous series of late recurrence lacked comparator populations and were unable to formally analyze risk factors.^{1,12,14,17,18,21,23-26} Several suggested it was more common among pre-menopausal women, possibly with lower extremity primary lesions, while others disputed the suggestion.

Other series used the overall melanoma population or those with no recurrence as comparators. Virtually all of these series were unable to identify factors specifically associated with late recurrence.^{8–11,16, 20} In part, this lack of significance may have been due to inadequate statistical power. For example, Shaw et al found non-significant trends for a relationship of late recurrence to younger age, female sex, thinner, non-ulcerated tumors and non-head/neck sites.²⁰

Two prior series compared late recurrence with early recurrence. Levy et al utilized their own series of 5 cases combined with 77 cases from the literature and defined early recurrence as a < 10 year DFI.¹⁵ They found the late recurrence group to contain a higher fraction of women, younger patients and thinner primary tumors. Brauer et al compared 320 early recurrence patients (<3 year DFI) to 70 LR (>8 year DFI) and found thinner, non-ulcerated lesions and a relative absence of previous non-melanoma skin cancers in the late recurrence group, but could not confirm the significance of age or sex on multivariate analysis.⁷ Our analysis would seem to unify the findings of these two prior, series in that age, gender, thickness and ulceration were all independently associated with late recurrence. While older patients may be less likely to develop late melanoma recurrences due to competing mortality risks, the mean age of the even the early recurrence cohort (51 years) would suggest that these patients would be likely to live well beyond 10 years, excluding their melanoma diagnosis. In addition, the location of the primary tumor, which had been suggested previously, was confirmed as well. This indicates that late recurrence is associated with both tumor- and host-dependent variables.

One substantial difference in recurrence patterns seen with late recurrence is the predominance of distant disease over locoregional. These patterns also appear to be influenced by the treatment at the time of primary diagnosis as had been suggested in an earlier study from our institution.⁵ In the current overall cohort, a significant number of patients did not undergo surgical staging of the regional nodal basin, and some locoregional early recurrence would have been avoided in this group if the nodes had been addressed at the time of presentation. However, this difference in recurrence site was not eliminated among patients who underwent initial nodal surgical staging. The tendency for patients with nodal metastasis at presentation to recur early and the relative absence of regional recurrence in the late recurrence population suggest that tumors that are able to spread via lymphatics are unlikely to become dormant.

What is the clinical outcome after dormancy? Very few prior series have been able to examine post-recurrence prognostic factors or even compare survival between late recurrence and early recurrence, and none to our knowledge have performed multivariate analysis. Although Crowley et al found a survival difference related to primary tumor site by univariate analysis, they stated that post-recurrence survival was dependent only on the location of the metastasis.¹ This echoed the suggestion by Shaw et al²⁰ and some others^{9,12} that late regional recurrences had better outcomes than late distant recurrences, though without statistical validation. Peters et al did not find an effect of DFI, primary site or sex on post-recurrence survival but also confirmed the significance of the site of metastasis, at least by univariate analysis.¹¹

In our study, since most late recurrences were distant and most early recurrences were regional, a comparison of all late and early recurrence patients' survivals would tend to understate the impact of DFI on outcome. However, despite this, late recurrence survivals were better. Controlling for the type of recurrence demonstrated the difference even more strikingly. Finally, multivariate analysis of the overall group demonstrated that not only site of metastasis, but also thickness, primary site, nodal status, and late vs. early recurrence

were independent and significant. With the exception of primary tumor site, these variables were confirmed on accelerated failure time modeling.

What are the implications of these findings for the study of tumor dormancy? First it provides an estimate for the frequency of clinically relevant dormant melanoma. In a recent meta-analysis of circulating tumor cell (CTC) studies in melanoma, 32% and 41.7% of Stage I and II patients respectively had positive tests.³ While there are almost certainly patients in late recurrence series with persistent, dormant melanoma who never suffer clinical recurrence, these CTC frequencies are much higher than the rate of late metastases and suggest that more work will be necessary to determine which of those positive tests are clinically relevant.

The mechanisms responsible for dormancy appear to be both host- and tumor-dependent. The same genetic and epigenetic determinants within the melanoma cells that result in thicker, ulcerated primaries may accelerate the progression of clinically undetectable disseminated cells into detectable, life-threatening metastases. Conversely, younger patients and women are more likely to delay the clinical appearance of metastases, possibly through a protective mechanism, such as immunosurveillance. It is now well established that immunocompetence declines with age, and it has recently been reported that this decline occurs earlier in men than women.²⁷ Since the mean age of female patients in the LR group was 39.2 years at the time of primary diagnosis, it is possible that exposure to female hormones has a moderating influence on disseminated tumor cells. Alternatively, the male hormonal milieu may stimulate tumor cell growth.

