Lymphatic versus Hematogenous Melanoma Metastases: Support for Biological Heterogeneity without Clear Clinical Application

Gyulnara G. Kasumova¹, Alex B. Haynes¹ and Genevieve M. Boland¹

Melanoma demonstrates considerable biological heterogeneity and is associated with several routes of dissemination including lymphatic and hematogenous. Locoregional control via surgery may improve outcomes for patients with limited lymphatic metastases. Once stage IV disease is diagnosed, clinical outcomes are determined by molecular and/or immunologic factors and identification of tumor/microenvironmental features correlating with distant metastases is critical for future prognostic stratification.

Characterizing patterns of metastatic dissemination and identifying molecular features correlating with site-specific metastases is crucial for optimal disease management and predicting responses to therapy in melanoma and other tumor types. It is clear from clinical experience that there are both hematogenous and lymphatic routes of metastasis, which may be of clinical relevance particularly in the setting of thick melanomas. Gassenmaier et al. (2017) perform a retrospective analysis of a large, prospectively maintained cohort of patients spanning nearly four decades (1976–2015) who presented initially with early stage (IA–IIC) primary cutaneous melanoma and subsequently progressed to either stage III or IV disease. The authors note three distinct subsets of disease progression: (i) isolated lymphatic spread without subsequent distant metastases, (ii) combined lymphatic and hematogenous distant metastases, and (iii) exclusive distant metastases. Their analysis excludes patients with isolated locoregional disease and focuses exclusively on patients with stage IV disease (Gassenmaier et al., 2017), demonstrating no difference in overall or metastasis-free survival in patients with stage IV disease regardless of the presence of previous or concurrent lymphatic spread. Although the authors describe a large clinical subset of patients with stage IV disease, it is critical to interpret these results with extreme caution for clinical use because the dataset spans an era of heterogeneous clinical management including the pre-sentinel lymph node biopsy (SLNB) era (1976–1996) in combination with the current era in which lymphatic staging has become the standard of care. Of note, patients with a positive sentinel lymph node (in the post-SLNB era) were excluded from analysis. Therefore, although descriptively interesting, these data cannot safely be applied to current clinical scenarios or patient management decisions.

The surgical approach to lymphatic management in melanoma has evolved over the last few decades. For the surgical oncologist, the goals of SLNB are to provide accurate staging and critical prognostic information. The modern era of the SLNB technique began in the early 1990s and has subsequently been adopted as an alternative to elective lymph node dissection (Morton et al., 1992). The Multicenter Selective Lymphadenectomy Trial (MSLT-I) randomized patients to either wide local excision and SLNB with immediate lymphadenectomy for a positive sentinel node or wide local excision and postoperative observation with...
Clinical Implications

- Hematogenous and lymphatic dissemination contribute to stage IV melanoma with distinct underlying biology.
- Surgery for lymphatic disease is evolving; sentinel lymph node biopsy remains critical for pathologic staging.
- Management of stage IV disease requires multidisciplinary melanoma team management.

delayed lymphadenectomy for clinically detectable nodal recurrences (Morton et al., 2006, 2014). The MSLT-I clearly supports the prognostic importance of sentinel lymph node staging as well as demonstrates improvements in 10-year melanoma-specific survival and distant disease-free survival with detection of early, low volume nodal burden in patients with intermediate-thickness melanomas (Morton et al., 2006, 2014).

Most patients with a positive SLN will have disease limited to the sentinel node alone, and the presence of non-sentinel nodal disease corresponds with poorer survival outcomes. The MSLT-II was specifically designed to evaluate the benefit of completion lymph node dissection for patients with a positive SLN, with subsequent randomization to either immediate completion lymph node dissection or nodal observation (Faries et al., 2017). Although immediate completion lymph node dissection was associated with prolonged disease-free survival and the presence of non-sentinel lymph node metastases was an important prognostic factor for recurrence, the study found no difference in the rates of 3-year melanoma-specific survival between treatment groups (Faries et al., 2017). It is important to note that more than 80% of patients in the MSLT-II had either an RT-PCR positive node or only one positive sentinel node, and that the results may not extrapolate to more high-risk patients with multiple positive sentinel nodes. The German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy Trial (DeCOG-SLT) trial similarly found no difference in melanoma-specific survival between completion lymph node dissection and observation in those with SLN-positive disease; however, this study was closed early because of limited accrual and underpowered to detect a difference (Leiter et al., 2016). In summary, the field of melanoma surgery is clearly moving toward a more parsimonious use of completion lymphadenectomy in patients appropriately staged with sentinel node biopsy, but guidelines for nodal management are still evolving and complete pathologic staging is now the norm.

