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Outcomes and prognostic factors in superficial spreading melanoma

Michael E. Egger, M.D.\textsuperscript{a}, Lindsay O. Stepp, M.D.\textsuperscript{a}, Glenda G. Callender, M.D.\textsuperscript{b}, Amy R. Quillo, M.D.\textsuperscript{a}, Robert C. G. Martin, II, M.D., Ph.D.\textsuperscript{a}, Charles R. Scoggins, M.D., M.B.A.\textsuperscript{a}, Arnold J. Stromberg, Ph.D.\textsuperscript{c}, Kelly M. McMasters, M.D., Ph.D.\textsuperscript{a,*}

\textsuperscript{a}Hiram C. Polk Jr MD Department of Surgery, University of Louisville, 550 South Jackson Street, Louisville, KY 40202, USA; \textsuperscript{b}Department of Surgery, Yale University School of Medicine, New Haven, CT, USA; \textsuperscript{c}Department of Statistics, University of Kentucky, Lexington, KY, USA

KEYWORDS:
Superficial spreading melanoma; Sentinel lymph node biopsy melanoma; Lymphovascular invasion; Nonsentinel lymph node melanoma; Melanoma histology; Melanoma prognosis

Abstract

\textbf{BACKGROUND:} Prognostic factors and risk factors for positive sentinel lymph node (SLN) biopsy results are important to identify in superficial spreading melanoma (SSM).

\textbf{METHODS:} A single-center database and a prospective clinical trial database were reviewed for all patients with diagnoses of SSM. Logistic regression, Kaplan-Meier survival analysis, and univariate and multivariate Cox models were used.

\textbf{RESULTS:} A total of 1,643 patients with SSM were identified. Independent risk factors for positive SLN biopsy results were Breslow thickness (BT) \( \geq 2.0 \) mm, age \(<60\) years, and presence of ulceration. BT \( \geq 2.0 \) mm, ulceration, lymphovascular invasion, and positive SLN and positive non-SLN biopsy results were independent risk factors for worse disease-free survival. Independent overall survival risk factors included BT \( \geq 2.0 \) mm, age \( \geq 60 \) years, ulceration, nonextremity tumor location, lymphovascular invasion, and positive SLN biopsy results.

\textbf{CONCLUSIONS:} BT, ulceration, lymphovascular invasion, and SLN and non-SLN status are important risk factors for SSM.

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Superficial spreading melanoma is a distinct histologic subtype of cutaneous melanoma characterized by a predominant radial growth phase.\textsuperscript{1} It is the most common histologic subtype in the United States and represents the highest proportion of fatal melanomas.\textsuperscript{2} The overall incidence of superficial spreading melanoma has increased in the United States, but relative survival has improved, and the incidence of fatal superficial spreading melanoma has remained steady.\textsuperscript{2} There has been a trend of reduced Breslow thickness at the time of diagnosis and an increase in stage I superficial spreading melanoma, suggesting improvements in detection of this subtype.\textsuperscript{3} Thus, superficial spreading melanoma remains an important histologic subtype to investigate.

The histologic findings of superficial spreading melanoma suggest that there are unifying molecular
characteristics distinguishing this subtype from others. The frequencies of BRAF and NRAS mutations are different for superficial spreading and nodular melanoma. Although survival rates for superficial spreading melanoma have increased over recent decades, it is still the most common subtype and remains the most common subtype for fatal cutaneous melanoma. This study was performed in an effort to describe the clinicopathologic factors of a large subset of patients with superficial spreading melanoma to identify factors associated with prognosis.

**Methods**

This study was a retrospective review of patients from the Sunbelt Melanoma Trial and the prospectively managed University of Louisville Melanoma Database. The institutional review boards of each participating center approved participation in the trial; review of deidentified data from the Sunbelt Melanoma Trial and the University of Louisville Melanoma Database was approved by the institutional review board of the University of Louisville. The details of the Sunbelt Melanoma Trial have been described previously. By virtue of the inclusion criteria of the trial, all patients in this study from the Sunbelt Melanoma Trial had primary melanoma with Breslow thickness $\geq 1.0$ mm and no clinical evidence of lymphatic or distant metastases. All were staged with sentinel lymph node (SLN) biopsies, and complete lymphadenectomy was performed for positive SLN biopsy results. Patients from the University of Louisville Melanoma Database were included with any Breslow thickness. Our general practice is to perform SLN biopsy in all patients with Breslow thickness $\geq 1.0$ mm or those with Breslow thickness $<1.0$ mm and aggressive features such as ulceration or high mitotic rate. In general, all patients underwent complete lymphadenectomy for positive SLN biopsy results, with the exception of extenuating clinical circumstances or enrollment in clinical trials. Patients with pathologic diagnoses of superficial spreading primary cutaneous melanoma were included in this study.

