Outcome of Thick (› 4 mm) Node-Negative Melanomas

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ABSTRACT: **Background:** Patients with thick melanomas › 4 mm deep are at great risk for regional and distant metastatic disease. Historically, the appropriate management of thick melanomas has remained unclear and there is no consensus in the literature. Many have taken the nihilistic view that surgical intervention to excise regional nodal basins is not justified in light of the poor overall prognosis and risk of occult distant disease.

Objectives: To review the outcome of patients with thick node negative melanoma treated at a multidisciplinary academic center

Methods: We retrospectively reviewed a database of melanoma patients to identify patients with thick melanomas, › 4 mm, who were either clinically or sentinel node biopsy negative, staged T4N0, stage IIb or IIc. The charts of these patients were reviewed and updated, with a median follow-up of 4 years.

Results: We identified 23 patients who fit these criteria. Of these, 18 (78%) remain alive with a median follow-up of 4 years. Five patients died of metastatic disease. Of the 18 surviving patients, 14 remained with no evidence of disease after initial resection of their primary lesions. The majority of the recurrences were non-nodal.

Conclusions: The overall survival of patients in our study remains above 75% at median follow-up of 4 years, even with thick initial index tumor depths. Most of the failures were due to hematogenous spread with lymphatic sparing. Tumor biology that may inhibit lymphatic spread could be a target of future investigation.

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Patients with thick melanomas > 4 mm deep are at great risk (up to 70%) for regional and distant metastatic disease [1] Historically, the appropriate surgical management of thick melanomas is unclear and no consensus is apparent in the literature. Many have taken the nihilistic view that surgical intervention to excise regional nodal basins is not justified considering the poor overall prognosis and high risk of occult distant disease [2]. However, in light of the overwhelming evidence that sentinel lymph node status remains the most significant prognostic indicator in melanoma [3,4], the outcome of node-negative thick melanomas may be instructive. In particular, although tumor thickness remains an important prognostic criterion, lesions that do not initially metastasize to their regional basin may comprise a distinctive group of tumors. In addition, the locus of failure in those patients who eventually develop recurrent disease, which may also be remote from nodal basins, may also be informative. There is a paucity of data regarding the outcome of node-negative T4 lesions, since they amount to a very small percentage of overall melanoma cases. The aim of this study was to evaluate the outcome of a cohort of node-negative T4 melanomas at a single melanoma referral center. The outcomes in this subgroup may have practical implications for surgical and adjuvant therapy and may represent a unique subset of tumors with its own particular biology.

PATIENTS AND METHODS

We retrospectively reviewed a large database of 496 melanoma patients in a university-affiliated teaching hospital which is a referral center for melanoma treatment. Patients with thick melanomas, > 4 mm, who were either clinically or sentinel node biopsy negative, staged as TMN T4N0, stage IIb or IIc, had their charts reviewed and updated, with a median follow-up of 4 years.

All patients underwent wide excision of their primary lesions. Sentinel lymph node biopsy was done using a standard technique that has been described extensively [5]. In brief, a combination of radio-isotope lymphscintigraphy and isosulfan blue 1% was used to identify a sentinel lymph node that was then sent for pathological evaluation. Patients electing not to undergo sentinel lymph node biopsy were staged by clinical examination and imaging including sonogram, computed tomography and fluorodeoxyglucose-positron emission tomography scan, or PET-CT scan.