It has been suggested that the clinical course of patients after recurrence implies the nature of dormancy prior to recurrence. If dormancy is characterized by slow, constant but undetectable tumor growth, late recurrence patients should enjoy markedly better outcomes than early recurrence patients as measured after the time of recurrence.²⁸ Alternatively, if dormancy is a period of tumor stasis, with complete inhibition of net growth, and clinical recurrence results from an event that allows unrestrained proliferation, outcomes after recurrence of late and early patients should be equally poor.^{14,13, 25, 29} Our data suggest each scenario is partially correct.

During the immediate post-recurrence time period, survival curves of the late and early recurrence groups overlap. After 1–2 years when approximately one half to one third of recurrences have occurred, the curves begin to separate and the differences increase from that point on. This suggests that for a substantial minority of patients, there is no protection offered by the extended disease-free interval. That is, whatever beneficial mechanisms existed to induce dormancy are totally lost. However, a substantial fraction of patients continue to enjoy relatively favorable tumor behavior even after recurrence, and for those patients some of the protective mechanisms may still be in place.

Overall, this represents the largest group of late recurrence patients yet reported. The late recurrence population appears to be weighted toward younger patients and women with generally more favorable tumor characteristics. By both univariate and multivariate analyses, survival after recurrence is improved among late recurrence patients relative to early recurrence patients. Tumor dormancy appears to be related to both patient and tumor factors and is only partially lost at the time of recurrence.

Acknowledgments

Supported by grants P01 CA29605 and P01 CA12582 from the National Cancer Institute and by funding from the Melanoma Research Alliance (Washington, DC), Dr Miriam & Sheldon G Adelson Medical Research Foundation (Boston, MA), the Lincy Foundation (Beverly Hills, CA), the Amyx Foundation, Inc. (Boise, ID), Alan and Brenda

Borstein (Los Angeles, CA), Mr and Mrs Louis Johnson (Stanfield, AZ), Heather and Jim Murren (Las Vegas, NV), the Wayne and Gladys Valley Foundation (Oakland, CA), the Lance Armstrong Foundation (Austin, TX), the Samueli Foundation (Corona del Mar, CA), the John Wayne Cancer Foundation (Newport Beach, CA), and the Wrather Family Foundation (Los Alamos, CA). Dr Steen is the Carolyn Dirks Fellow (Los Angeles, CA). The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Cancer Institute or the National Institutes of Health.

References

1. Crowley NJ, Seigler HF. Late recurrence of malignant melanoma. Analysis of 168 patients. *Ann Surg.* 1990; 212:173–177. [PubMed: 2375648]
2. Aguirre-Ghiso JA. Models, mechanisms and clinical evidence for cancer dormancy. *Nature reviews Cancer.* 2007; 7:834–846.
3. Mocellin S, Hoon D, Ambrosi A, et al. The prognostic value of circulating tumor cells in patients with melanoma: a systematic review and meta-analysis. *Clin Cancer Res.* 2006; 12:4605–4613. [PubMed: 16899608]
4. Hoshimoto S, Shingai T, Morton DL, et al. Association between circulating tumor cells and prognosis in patients with stage iii melanoma with sentinel lymph node metastasis in a phase III international multicenter trial. *J Clin Oncol.* 2012 Sep 24. [Epub ahead of print].
5. Shen P, Guenther JM, Wanek LA, et al. Can elective lymph node dissection decrease the frequency and mortality rate of late melanoma recurrences? *Ann Surg Oncol.* 2000; 7:114–119. [PubMed: 10761789]
6. Mackie R, Reid R, Junor B. Fatal melanoma transferred in a donated kidney 16 years after melanoma surgery. *N Engl J Med.* 2003; 34:567–568. [PubMed: 12571271]
7. Brauer JA, Wriston CC, Troxel AB, et al. Characteristics associated with early and late melanoma metastases. *Cancer.* 2010; 116:415–423. [PubMed: 19918926]
8. Hansel G, Schonlebe J, Haroske G, et al. Late recurrence (10 years or more) of malignant melanoma in south-east Germany (Saxony). A single-centre analysis of 1881 patients with a follow-up of 10 years or more. *J Eur Acad Dermatol Venereol.* 2010; 24:833–836. [PubMed: 20070457]
9. Leman JA, Mac Kie RM. Late (> 10 years) recurrence of melanoma: the Scottish experience. *Br J Dermatol.* 2003; 148:372–373. [PubMed: 12588404]
10. Schmid-Wendtner MH, Baumert J, Schmidt M, et al. Late metastases of cutaneous melanoma: an analysis of 31 patients. *J Am Acad Dermatol.* 2000; 43:605–609. [PubMed: 11004614]
11. Peters A, Lippold A, Hundeiker M. [First melanoma metastases after 10 years and more of remission]. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete.* 1997; 48:311–317.
12. Tsao H, Cosimi AB, Sober AJ. Ultra-late recurrence (15 years or longer) of cutaneous melanoma. *Cancer.* 1997; 79:2361–2370. [PubMed: 9191524]
13. Pearlman NW, Takach TJ, Robinson WA, et al. A case-control study of late recurrence of malignant melanoma. *Am J Surg.* 1992; 164:458–460. discussion 460–461. [PubMed: 1443369]
14. Tahery DP, Moy RL. Lack of predictive factors in late recurrence of stage I melanoma. *Int J Dermatol.* 1992; 31:629–631. [PubMed: 1459759]
15. Levy E, Silverman MK, Vossaert KA, et al. Late recurrence of malignant melanoma: a report of five cases, a review of the literature and a study of associated factors. *Melanoma Res.* 1991; 1:63–67. [PubMed: 1822771]
16. McEwan L, Smith JG, Matthews JP. Late recurrence of localized cutaneous melanoma: its influence on follow-up policy. *Plast Reconstruct Surg.* 1990; 86:527–534.
17. Callaway MP, Briggs JC. The incidence of late recurrence (greater than 10 years); an analysis of 536 consecutive cases of cutaneous melanoma. *Br J Plast Surg.* 1989; 42:46–49. [PubMed: 2917216]
18. Gutman M, Klausner JM, Inbar M, et al. Late recurrence of stage I malignant melanoma. *J Surg Oncol.* 1989; 42:96–98. [PubMed: 2796353]
19. Landthaler M, Braun-Falco O, Schlamminger F, et al. Late metastasis in malignant melanoma of the skin. *Deutsche medizinische Wochenschrift.* 1989; 114:1149–1152. [PubMed: 2752919]

