
Status of the Regional Nodal Basin Remains Highly Prognostic in Melanoma Patients with In-Transit Disease



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- BACKGROUND:** The role of SLNB for in-transit (IT) melanoma is controversial. The objective of this study was to determine the rate and prognostic significance of occult nodal disease in patients undergoing surgical nodal staging for IT disease.
- STUDY DESIGN:** We conducted a retrospective review of patients with IT melanoma from May 2005 through September 2014. Analysis was limited to patients with a first-time IT event who underwent surgical excision. Associations between clinicopathologic characteristics, patterns of recurrence, and survival were analyzed.
- RESULTS:** A total of 261 patients treated at our center were identified and 157 met inclusion criteria, of which 135 (86%) presented with no evidence of nodal disease. At the time of surgical excision of the IT lesion, 80 (58%) clinically node-negative patients underwent observation of the nodal basin and 55 (41%) surgical nodal staging. Twenty (36%) clinically node-negative but surgically staged patients were found to have nodal disease. Distant metastasis-free survival was 70.8 months for surgically staged node-negative patients, 19.2 months for surgically staged node-positive patients, 22.8 months for those staged node-negative by clinical examination only and 4.8 months for those with clinical nodal disease ($p = 0.01$). The regional nodal basin was the first site of failure in 14 of 66 (21%) clinically staged patients, 5 of 50 (10%) for those surgically staged, and 6 of 16 (38%) for those with clinical nodal disease.
- CONCLUSIONS:** Patients with IT disease are at high risk for occult nodal metastasis. Because clinical staging is unreliable, SLNB should be considered. For patients with IT recurrence, the status of the regional basin is strongly prognostic and stratifies patients into low-, intermediate-, and high-risk groups. (*J Am Coll Surg* 2016;223:77–86. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)
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In-transit (IT) melanoma is a form of locoregional recurrence thought to represent lymphatic metastatic spread, which manifests as cutaneous or subcutaneous tumor nodules located between the primary melanoma site and the regional draining lymph node (LN) basin(s). In-transit metastases appear as the initial site of recurrence in approximately 10% of patients after management of the primary tumor.¹⁻⁴ These lesions portend a poor prognosis, with 5-year survival rates ranging from 5% to 40%.^{2,5-7} Different terminology has been used to describe this disease, using distance from the primary scar to classify them as local recurrence, satellites, or IT events. However, these terms are arbitrary and IT lesions are all considered a result of intralymphatic contamination and have a similar natural history, with the exception of true local recurrences secondary to

Abbreviations and Acronyms

CLND	= complete lymph node dissection
DFS	= disease-free survival
DMFS	= distant metastasis-free survival
ELND	= elective lymph node dissection
IT	= in transit
LN	= lymph node
OS	= overall survival

residual primary disease due to inadequate resection.⁸ In-transit disease is considered stage III and is classified by the American Joint Committee on Cancer as either stage IIIB or IIIC, depending on whether the regional LNs are also involved.⁷ This pattern of advanced extremity disease can be challenging to control and a source of morbidity.

Sentinel lymph node biopsy is a surgical staging technique with minimal morbidity that has a well-established role in the management of primary cutaneous melanoma. The status of the sentinel lymph node is the strongest predictor of prognosis in patients with clinical stage I to III disease.⁹ In addition, some studies have suggested that SLNB has a possible therapeutic benefit for those patients harboring microscopic nodal disease.¹⁰ Nevertheless, the role of performing SLNB for the management of patients with IT disease is less clear. Because IT metastases are already considered stage III disease, it is not evident how subcategorizing the regional nodes as positive or negative would impact clinical management. Even though this disease is frequently managed with local-regional approaches, such as surgical excision, topical or intralesional therapy, and regional infusion/perfusion, there is an understanding of the inherent risk of additional distant failure in these patients. Because systemic disease eventually develops in approximately 50% of patients, there is some skepticism about the benefit of searching for nodal disease or attempting to prophylax against regional nodal failure.¹¹

The National Comprehensive Cancer Network recommends resection of single or multiple IT metastases when feasible and to consider SLNB in the absence of extensive metastatic disease.¹² The purpose of our study was to identify the rate of occult nodal disease in patients undergoing surgical nodal staging for IT disease and to evaluate its prognostic significance.

METHODS

After IRB approval, patients 18 years of age or older who presented with IT disease as their first recurrent event and

underwent wide local excision at Mayo Clinic in Rochester, MN, between May 2005 and September 2014 were included in the study. Patients who presented with evidence of distant involvement at presentation of either their primary melanoma or their IT disease were excluded from the study.

In-transit disease was defined broadly as any recurrence in the skin or subcutaneous tissue between the primary melanoma and regional nodal basin regardless of distance. Cases consistent with a true local recurrence in the primary scar secondary to inadequate primary resection based on National Comprehensive Cancer Network guidelines were excluded (n = 7). Some IT events are known to occur in a retrograde fashion; for extremity melanoma, skin and subcutaneous metastases occurring in the same limb but distant from the original primary were included.

Patients with IT disease were identified using the Advanced Cohort Explorer, an advanced query tool that allows authorized users to access clinical and administrative data from multiple clinical and hospital source systems within Mayo Clinic Rochester. The search strategy included using melanoma ICD-9 codes in combination with keywords such as *local recurrence*, *IT recurrence*, and *subcutaneous metastasis*. In addition, we used the Mayo Clinic Cancer Registry and known cases of IT from physicians' personal databases to cross reference with our search results to confirm it was broad enough to include all cases of IT disease. Using the most comprehensive search strategy, a list of 2680 patients was generated and each electronic medical record was individually reviewed and the reason for exclusion was recorded. In total, 261 patients were identified to have at least one IT lesion treated at our institution during the determined time period.

Data collected for all patients included demographic characteristics (age and sex), location on the body (head and neck, trunk or extremity), primary tumor characteristics (Breslow thickness, ulceration, tumor mitotic rate, angiolymphatic invasion), and lymph node features (pathologic status, number of positive nodes, microscopic or macroscopic disease, and microscopic tumor burden in the lymph node). We also recorded adjuvant therapy, if any, the patient received. At the time of each intervention, we recorded distance from primary, location (head and neck, trunk or extremity) as well as location in the skin (dermal or subcutaneous), number of IT lesions, diameter of the largest IT lesion, and disease-free interval from initial operation until development of IT disease. Detailed information about each intervention for IT metastasis was also documented. For instances where the distance of the lesion was not overtly documented, photographs from the

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