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EDITORIAL

Nonsentinel Node Metastases in Melanoma: Do They Reflect the Biology of the Tumor, the Lymph Node or the Surgeon?

Editorial to Accompany Ghaferi et al., ASO-2009-03-0312.R1

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Two decades ago, elective lymph node dissection was essentially abandoned as a surgical strategy for melanoma patients for clinically negative (cN0) regional lymph nodes, based on three key facts: (1) less than 20% of patients with cN0 intermediate-thickness melanomas have histopathologic evidence of nodal involvement (pN1), (2) an effective salvage strategy—therapeutic lymph node dissection at the time of nodal relapse—was felt to exist for pN1 patients upon nodal relapse, and (3) there was no compelling evidence that elective node dissection conveyed outcome advantages for pN1 patients (in particular, improved survival, better regional disease control or decreased surgical morbidity) of sufficient magnitude to offset the inescapable drawback that 80% or more of the patients subjected to the procedure were incurring morbidity without any expectation of oncologic benefit. Elective node dissection has now been replaced by sentinel node biopsy, and we find ourselves today in an eerily parallel situation regarding completion node dissection for our sentinel node-positive patients. Specifically, (1) less than 20% of patients with a positive sentinel node have histopathologic evidence of involvement of nonsentinel nodes (usually arbitrarily defined as those regional nodes not removed at sentinel node biopsy for whatever reason), (2) an effective salvage strategy—therapeutic lymph node dissection at the time of nodal relapse—may exist for sentinel node-positive patients upon nodal relapse, and (3) there is as yet no compelling evidence that completion node dissection conveys outcome advantages for sentinel node-positive patients (in particular, improved survival) of sufficient magnitude to offset the drawback that all sentinel node positive patients are incurring morbidity including some as yet undefined percentage who would never relapse in the remaining regional nodes.[1–3]

However, it is well to introduce the caution that these two situations—elective node dissection in the absence of any clinical evidence of nodal involvement, and completion node dissection in the presence of histopathologic proof of sentinel node involvement—are not entirely analogous. The sentinel node biopsy experience has taught us that some regional lymph node metastases undetected on routine histologic evaluation of a bisected lymph node submitted as part of a node dissection are readily apparent—and unequivocally clinically significant—when the node is serially sectioned and evaluated with immunohistochemical stains for melanocyte antigens. Since "nonsentinel nodes" are almost never examined using serial sectioning and immunohistochemistry, we must assume that the frequency of involvement of nonsentinel nodes is greater than currently recognized—and the yield (if not necessarily the benefit) of completion node dissection is almost surely underestimated. Nonetheless, understanding the clinicopathologic factors that predict nonsentinel node involvement would surely inform the decision of whether or not to pursue completion dissection in all cases of positive sentinel nodes. So what have we learned about the biology of melanoma metastasis as it relates to the nonsentinel node?

TWO NODES ARE WORSE THAN ONE

While the majority of sentinel node-positive patients have only one positive sentinel node and no other sentinel

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or nonsentinel nodal involvement identified, patients with pathologically involved nonsentinel nodes, by definition, have at least two positive nodes. Since the number of pathologically involved nodes is a recognized prognostic factor, it is evident that positive nonsentinel nodes will convey a poor prognosis, which would be statistically significant in any series with adequate power to detect a nonrandom difference. In this issue of the *Annals of Surgical Oncology*, Ghaferi et al. attempt to evaluate the biologic implications of nonsentinel node involvement by comparing 90 patients with two or three positive sentinel nodes and no nonsentinel node involvement with 41 patients with the same number of positive nodes in whom at least one involved node was a nonsentinel node.[3] Distant disease-free and overall survival were both statistically significantly worse for the nonsentinel node-positive cohort, although the authors do not present a multivariate analysis to evaluate whether other factors may account for this difference. Even if a multivariate analysis did indicate a difference, we still would need to account for the difference in tumor burden between patients with two nodal micrometastases seen only on immunohistochemistry and those with at least one nodal metastasis large enough to be seen on routine evaluation of a bisected node. To date, we simply do not know enough about how to make this adjustment to accept on face value the conjecture that nonsentinel node metastasis indicates an inherent biologic ability of a melanoma to spread systemically, simply because it could spread within a nodal basin.