Risk factors for positive SLN biopsy results were analyzed using univariate and multivariate logistic regression analysis; odds ratios with 95% confidence intervals (CIs) are reported. Univariate and multivariate Cox proportional-hazards models were used to estimate risk factors for survival; 95% CIs are reported. Variables were entered into the multivariate model if their $P$ values on univariate analysis were $\leq .10$. Survival time was measured from the time of SLN biopsy or wide local excision in instances in which SLN biopsy was not performed. Overall survival (OS) event was death from any cause, disease-free survival (DFS) event was any type of recurrence, and local and in-transit recurrence-free survival (LITRFS) event was defined as a recurrence within 5 cm of the primary tumor or between the primary tumor and the draining nodal basin. Kaplan-Meier survival analysis was performed for the aforementioned survival times, and the log-rank test was used to determine survival differences. Statistical significance was considered at $P$ values $<.05$. JMP version 9.0 (SAS Institute Inc, Cary, NC) was used for analysis.

**Results**

There were 1,643 patients identified with superficial spreading primary melanoma. 1,169 from the Sunbelt Melanoma Trial (71.2%) and 474 from the University of Louisville Melanoma Database (28.8%), with a median follow-up duration of 62 months. All patients from the Sunbelt Melanoma Trial had primary melanoma with Breslow thickness $\geq 1.0$ mm. In the University of Louisville database, 295 patients had primary melanoma with Breslow thickness $<1.0$ mm; 18 of these underwent SLN biopsy, and all results were negative. A slight majority of patients were men (55.3%). Regression and ulceration were relatively uncommon (18.6% and 18.1%, respectively). Lymphovascular invasion (LVI) was present in only 5.9% of patients. SLN biopsy results were positive in 220 patients (17.6% of those who underwent SLN biopsy). Multivariate logistic regression determined that Breslow

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tr>
<td></td>
<td>Risk ratio (95% CI)</td>
<td>$P$</td>
</tr>
<tr>
<td>Breslow thickness $\geq 2.0$ mm</td>
<td>3.54 (2.69–4.64)</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Age $\geq 60$ y</td>
<td>1.13 (.84–1.49)</td>
<td>.4207</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.20 (.91–1.58)</td>
<td>.1970</td>
</tr>
<tr>
<td>Clark level $\geq IV$</td>
<td>2.05 (1.48–2.89)</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Regression present</td>
<td>.72 (.45–1.09)</td>
<td>.1272</td>
</tr>
<tr>
<td>Ulceration present</td>
<td>3.15 (2.35–4.18)</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Extremity tumor location</td>
<td>.84 (.64–1.10)</td>
<td>.1964</td>
</tr>
<tr>
<td>LVI present</td>
<td>2.70 (1.67–4.13)</td>
<td>.0002</td>
</tr>
<tr>
<td>SLN positive</td>
<td>2.86 (2.11–3.82)</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Non-SLN positive</td>
<td>3.72 (2.24–5.94)</td>
<td>$&lt;.0001$</td>
</tr>
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Factors with univariate $P$ values $>.10$ were not considered in the multivariate model. CI = confidence interval; LVI = lymphovascular invasion; SLN = sentinel lymph node.
thickness \( \geq 2.0 \text{mm} \) (adjusted odds ratio, 3.90; 95% CI, 2.78 to 5.48; \( P < .0001 \)) and ulceration (adjusted odds ratio, 2.58; 95% CI, 1.81 to 3.67; \( P < .0001 \)) were independent risk factors for positive SLN biopsy results, while age \( \geq 60 \) years reduced the risk for positive SLN biopsy results by nearly 50% (adjusted odds ratio,.53; 95% CI,.35 to .78; \( P = .0011 \)).

Univariate and multivariate risk factors for worse DFS are summarized in Table 1. Breslow thickness \( \geq 2.0 \text{mm} \), ulceration, presence of LVI, positive SLN biopsy results, and positive non-SLN biopsy results after lymphadenectomy were significant independent risk factors on multivariate analysis. Independent risk factors for LITRFS included Breslow thickness \( \geq 2.0 \text{mm} \) (risk ratio, 2.44; 95% CI, 1.56 to 4.06; \( P = .0007 \)), ulceration (risk ratio, 1.98; 95% CI, 1.20 to 3.19; \( P = .0078 \)), LVI (risk ratio, 2.52; 95% CI, 1.21 to 4.71; \( P = .0156 \)), and positive SLN biopsy results (risk ratio, 1.75; 95% CI, 1.02 to 2.93; \( P = .0418 \)) and non-SLN after lymphadenectomy (risk ratio, 3.12; 95% CI, 1.45 to 6.14; \( P = .0051 \)). Independent risk factors for worse OS included Breslow thickness \( \geq 2.0 \text{mm} \), age \( \geq 60 \) years, nonextremity tumor location, ulceration, LVI, and positive SLN biopsy results (Table 2).