PET-CT = positron emission tomography-computed tomography

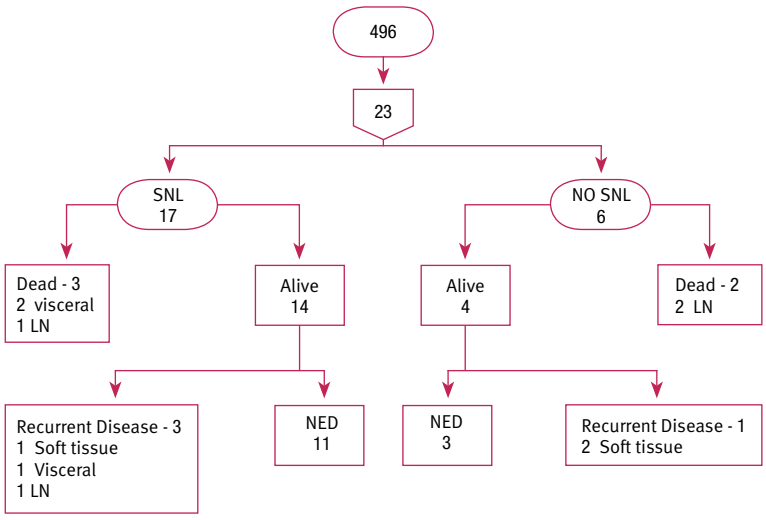
Following surgery, patients were seen in the outpatient melanoma clinic every 3 months for 2 years and subsequently every 6 months a year. Follow-up included routine physical examination and blood tests. Patients were referred for further imaging studies if a clinical suspicion of recurrent disease was noted. Follow-up was calculated from the initial diagnosis until the last visit or death. Only patients who were deemed stage IIb or IIc after their initial surgery were included in this analysis. Overall survival and disease-free survival was calculated. In addition, the site of first recurrence was noted in those patients who ultimately developed metastatic disease.

RESULTS

We identified 23 patients (4.6% of the database) who fit these criteria. There were 15 females and 8 males with a mean age at diagnosis of 46.3 years (range 13–80). The average Breslow depth of the lesions was 6.0 mm (range 4–9.2 mm). Four patients had additional thinner melanoma sites. Tumor locations included 8 limb lesions, 13 trunk lesions and 2 head and neck lesions. All patients underwent wide local excision with clear margins of at least 2 cm around the initial index site.

Sentinel lymph node biopsies, which were negative, were performed in 16 patients, and 1 patient had an elective inguinal groin dissection that was negative. Lymph node biopsy was not done in six patients according to patient or physician choice; these six patients were clinically and radiologically negative and thus staged as having stage II disease. However, since they did not have a histologically proven negative sentinel node, this group of patients was analyzed independently of the other 17 patients with histologically negative regional nodes. Adjuvant therapy with high dose interferon post-surgery was administered to seven patients. A schematic diagram of the outcome of the cohort is presented in Figure 1.

Figure 1. Diagram of the outcome of the cohort. Subtexts refer to sites of first recurrence. LN = lymph node, NED = no evidence of disease.



SURVIVAL

Of the 23 patients 18 (78%) remain alive with a median follow-up of 4 years. Five patients died of metastatic disease. Fourteen patients (61%) remained without evidence of disease after the initial surgical procedure.

SITE OF FIRST RECURRENCE

Of the five patients who died, three had regional lymph node metastasis as their first site of recurrence; one was from the histologically negative group and the other two were from the clinically negative group. The remaining two patients, both from the histologically negative group, had visceral metastasis as the first locus of recurrence. In the remaining 18 patients, there were 4 recurrent events, 3 from the histologically negative group and 1 from the clinically negative group. The three recurrences from the first group included one lymph node metastasis, one soft tissue metastasis and one visceral metastasis, and the recurrence from the second group was a soft tissue metastasis. The two patients with soft tissue recurrences were operated on and are currently without evidence of disease. Two patients (one with previous lymph node failure) have visceral metastasis but remain free of progression with medical treatment.

DISCUSSION

Our data confirm that the overall prognosis of thick melanomas is not as uniformly dismal as previously thought. The overall survival of patients in our cohort with deep stage 2 melanomas remains above 75%, even with thick initial index tumor depths. In addition, after the initial excision 14 of the 23 patients (61%) remained free of disease. This is particularly interesting in light of the fact that, historically, many centers have taken a pessimistic view in formulating the best management policy for cases of thick melanoma [6].

