Regional Therapies for In-transit Disease

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KEYWORDS

• In-transit melanoma • Regional therapy • Isolated limb infusion
• Isolated limb perfusion

KEY POINTS

- In-transit disease is a challenging pattern of recurrence to manage, occurring in up to 10% of patients with melanoma.
- Regional therapy, by isolated limb infusion or hyperthermic isolated limb perfusion, offers treatment options for patients with nonresectable disease.
- Regional therapies are generally well tolerated, and offer complete response rates of 25% to 50%, although long-term responses are often not durable.
- Future management of in-transit melanoma is likely to involve combination therapies, joining cytotoxic regional therapy and systemic immune-modulating drugs such as anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) and anti-programmed cell death 1 surface protein molecule agents.

INTRODUCTION

In-transit melanoma occurs in up to 10% of patients with melanoma, and is a pattern of recurrence that presents unique management challenges and opportunities for treatment. In-transit disease is defined as tumor deposits that usually occur somewhere between the primary lesion and its draining regional lymph node basin.[1,2] Although often associated with distant metastases, the presence of in-transit disease is an independent adverse prognostic factor. Unique treatment modalities, in the form of regional chemotherapy, are often necessary because this pattern of recurrent disease is often not amenable to surgical resection.

BACKGROUND

Incidence

In-transit disease is uncommon, occurring in less than 10% of patients diagnosed with melanoma and accounting for 12% to 22% of melanoma recurrences. The presence

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of positive nodal disease significantly increases the risk of developing in-transit disease, with estimates suggesting risks as high as 31% when at least 3 positive nodes are present.[3] Although initial disease stage seems to be the most important factor in predicting in-transit recurrences, lesion location may also play a role, with higher rates in the lower extremities versus upper extremities. Early observations also suggested an association between surgical lymphadenectomy and the development of in-transit disease, presumably caused by lymphatic trapping in which outflow obstruction of the draining lymphatic system led to stasis and trapping of tumor deposits. However, in recent larger studies, neither lymphadenectomy nor sentinel lymph node biopsy were associated with an increased risk of developing in-transit metastases.[4–7]

Biology

Although the true underlying biology of in-transit melanoma is unknown, it is thought to be related to small tumor emboli disseminating along the path of lymphatic drainage from the primary tumor to its draining nodal basin. These migrating tumor cells are thought to become ensnared in the draining dermal and subdermal lymphatics, eventually progressing to clinically detectable lesions. Although tumor deposits becoming trapped along the lymphatic drainage remains the most likely biological explanation, other mechanisms have been suggested, including hematogenous spread, similar to that of distant metastases.[8,9] Supporters of this alternative theory argue that, if the lymphatic concept is true, wider margins during primary excision would be expected to include a higher proportion of trapped occult cells and lead to superior clinical outcomes, which is not consistent with current observations. However, the hematogenous theory is not supported by the significant differences in long-term survival observed for patients with stage III versus stage IV disease.

Nomenclature

Several different terms have been used in the literature to describe what is likely to be the same underlying oncologic process. In the past, terms such as satellitosis, locoregional recurrence, and in-transit disease have each been used to describe various clinical findings. Satellitosis was usually defined as a locoregional recurrence that was located within either 2 cm of the excision scar or 5 cm of the initial lesion, whereas the term in-transit disease was reserved for a recurrence occurring at greater distances from the initial lesion or scar. Because such lesions all likely reflect tumor deposits proliferating along paths of lymphatic drainage, it has more recently become apparent that distance from the primary lesion to the site of locoregional recurrence does not carry meaningful prognostic value.[10–13] Consequently, the most recent American Joint Committee on Cancer (AJCC) staging system for melanoma does not distinguish between traditional satellitosis and in-transit lesions, with both being designated as N2 or N3 disease, depending on regional node status.[14] To address the ongoing ambiguity arising from nomenclature issues, many authorities no longer use the term satellitosis, instead referring to all regional nonnodal metastatic disease as in-transit melanoma.

PATIENT EVALUATION OVERVIEW

Presentation

By definition, in-transit melanoma represents locoregionally advanced disease, and is typically discovered months to years after the initial surgical excision of the primary lesion, with a disease-free interval to recurrence ranging from 12 to 16 months.[15,16]