20. Shaw HM, Beattie CW, McCarthy WH, et al. Late relapse from cutaneous stage I malignant melanoma. *Arch Surg.* 1985; 120:1155–1159. [PubMed: 4038058]
21. Briele HA, Beattie CW, Ronan SG, et al. Late recurrence of cutaneous melanoma. *Arch Surg.* 1983; 118:800–803. [PubMed: 6860127]
22. Wilbur D, Hartman H. Malignant melanoma with delayed metastatic growths. *Ann Intern Med.* 1931; 5:201–211.
23. Gamel JW, George SL, Edwards MJ, et al. The long-term clinical course of patients with cutaneous melanoma. *Cancer.* 2002; 95:1286–1293. [PubMed: 12216097]
24. Koh HK, Sober AJ, Fitzpatrick TB. Late recurrence (beyond ten years) of cutaneous malignant melanoma. Report of two cases and a review of the literature. *JAMA.* 1984; 251:1859–1862. [PubMed: 6700088]
25. Raderman D, Giler S, Rothem A, et al. Late metastases (beyond ten years) of cutaneous malignant melanoma. Literature review and case report. *J Am Acad Dermatol.* 1986; 15:374–378. [PubMed: 3734186]
26. Kofler R, Rieger E, Soyer HP, et al. [Late metastasis of malignant cutaneous melanoma]. *Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und verwandte Gebiete.* 1994; 45:145–148.
27. Yan J, Greer JM, Hull R, et al. The effect of ageing on human lymphocyte subsets: comparison of males and females. *Immunity Ageing.* 2010; 7:4. [PubMed: 20233447]
28. Karakousis CP, Temple DF, Moore R, et al. Prognostic parameters in recurrent malignant melanoma. *Cancer.* 1983; 52:575–579. [PubMed: 6861095]
29. Yarnold JR, Cochrane JP. Malignant melanoma: significance of disease-free interval. *Br J Radiol.* 1980; 53:1068–1070. [PubMed: 7426933]

Figure 1.

(A) Distribution of recurrence types in early recurrence (1, 2) and late recurrence (3, 4) for the overall cohort (1, 3) and for patients who had undergone negative surgical staging of regional lymph nodes at the time of presentation (2, 4). Light gray slice, regional metastasis; dark gray slice, distant metastasis. (B) Distribution of distant recurrence types, (1) early recurrence; (2) late recurrence ($p=0.38$). Light gray slice, M1a; medium gray slice, M1b; dark gray slice, M1c.

Figure 2. Melanoma-specific survival, comparison for late recurrence and early recurrence patients. (A) All patients combined; (B) by stage of recurrence.