There is considerable evidence that the most significant prognostic indicator in intermediate thickness melanoma is sentinel node status, and sentinel node biopsy may even confer a survival advantage. This was recently shown in the publication of the 5 year interim results of the Multicenter Selective Lymphadenectomy Trial (MSLT-1) by Morton and colleagues [7]. In this study, immediate sentinel lymph node biopsy was found to confer a survival advantage in patients with intermediate thickness melanoma (1.2–3.5 mm). However, the role of sentinel node biopsy in thick melanomas is less clear, since the risk of distant metastases is so high and may even exceed the risk of regional metastases. This was the rationale for avoiding

elective prophylactic lymph node dissection in the pre-sentinel node era in cases of thick melanoma [8]. However, now that the sentinel lymph node biopsy has reduced the morbidity of regional staging, the question again arises whether nodal status has a role in these patients. We decided to look at patients in our database who had thick melanomas but were classified as Stage II, either via sentinel node, or in a minority of cases where the regional was not sampled but there were no clinical and radiological criteria for nodal disease. Although several investigators have analyzed the prognostic factors contributing to survival in thick melanomas [9,10], we decided to focus our retrospective analysis on patients who were deemed node negative. In this particular subgroup, although index tumor characteristics may be unfavorable, the lack of nodal metastases may signify a population with better prognosis. In addition, we looked at the recurrence patterns in patients who eventually did develop metastatic disease to see if the failure was nodal or distant.

Our group of 23 patients included 6 whose nodal basins were not sampled surgically due to patient or physician choice. It should be noted that there are still surgeons and oncologists who are reluctant to refer patients with thick melanomas for sentinel node biopsy, due to the perceived poor prognosis. This smaller group of six patients had two early lymph node failures, which most certainly represent occult nodal disease present at the initial diagnosis, and may well have been sentinel lymph node positive had they undergone regional surgery. The remaining four patients remained free of nodal disease; thus, all 21 patients could be accurately classified as stage II.

We then looked at the recurrence patterns of patients who went on to have recurrent disease. Altogether, nine patients had recurrent disease, although as mentioned previously, two were not regionally staged and eventually developed clinically positive regional nodes. Of the remaining seven cases, five had non-nodal recurrence (three visceral metastases and two soft tissue nodules). Only two patients had nodal recurrences, both from the sentinel lymph node group. These two may represent false negative cases, which in most series can be found in 5–7% of nodal samplings. The majority of cases, when they recurred, recurred as either soft tissue nodules or visceral metastasis. This seems to signify a possible predilection for hematogenous spread with nodal sparing in some patients with thick melanomas. Owing to the small number of cases, no clear significant clinical parameters can be delineated to characterize these patients. Nonetheless, a potential target for future investigation of thick melanomas could include tumor biology, which specifically inhibits lymphatic spread while allowing hematogenous dissemination.

Another aspect that needs to be considered is the use of adjuvant therapy in this population. Currently, the Food and Drug Administration has approved the use of high dose adjuvant interferon alpha-2b for use in high risk melanoma, including thick > 4 mm melanoma, even in the absence of nodal metastases. For example, the authors of the ECOG Trial E 1684 conceded that although the number of patients with thick melanomas without concomitant metastases was small, they recommended that these patients also receive adjuvant treatment [11]. However, there is a lack of data on this particular issue, and our results imply that tumor thickness alone may not be a necessary criterion for determining eligibility for treatment.

This study has several drawbacks. We describe a very small cohort of patients that represents a small percentage of our single center database of melanoma patients. However, it should be noted that the group of node-negative thick melanomas has always been a very small subset of the much larger group of melanoma patients. A single-center retrospective study at the University of Illinois at Chicago assessing patients over a 25 year period was able to identify only 85 patients who fit the criteria of thick > 4 mm node-negative melanoma, with a 5 year overall survival of 61% [12]. The SEER database melanoma registry of 41,417 melanoma patients has only 1599 T4N0 patients, which amounts to only 3.8% of the total melanoma population [13]. Our group of 23 patients comprises 4.6% of our total database of 496 patients. Thus, this subgroup of patients remains a very small segment of melanoma cases, making statistical analysis difficult and underpowered at best.

In addition, even within our small group, we included patients who did not have surgical lymph node staging, which potentially introduced a different population of patients into the cohort. Nonetheless, it is hoped that our data can contribute, if only to a small degree, to dispel this type of management tactic.

In conclusion, our data show that the outcome of this group is less severe than has been historically described. We recommend sentinel lymph node biopsy in all patients with thick melanomas > 4 mm. Patients found to be node negative should only receive adjuvant therapy in the context of a clinical trial. In addition, careful follow-up with physical examination and whole-body imaging such as CT or PET-CT should be utilized to rule out distant disease even when regional basins remain negative.

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