Kaplan-Meier survival analysis demonstrated that age \( \geq 60 \) years, male gender, Breslow thickness \( \geq 2.0 \text{mm} \), nonextremity primary tumor location, presence of ulceration or LVI, and positive SLN and non-SLN status were all associated with worse OS (Fig. 1). Clark level \( \geq IV \) was also an independent risk factor for OS, DFS, and LITRFS (not shown). Statistically significant DFS and LITRFS risk factors were the same: Breslow thickness \( \geq 2.0 \text{mm} \), presence of ulceration or LVI, and positive SLN or non-SLN status (Fig. 2; LITRFS not shown).

**Comments**

The most important finding in this work is that in addition to the usual prognostic factors such as Breslow thickness, ulceration, and SLN status, we identified additional risk factors for worse outcomes in patients with superficial spreading melanoma. A positive non-SLN after completion lymphadenectomy was a significant risk factor for recurrence, including local and in-transit recurrence. The presence of LVI was a significant risk factor for both worse recurrence risk and survival.

Superficial spreading melanoma is increasing in incidence and remains the most common histologic subtype, in general and in young adults. Non-SLN positive 1.72 (1.00–2.81) .0516 1.08 (.64–1.74) .7532

Superficial spreading melanoma is increasing in incidence and remains the most common histologic subtype, in general and in young adults. Although tumor characteristics other than histologic subtype are used in the American Joint Committee on Cancer 2009 staging guidelines, it is important to identify unique risk factors for each histologic subtype. These subtypes may have unique associations with gene mutations and sun exposure patterns, which may influence how they progress and how they can be treated. Superficial spreading melanoma appears to be more strongly related to intermittent sun exposure and sunburn. The V600E BRAF mutation is more common in superficial spreading melanoma, which has important implications for treatment options in stage IV disease. For these reasons, it is important to define the specific prognostic factors in superficial spreading melanoma.

Breslow thickness, ulceration, and the status of the SLN are the most powerful predictors of prognosis in all types of cutaneous melanoma. The findings in this study confirm the importance of these 3 factors when considering only superficial spreading melanoma. These factors were all independently associated with worse OS, DFS, and LITRFS. Breslow thickness and ulceration were also independent risk factors for positive SLN biopsy results. Similar to other reports that included all histologic subtypes, age was inversely related to the risk for positive SLN biopsy results. In this series, patients aged \( \geq 60 \) years with superficial spreading melanoma had nearly half the risk for positive SLN biopsy compared with younger patients. The reasons for this inverse relationship remain to be elucidated.

**Table 2** Univariate and multivariate analyses of risk factors for overall survival in superficial spreading melanoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk ratio (95% CI)</th>
<th>( P )</th>
<th>Risk ratio (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow thickness ( \geq 2.0 \text{mm} )</td>
<td>2.93 (2.32–3.68)</td>
<td>&lt;.0001</td>
<td>1.85 (1.40–2.43)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age ( \geq 60 ) y</td>
<td>1.65 (1.31–2.07)</td>
<td>&lt;.0001</td>
<td>1.77 (1.39–2.25)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.66 (1.31–2.11)</td>
<td>&lt;.0001</td>
<td>1.17 (.90–1.52)</td>
<td>.2384</td>
</tr>
<tr>
<td>Clark level ( \geq IV )</td>
<td>1.67 (1.28–2.18)</td>
<td>&lt;.0001</td>
<td>1.21 (.92–1.61)</td>
<td>.1788</td>
</tr>
<tr>
<td>Regression present</td>
<td>.85 (.59–1.20)</td>
<td>.3698</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration presence</td>
<td>2.84 (2.22–3.62)</td>
<td>&lt;.0001</td>
<td>1.89 (1.44–2.47)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Extremity tumor location</td>
<td>.60 (.47–.76)</td>
<td>&lt;.0001</td>
<td>.63 (.49–.81)</td>
<td>.0004</td>
</tr>
<tr>
<td>LVI present</td>
<td>2.16 (1.41–3.16)</td>
<td>.0007</td>
<td>1.73 (1.13–2.54)</td>
<td>.0135</td>
</tr>
<tr>
<td>SLN positive</td>
<td>2.94 (2.28–3.75)</td>
<td>&lt;.0001</td>
<td>2.11 (1.58–2.81)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-SLN positive</td>
<td>1.72 (1.00–2.81)</td>
<td>.0516</td>
<td>1.08 (.64–1.74)</td>
<td>.7532</td>
</tr>
</tbody>
</table>

Factors with univariate \( P \) values >.10 were not considered in the multivariate model.

