Editorial Commentary

Identifying high-risk stage IIIA cutaneous melanoma patients who might benefit from adjuvant therapy: the importance of micrometastatic tumor burden

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Effective adjuvant therapy has dramatically improved prognosis for patients with high-risk stage III melanoma. Before effective targeted and immunotherapy agents, providers had few effective treatments that were safe and well tolerated enough to offer to most patients with positive sentinel lymph nodes (SLNs), even though they had a high-risk of recurrence. The treatment paradigm was to perform a complete lymph node dissection (CLND) after a positive SLN biopsy and observe closely for recurrence. Now we have effective, well tolerated agents that can be given to most patients with high-risk stage III disease after surgery, while omitting a CLND and reducing the risk of recurrence.

This treatment paradigm evolved from the reconciliation of two series of clinical trials, one surgical and one medical. First were the results of the MSLT-2 and DeCOG studies, which showed that a CLND after a positive SLN biopsy did not improve melanoma-specific survival (1,2). The patients in the non-surgical arms of these studies were simply observed with serial imaging after a positive SLN biopsy, with no additional adjuvant therapy. The second series of trials were the studies showing a reduced risk of recurrence in high-risk stage III patients treated with adjuvant PD-1 inhibitor therapy or targeted therapies (3-5). All of these patients were treated with a CLND after a positive SLN biopsy prior to starting adjuvant therapy. We have effectively taken the findings from each series of studies and merged them, such that we now treat high-risk SLN positive stage III patients with adjuvant therapy and omit a CLND.

One must carefully consider the populations that were considered "high-risk" stage III in the adjuvant therapy trials. The KEYNOTE-054 trial evaluating pembrolizumab *vs.* placebo allowed IIIA patients to be enrolled, but only if they had a micrometastatic tumor burden of at least 1.0 mm (5). The COMBI-AD trial, which evaluated dual BRAF/MEK inhibition with dabrafenib and trametinib in resected high-risk stage III melanoma, similarly enrolled IIIA patients only if they had a micrometastatic tumor burden of at least 1.0 mm (3). In general, subgroup analyses of these studies showed consistent benefit across stage subgroups. The CheckMate 238 trial comparing adjuvant nivolumab *vs.* ipilimumab in resected stage III melanoma only enrolled stages IIIB, IIIC, or IV patients (4). However, it is important to remember that these studies used the 7th edition AJCC staging guidelines, in which stage IIIB and IIIC patients were largely defined based on the presence of ulceration across the different tumor thicknesses for those with SLN positive disease (6). In contrast, stage III subgroups are defined by both tumor thickness and ulceration in the 8th edition (7). The substage definitions in the 7th edition used in these studies are different than those currently used in the 8th edition.

So how do we reconcile all these studies to form a rational treatment strategy for SLN positive stage III patients?

Most centers are considering adjuvant immunotherapy for IIIB/IIIC/IIID patients (defined in the 8th edition AJCC). These patients have a risk of recurrence that approaches that of the patients in the stage III adjuvant therapy trials. The challenge is to decide which IIIA patients have a high enough risk of recurrence to justify adjuvant therapy. This is a sizable minority of the stage III patients seen on a population level, as IIIA patients may be close to 20% of the total stage III patient population (8). The article by Moncrief *et al.* provides evidence that the micrometastatic tumor burden can stratify IIIA patients into high and low risk cohorts based on risk of recurrence (9). This risk stratification may help guide adjuvant decision making.

In this multi-institutional, international study, the authors evaluate 3,607 patients with pT1b or pT2a primary cutaneous melanomas who underwent SLN biopsy as part of their staging. This is a cohort of patients who if found to have a positive SLN would be considered stage IIIA by AJCC 8th edition. The rate of a positive SLN biopsy (and thus IIIA disease) in this cohort was 11%. The disease-specific survival in the entire IIIA cohort was ~85%; survival for N1a or N2a patients was worse compared to the N0, stage IB patients. Importantly, the authors found that there was no difference in survival between the patients with a single positive SLN (N1a) compared to those with two or three positive SLNs (N2a). This is consistent with previous work evaluating overall survival in the National Cancer Database, in which there was no difference in overall survival between N1a and N2a stage IIIA patients who did not undergo CLND (10). Thus, we cannot use the absolute number of positive SLNs in this group to risk stratify them. In the past, we would count on the status of the non-SLNs in the CLND specimen to further risk stratify this group, since it is abundantly clear that patients with metastases to the non-SLNs have worse prognosis compared to those with metastases confined to the SLNs (11-14). However, since we no longer perform CLND, is there any additional clinicopathologic information we can gather after a SLN biopsy to help risk stratify these patients and inform adjuvant decision making?

