



Locoregional melanoma: identifying optimal care in a rapidly changing landscape

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“highlight the need for a more strategic approach from the melanoma community to study patients with locoregional melanoma independently from patients with more advanced metastatic disease”

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The natural history of patients with cutaneous melanoma can be unpredictable. Most patients will present with an early stage, primary lesion which is managed with curative intent wide surgical excision. For those patients whose disease recurs, the disease course can be highly variable. Some patients, regardless of primary tumor characteristics, will develop rapidly progressive disease which metastasizes widely, whereas others will develop relatively indolent locoregional recurrences over many years or even decades. The latest issue of *Melanoma Management* presents a number of review papers that describe the current evidence base for clinical decision making for patients with locoregionally advanced melanoma. This in itself is a broad term describing the full spectrum of patients from those with micrometastatic disease in their sentinel lymph node (SLN) to those with unresectable multifocal in-transit metastases.

Currently, there are no biomarkers that can accurately predict the tempo or distribution of disease progression for patients with primary melanoma at the outset. The most reliable prognostic factors for patients undergoing treatment for primary melanoma are a combination of the primary tumor characteristics as well as the status of the SLN which together have allowed the American Joint Committee on Cancer (8th Edition) to create a high-quality evidence-based prognostic framework [1]. For patients with a positive SLN, the last 5 years have seen a dramatic change in the management algorithm. In this issue, Downs *et al.* [2] describe the findings from two recent large, randomized controlled trials demonstrating no survival benefit to immediate completion lymph node dissection. Interestingly, these new data showing no survival benefit for completion node dissections in the setting of sentinel node positive disease in certain patient populations emerged at the same time as multiple landmark prospective randomized clinical trials demonstrated survival benefit with the use of adjuvant systemic therapies (both immunotherapy with anti-PD-1 inhibitors and targeted therapy with BRAF/ MEK inhibition) in the same patient population [3,4]. These practice-changing studies are described in detail by Samuel *et al.* [5] where the role of adjuvant therapy in patients with resected stage III melanoma is described as a rapidly evolving field and discussed in detail. In recent years, preclinical and clinical data from small series have emerged supporting the use of systemic therapies in a neoadjuvant setting. This approach provides the treating team with an *in vivo* assessment of clinical response as described by Sun *et al.* [6]. The authors describe the clinical trials that are currently underway looking at neoadjuvant therapy and the promising preliminary results, allowing for presurgical management of a disease that previously had few options in that arena.

Furthermore, for patients with unresectable locoregional melanoma, a wide variety of regional therapies have demonstrated clinical benefit including intra-arterial therapies, as outlined by Broman *et al.* [7], and topical and intralesional therapies, documented by Henderson [8]. Both Broman and Henderson discuss innovative minimally

invasive therapies, such as isolated limb infusion, topical dyphenyprone and intralesional oncolytic viral therapy, and their role in the treatment of regionally advanced metastatic melanoma. Although there is clearly compelling data for the efficacy of these therapies, they were largely developed and their evidence base established in the era before effective systemic therapies for melanoma which have revolutionized care over the last decade. The evidence for the use of these therapies, including BRAF and MEK inhibitors as well as checkpoint blockade immunotherapies, for patients with unresectable locoregional melanoma is described by NanTie *et al.* [9]. However, as the authors point out, there is minimal evidence to guide the incorporation of systemic immunotherapies or targeted therapies into current treatment paradigms for unresectable stage III locoregionally metastatic disease. The authors do go on to mention that further evidence is needed to establish the benefit of systemic therapies in the regionally metastatic population.

All of this leaves clinicians managing this patient population with a difficult conundrum as to the optimal management algorithm. Taken together, the review papers in this issue highlight the need for a more strategic approach from the melanoma community to study patients with locoregional melanoma independently from patients with more advanced metastatic disease. It remains unclear which patients should receive locoregional therapies as first line and which patients would benefit from systemic therapy upfront. Or, even whether some patients should receive combinations of these. Quality of life and health economic implications also need to be considered given the increasing cost of care and the aging population.

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