Given the ongoing evolution of surgical management, it is important to note that the study cohort described by Gassenmaier et al. (2017) spans the pre- and post-SLNB eras and excluded all SLNB-positive patients, the exact patients studied in the MSLT-II and DeCOG-SLT trials (Figure 1). Therefore, the results as they relate to surgical management of locoregional disease should not be applied to current clinical scenarios or patient decision making. Because Gassenmaier et al. (2017) excluded patients with a positive SLN, the analysis does not include individuals in whom nodal surgery alone may have been curative. Amongst patients included in follow-up, more than a third (38.4%) developed isolated lymphatic disease, encompassing more than half (51.4%) of patients who progressed to stage III disease. Not surprisingly, those with isolated stage III disease had significantly longer 5-year melanoma-specific survival (98.4%) than those who progressed to stage IV disease (48.5%), once again highlighting the subset of patients with isolated nodal involvement in which lymph node surgery was curative.

Rather than refuting the Halstedian hypothesis of metastatic spread, patients with stage III disease who are cured by surgery reinforce this nonexclusive pattern of dissemination, and the data presented in this work support the existing pool of literature supporting multiple, parallel routes of metastasis that should be accounted for when selecting surgical and/or systemic treatment options.

Support for biological heterogeneity in metastasis

A prominent feature of cancer is its molecular heterogeneity. Differentiating individuals who have unfavorable biology is critical for the optimal management of disease at all stages, and the field of oncology is actively pursuing the identification of early markers of tumor aggressiveness. Patients with isolated locoregional melanoma and/or...
more indolent biology may potentially be cured with surgery alone, and studies of the surgical management of oligometastatic stage IV disease support the association between indolent tumor biology and clinical outcomes (Howard et al., 2012; Sosman et al., 2011). Using clinical data, Gassenmaier et al. (2017) found that the only significant independent predictor of direct progression to stage IV disease (distant hematogenous metastases only) was the initial site of tumor location, which they divided into either TANS (thorax, upper arm, neck, scalp) or all other regions. Interestingly, whole exome sequencing of melanoma reveals that chronically sun-exposed skin has more than a 50-fold higher rate of somatic single nucleotide variants than intermittently exposed skin, which may contribute to a more aggressive tumor biology (Sanborn et al., 2015). Clearly, site-specific and molecular/immunological differences across primary tumors are critical for the subsequent clinical pattern of dissemination and responsivity to therapy. Given the limitations of a retrospective analysis spanning eras of ongoing change in both the surgical and systemic management of melanoma, the authors provide a thorough description of clinical stage IV disease that supports hematogenous metastatic dissemination in isolation or in parallel with locoregional disease, as previously described through genomic analysis.

Two prominent genomic studies reveal that both sequential and parallel metastases occur in cancer. Sanborn et al. (2015) evaluated the number of somatic single nucleotide variants per exome in melanomas to examine the phylogenetic relationship between the primary tumor and multiple metastatic lesions. The study reveals that each primary tumor may contain multiple tumor subpopulations that can result in parallel metastatic spread, and that one metastatic lesion can be seeded by more than one of the distinct tumor subpopulations (Sanborn et al., 2015). Three of seven patients in this study had both lymph node metastases and distant metastases, with one of the three demonstrating genomic patterns consistent with direct spread from a lymph node to a distant site supporting both parallel and sequential dissemination (Sanborn et al., 2015). A recent analysis of metastatic colorectal cancers also supports the nonexclusive presence of both parallel and sequential metastatic pathways. The study by Naxerova et al. (2017) looked at hypermutable regions of DNA (non-coding polyguanine repeats) and found that approximately a third (33%) of patients demonstrated a common phylogenetic origin of lymphatic and distant metastasis, in support of a sequential model of metastasis/tumor progression. In the remaining two-thirds (65%), there were multiple, distinct subclonal origins of lymphatic and distant metastases, consistent with parallel spread (Naxerova et al., 2017). Both studies propose that regional metastases may grow faster than distant tumors, leading to earlier detection and thereby serving as a prognosticator because they are seeded earlier, more frequently, and potentially more efficiently (Naxerova et al., 2017; Sanborn et al., 2015). Consistent with the clinical findings presented by Gassenmaier et al. (2017) once distant metastases are seeded, either alone or simultaneously with regional sites, a difference in distant metastasis-free survival is not expected given the aggressive biology of the majority of stage IV disease.

The study by Gassenmaier et al. (2017) and the two genomic studies highlight diverse and overlapping patterns of metastatic dissemination, which are the result of intrinsic tumoral biological heterogeneity. Rather than refuting or supporting a specific hypothesis of metastasis, the field of melanoma oncology should focus on underlyng tumor and immune-based biology that correlates with differences in metastatic patterns and the timing/location of failures. Molecular analyses in conjunction with clinical correlations can potentially be used to guide the optimal choice of regional versus systemic therapy in a personalized fashion. The current paper offers a thorough description of this heterogeneous clinical phenomenon during an era in which significant changes have occurred in both the surgical and systemic management of melanoma.

Moving forward, integration of tumor intrinsic and/or patient immunologic characteristics into a multimodality treatment plan for stage IV disease combining surgery and systemic therapy will be critical given the rapidly expanding therapeutic options for patients with melanoma.

**CONFLICT OF INTEREST**
The authors state no conflict of interest.

**REFERENCES**