The micrometastatic tumor burden is a well-known factor of prognostic significance in patients with positive SLNs (15,16). In this study by Moncrief *et al.*, they evaluated multiple cutoffs for micrometastatic tumor burden, as determined by the long diameter of the largest micrometastatic tumor deposit, in order to determine the optimal cutoff for risk stratifying IIIA patients. They found that a cutoff of 0.3 mm was the best at separating these IIIA patients into two groups with different disease-specific and disease-free survivals. The low risk patients (<0.3 mm deposit) had survival that mimicked that of the stage IB (N0) patients, while the high-risk group (≥0.3 mm deposit) had statistically significantly worse disease free-, distant metastasis free-, and disease specific-survival compared to the low risk and N0 groups. The 5-year distant metastasis-free survival was 72% in the high-risk group, compared to 92% in the low risk group. Having shown that the low risk N1a–N2a patients with a micrometastatic tumor burden <0.3 mm have a survival that approximates the node-negative, stage IB patients, the authors propose that these patients can be safely observed without adjuvant therapy. However, those with high-risk micrometastatic volume exceeding 0.3 mm have survival that is similar to IIIB and IIIC patients, and thus would likely benefit from adjuvant therapy.

These findings are important, because it helps clinicians make adjuvant therapy decisions with the more limited information we have on stage III patients who are no longer undergoing a CLND. Clearly, not all stage III patients need adjuvant therapy. The IIIA subgroup has a 10-year melanoma specific survival of 88%, which is better than the higher risk IIB and IIC groups with thicker melanomas that are SLN-negative (17). However, there are some higher risk stage IIIA patients that would likely benefit from risk reduction with adjuvant therapy. The question is how do we identify these patients? Moncrief *et al.* provide compelling evidence that the micrometastatic tumor burden, specifically a cutoff of 0.3 mm, can be used to identify high-risk IIIA patients who may benefit from adjuvant therapy. One must acknowledge that the authors have only identified a group with high-risk of recurrence. No evidence is presented that adjuvant therapy in this subgroup is associated with reduced risk of recurrence. However, we know that adjuvant therapy can reduce the risk of recurrence in multiple stage III subgroups, so it is reasonable to infer that these patients should be considered for adjuvant therapy. This study is a nice example of how multi-institutional collaborations can provide practice-changing recommendations based on observational data. I will certainly use these findings to inform our adjuvant therapy recommendations in this subgroup of patients.

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References

1. Faries MB, Thompson JF, Cochran AJ, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med 2017;376:2211-22.
2. Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol 2016;17:757-67.
3. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med 2017;377:1813-23.
4. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377:1824-35.
5. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 2018;378:1789-801.
6. Edge SB, Fritz AG, Byrd DR, et al. editors. AJCC Cancer Staging Manual. Chicago, IL: American Joint Committee on Cancer, 2010.
7. Amin MB, Edge SB, Greene FL, et al. AJCC cancer staging manual. New York: Springer, 2017.
8. Hynes MC, Nguyen P, Groome PA, et al. A population-based validation study of the 8th edition UICC/AJCC TNM staging system for cutaneous melanoma. BMC Cancer 2022;22:720.
9. Moncrieff MD, Lo SN, Scolyer RA, et al. Clinical outcomes and risk stratification of early-stage melanoma micrometastases from an international multicenter study: implications for the management of American Joint Committee on Cancer IIIA Disease. J Clin Oncol 2022;40:3940-51.
10. Woeste MR, McMasters KM, Egger ME. Stage IIIa Melanoma and Impact of Multiple Positive Lymph Nodes on Survival. J Am Coll Surg 2021;232:517-524.e1.
11. Jakub JW, Huebner M, Shivers S, et al. The number of lymph nodes involved with metastatic disease does not affect outcome in melanoma patients as long as all disease is confined to the sentinel lymph node. Ann Surg Oncol 2009;16:2245-51.
12. Wiener M, Acland KM, Shaw HM, et al. Sentinel node positive melanoma patients: prediction and prognostic significance of nonsentinel node metastases and development of a survival tree model. Ann Surg Oncol 2010;17:1995-2005.
13. Leung AM, Morton DL, Ozao-Choy J, et al. Staging of regional lymph nodes in melanoma: a case for including nonsentinel lymph node positivity in the American Joint Committee on Cancer staging system. JAMA Surg 2013;148:879-84.
14. Brown RE, Ross MI, Edwards MJ, et al. The prognostic significance of nonsentinel lymph node metastasis in melanoma. Ann Surg Oncol 2010;17:3330-5.
15. van Akkooi AC, Nowecki ZI, Voit C, et al. Sentinel node tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients: a multicenter study in 388 patients with positive sentinel nodes. Ann Surg 2008;248:949-55.
16. Egger ME, Bower MR, Czyszczon IA, et al. Comparison of sentinel lymph node micrometastatic tumor burden measurements in melanoma. J Am Coll Surg 2014;218:519-28.
17. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:472-92.

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