Table 1

Demographic and Pathologic Characteristics

	Late, n=408	Early, n=3127	Univariable p value	Multivariable p value
Age, mean, y	41	51	<0.001	p=0.002
Sex male:female, n (%)	235:171 (57:43)	2054:1070 (66:34)	0.002	NS
Breslow	1.23	2.93	<0.001	p<0.001
Clark				
I-III	196 (45)	816 (27)	<0.001	NS
IV	75 (17)	1382 (45)		
V	4 (0.9)	339 (10)		
Unknown	163 (37)	553 (18)		
Ulcerated, %	5.4	24.0	<0.001	NS
Primary site, n (%)				
Extremity	155 (38)	1082 (35)	0.011	NS
Trunk	185 (45)	1307 (42)		
Head/neck	68 (17)	716 (23)		
Node status, -:+, n (%)	100:12 (89:11)	675:752 (47:53)	<0.001	p<0.001

Table 2

Demographic and pathologic characteristics: Homogeneous cohort

	Late, n=58	Early, n=297	Univariable p value	Multivariable p value
Age, mean, y	45	53	<0.001	0.008
Sex male:female, n (%)	41:17 (71:29)	199:98 (67:33)	0.56	NS
Breslow	1.50	3.10	<0.001	<0.001
Ulcerated, %	15	38	0.002	NS
Primary site, n (%)				
Extremity	20 (34)	101 (34)	0.064	NS
Trunk	28 (48)	104 (35)		
Head/neck	10 (17)	92 (31)		

Published Series of Late Recurrence in Melanoma

Table 3

					Sex				Primary site			Recurrence type			Distant disease type			
First author	Year	LR, n	>10 y, n		Female, n	Male, n	Age, y, mean		Extremity	Trunk	H/N	Loco-regional	Distant	Mla	Mlb	Mlc	Breslow, mean	
Braue ^{7,*}	2010	70	NR	NR	NR	NR	46		NR	NR	NR	23	42	NR	NR	NR	1.48	
Hansel ⁸	2010	19	1881		12	7	46		13	6	0	12	7	2	2	3	2.24	
Lenan ⁹	2003	25	3822		13	12	54		NR	NR	NR	7	17	NR	NR	NR	2.21	
Schmidt-Wendner ¹⁰	2000	31	1026		15	16	43		9	16	6	15	14	1	4	9	1.42	
Shen ^{5,†}	2000	217	1907		96	121	38		73	103	40	127	90	NR	NR	NR	1.3	
Peters ¹¹	1997	36	1015		20	16	46		16	12	8	13	23	NR	NR	NR	1.78	
Tsao ^{12,‡}	1997	20	1010		10	10	36		10	7	3	9	11	2	3	6	1.38	
Pearlman ¹³	1992	19	NR	NR	NR	NR	NR		NR	NR	NR	10	9	NR	NR	NR	NR	
Tahery ¹⁴	1992	8	956		3	5	45		6	2	0	5	3	NR	NR	NR	1.85	
Levy ¹⁵	1991	5	NR	NR	4	1	29		3	2	0	2	3	0	0	3	1.03	
Crowley ¹	1990	168	651		89	79	40		67	67	21	88	66	7	26	33	1.6	
McEwan ¹⁶	1990	11	264		7	4	45		6	3	2	7	4				1.31	
Callaway ¹⁷	1989	5	NR	NR	5	0	51		4	0	1	5	0	0	0	0	1.8	
Gutman ¹⁸	1989	6	94		2	4	39		4	2	0	0	6	2	0	4	NR	
Landthaler ¹⁹	1989	10	NR	NR	7	3	45		4	4	2	6	4	NR	NR	NR	1.71	
Shaw ²⁰	1985	34	1283		16	18	39		18	11	5	18	16	7	3	6	2	
Briele ²¹	1983	7	105		6	1	33		6	1	0	7	0	0	0	0	1.91	
Wilbut ²²	1931	3	NR	NR	2	1	42		1	0	2	0	3	NR	NR	NR	NR	
Summary (non-JWCI)		477	3.01% of 12,107		204 (54%)	174 (46%)	40		163 (48%)	129 (38%)	48 (14%)	198 (52%)	182 (48%)	21 (17%)	38 (31%)	64 (52%)	1.64	
Present study	2011	408	6.9% of 3,538		171 (42%)	235 (58%)	41		155 (38%)	185 (45%)	68 (17%)	186 (46%)	222 (54%)	63 (28%)	52 (23%)	107 (48%)	1.23	

* Late recurrence 8 y.

‡ John Wayne Cancer Institute study (not included in summary totals).

‡ Late recurrence 15 y.

LR, late recurrence; H/N, head and neck, NR: Not reported.