\( CI = \) confidence interval; LVI = lymphovascular invasion; SLN = sentinel lymph node.
In this study, the status of the non-SLNs had important prognostic significance. A positive non-SLN was an independent risk factor for worse DFS and LITRFS but not OS. In all histologic subtypes, there is emerging evidence that the status of the non-SLN carries important prognostic significance independent of any increase in the absolute positive lymph node count.\textsuperscript{17–20} The status of the non-SLN is an important factor in the survival estimates calculated by our electronic melanoma risk calculator (http://www.melanomacalculator.com, and melanoma calculator app available for handheld devices).\textsuperscript{21} In superficial spreading melanoma, the importance of the status of the non-SLN seems to be related to the risk for recurrence, especially local disease control failure. Although worse DFS was seen in superficial spreading melanoma for patients with positive non-SLNs, there was no

Figure 1  Risk factors for worse overall survival in superficial spreading melanoma include Breslow thickness $\geq 2.0$ mm (A), positive SLN biopsy results (B), age $\geq 60$ years (C), nonextremity primary tumor location (D), and presence of ulceration (E) or LVI (F).
difference in OS on multivariate Cox survival analysis, though there was a significant difference in OS on univariate Kaplan-Meier analysis (data not shown). The significant increase in local and in-transit recurrence risk might explain this discrepancy. The recurrences for patients with positive non-SLN seem to be mostly local disease control failure, which is much easier to treat than systemic recurrences and likely does not affect OS to the degree that systemic recurrences would. Regardless, the status of the non-SLN is an important prognostic factor to consider in superficial spreading melanoma.

An interesting finding in this study is that the presence of LVI was an independent risk factor for worse DFS, LITRFS, and OS. LVI was relatively rare in this

![Figure 2](image.png)

**Figure 2** Risk factors for worse DFS in patients with superficial spreading melanoma include Breslow thickness $\geq 2.0$ mm (A), presence of ulceration (B) or LVI (C), and positive SLNs (D) or non-SLN (E).
population (5.9%). Previously, we found that LVI was an independent risk factor for positive SLN biopsy results but was not an independent risk factor for worse DFS and OS in an analysis of all histologic subtypes from the Sunbelt Melanoma Trial. In this study of superficial spreading melanoma, LVI was not associated with positive SLN biopsy results. The importance of LVI in melanoma is not well understood. Relatively few studies have found that LVI is an important risk factor for survival in melanoma. Larger series have found that LVI may be associated with positive SLN biopsy results and that dedicated immunohistochemical studies may improve the detection and prognostic significance of LVI. In previous studies examining nodular and acral lentiginous melanoma, we found the LVI was not a risk factor for worse survival, suggesting that LVI may play a unique role in the risk assessment of superficial spreading melanoma. Previous work examining only thin (≤1.0 mm) melanomas staged with SLN biopsy found that LVI was a risk factor for a positive SLN; the majority of these patients had superficial spreading histology. The effect of LVI may be more pronounced in thinner melanomas, which is also consistent with superficial spreading histology and our findings in this study.

Although we examined a large series of patients with superficial spreading melanoma from multiple institutions, the findings need to be interpreted with its limitations in mind. This was a retrospective review and was thus subject to the inherent limitations of retrospective studies. Determining survival differences among different histologic subtypes was not a primary aim of the Sunbelt Melanoma Trial. Although the external validity of the study may have been improved by including our local experience from the University of Louisville Melanoma Database and increasing the heterogeneity of the study population, concerns with drawing conclusions from multiple study populations are reasonable. Most of the patients in this study (71.2%) were from the Sunbelt Melanoma Trial and were thus limited to those with Breslow thickness ≥1.0 mm and no clinical evidence of stage III or IV disease. Most of the University of Louisville patients had Breslow thickness <1.0 mm. Our findings are thus limited to patients with no clinical evidence of stage III or IV disease with superficial spreading melanoma, but they may be valid over a range of Breslow thicknesses. We used OS as an end point rather than melanoma-specific survival. Although OS is a useful survival measure, we may have captured a small but significant number of patients who died of non-melanoma-related causes, particularly in the elderly. Mitotic rate is another pathologic measure of interest in melanoma prognosis, particularly in thinner melanomas, that was lacking in this study. Mitotic rate was inconsistently reported in the Sunbelt Melanoma Trial experience, so we do not have these data for all patients in this study.

Conclusions

We report one of the largest series exclusively examining superficial spreading melanoma. In addition to the usual prognostic factors for cutaneous melanoma, which include Breslow thickness, ulceration, and SLN status, we found that the status of the non-SLN and the presence of primary tumor LVI were important risk factors for recurrence and survival. Patients with superficial spreading melanoma and LVI should be considered at increased risk for local recurrence and decreased survival.

References


Discussion

Barbara Pockaj, M.D. (Phoenix, AZ): I want to thank the authors from the University of Louisville to further enhance our understanding of melanoma and its associated risk factors for both lymph node metastasis and survival. I enjoyed reading your manuscript and I have a couple of questions: (1) Mitotic index has been shown to be an important prognostic factor for melanoma especially when associated with survival. In your paper there is no discussion of mitotic index. Can you explain why this was left out? (2) Factors for disease free survival and local-in transit free survival were similar with regard to multivariate analysis. Do you think that melanoma specific survival may be a better indicator of the impact of these risk factors? (3) Lymphovascular invasion is a poor prognostic marker for a variety of cancers, such as breast and colon cancer. Other investigators have shown that lymphovascular invasion to be an important prognostic factor for sentinel lymph node metastases, in transit recurrences, and overall survival. Can you comment or give a biologic reason why in your series this was only shown for superficial spreading melanomas and not the other types of melanoma?

Michael E. Egger, M.D. (Louisville, KY): Thank you for the questions. Mitotic index is not reported. We don’t have those data for the majority of patients, both in Sunbelt or U of L. We have previously looked back at about 500 of the 3,000 patients from Sunbelt for whom we did have mitotic indices and in that analysis we did not find that mitotic index was that significant. But perhaps mitotic index may be an important, subtle risk factor in this subgroup of superficial spreading melanoma, similar to lymphovascular invasion. It’s certainly worthwhile to go back and see what kind of data we have in this subset. We don’t have melanoma specific survival in our database. I agree that melanoma specific survival may be a more precise outcome compared to overall survival. However, we also like to use overall survival because it is certainly less subjective in its measurement as opposed to trying to figure out what exactly is melanoma specific survival.

Regarding lymphovascular invasion: perhaps it is a subtle risk factor and so when one combines all the histologies together, you lose the importance of lymphovascular invasion in the face of more powerful risk factors. Certainly when you start considering nodular melanoma, when they are already such thick tumors and have such high rates of ulceration, I think those risk factors really overpower any of the subtle differences you may see with lymphovascular invasion. It appears that in the superficial spreading population, they are relatively thin lesions and those patients should do relatively well, but the subtle prognostic value of lymphovascular invasion comes into play. As far as a more precise biologic reason for why this is the case, as we move towards a molecular classification of melanoma rather than the histologic evaluations that we are using now, as we start teasing out the mutations and the drivers behind these different melanomas, hopefully some answers will emerge and we can start making sense on why certain things like mitotic index, lymphovascular invasion, etc. are or are not important.

Randall Smith, M.D. (Temple, TX): It looked like the Sunbelt patients and the University of Louisville patients were 2 different groups of patients. Why group them together?

Dr Egger: Whenever we look at Sunbelt patients, one reasonable criticism is they are a very select group of patients. Breslow thickness is at least 1 mm and they are clinically node negative patients. We combined the databases in this analysis to make our conclusion more generalizable to wider patient populations. Because superficial spreading melanomas are relatively thin, the University of Louisville data brought about 300 patients that were <1 mm thick, so we can start gathering some prognostic information from those thinner patients and maybe some of these risk factors can be applicable to that population as well.

Ken Westbrook, M.D. (Little Rock, AR): I enjoyed your presentation and I think you have shown very clearly that multiple factors influence the status of the lymph nodes and long-term outcome. Let me ask you a more basic question. Do you believe that sentinel lymph node biopsy improves the long-term outcome in melanoma?
Dr Egger: What an excellent question. Certainly MSLT2 is trying to answer that question. I think there is certainly prognostic benefit to a sentinel lymph node biopsy. I think the information that we are able to gather from the sentinel lymph node biopsy and then the subsequent lymphadenectomy in select cases certainly gives us a lot of prognostic information. Whether there is a therapeutic benefit to identifying micrometastatic disease in a sentinel lymph node and then performing a lymphadenectomy afterwards, I don’t know the answer to that. It seems like a reasonable course of action with the data we have currently. Hopefully MSLT2 will shed some light on that question.