NOT ALL NODES ARE THE SAME

Ghaferi et al. found that older patients were more likely to have positive nonsentinel nodes, and even more significantly, that older age and the presence of a nonsentinel node metastasis were the only factors statistically significantly correlated with worse distant disease-free and overall survival in their multivariate model.[3] While it is possible that melanomas arising in older patients have an inherently different biology with more frequent hematogenous spread, it is also plausible that older nodes are different from younger nodes in terms of their filtration efficiency and/or immunologic functionality. A recent observation that sentinel nodes in older patients demonstrated lower levels of radioactivity than those from younger patients supports the concept that lymphatic flow and/or nodal filtration efficiency may decrease as we age, with potential oncologic consequences.[4] Furthermore, emerging evidence suggests older patients are more likely to have false-negative sentinel nodes, which adds some credence to the idea that tumor cells may more readily pass through the "inefficient" sentinel node in older patients and gain access to second-echelon nodes and the systemic circulation.[5]

NOT ALL SURGEONS ARE THE SAME

Before we ascribe too much biologic significance to nonsentinel node metastases, we need to recognize the potential confounding role of the surgeon. Not all surgeons—even in a single center with established protocols for defining the sentinel node—are equally aggressive in pursuing every lymph node with radioactivity above baseline. It stands to reason that any "hot" node, even one containing just a fraction of the radioactivity of the hottest node, is more likely to harbor metastatic melanoma than a completely cold node; so the diligence with which sentinel nodes are cleared by the surgeon will directly influence the likelihood with which "nonsentinel node" metastases are found—since sentinel nodes left behind become nonsentinel nodes when the completion node dissection is performed. It is also predictable that surgeons may be less likely to pursue every sentinel node in a basin when they suspect that the initial sentinel node has a very high likelihood of harboring metastases (to avoid extensive operative manipulation of a basin that will require completion dissection). Future series reviewing nonsentinel node metastasis frequency should include the surgeon as a potential predictive variable, and should also include evaluating the lymphoscintigram to determine how many radioactive nodes were visualized compared with how many sentinel nodes were removed.

However, all of this discussion centering around the frequency of positive nonsentinel nodes addresses only one of the factors that will determine whether completion node dissection can safely be omitted in some sentinel node-positive patients.[6,7] We must also understand the safety and efficacy of salvage node dissection at the time of nodal relapse. Available data suggest that lymphadenectomy performed for clinically evident nodal disease is associated with more complications and poorer regional control rates than when the same procedure is done for microscopic disease.[8] We all look forward to the results of the second Multicenter Selective Lymphadenectomy Trial (MSLT-2), a prospective randomized evaluation of nodal observation as an alternative to completion dissection after a positive sentinel node biopsy, which will shed considerable light on this issue. However, we also have to be aware of some potential pitfalls regarding the MSLT-2 trial.

This trial includes patients whose sentinel node is positive only by reverse-transcriptase polymerase chain reaction (RT-PCR), a technique that has not been validated as predictive of worse survival or of increased risk of nonsentinel node metastasis. In fact, the results of RT-PCR

analysis of the sentinel node in the Sunbelt Melanoma Trial indicated that the outcome for histologically negative sentinel nodes was identical regardless of RT-PCR status.[9] While MSLT-2 uses different primers and paraffin-embedded rather than fresh nodal tissue, concerns remain about the validity of including these patients in any analysis of the impact of completion lymph node dissection.[10] MSLT-2 is also likely to be impacted by selection bias, as patients who are known or suspected to be at high risk of having nonsentinel node involvement (e.g., older patients, those with thick, ulcerated or high mitotic rate primaries, and those with multiple positive sentinel nodes) may be less likely to be recruited to the trial and less likely to consent to randomization if they are approached. If the group of patients most likely to benefit from completion lymph node dissection is underrepresented in the MSLT-2 trial, the results may not be generalizable; patients and physicians may use them indiscriminately to make decisions nonetheless. Finally, the primary endpoint of MSLT-2 is survival, yet regional failure and morbidity rates may be equally compelling reasons to recommend completion lymphadenectomy even in the absence of a survival benefit. The data generated from MSLT-2 will be highly informative, but experience has shown that patients and even physicians do not always see eye to eye when interpreting the results of randomized trials.

A final, completely anecdotal word of caution, based on a recent case. A woman in her mid-30 s with a 1.1-mm melanoma on the thigh was found to have a solitary micrometastasis (<0.1 mm in greatest dimension and apparent only after immunohistochemical staining) in an inguinal sentinel node. Her lymphoscintigraphy indicated only a single inguinal hot spot, with no through transit into the pelvis, which corresponded well to the counts observed in the solitary blue lymph node removed at surgery. Clearly, this was a woman who would be considered to be at very low risk for finding nonsentinel node metastases on completion node dissection. She was offered participation in the MSLT-2 trial, but for professional and personal reasons refused to even consider inguinal node dissection and declined surgery. Eighteen months later, she developed palpable disease in the same groin and a superficial and deep inguinal node dissection indicated more than a dozen involved nodes, including pelvic nodal metastases. Was she just an "outlier" and would all of these nodes have been discovered had the same surgery been performed a year and a half earlier? Perhaps, but that seems unlikely. Conversely, it is easy to imaging that the very morbidities this patient sought to avoid are now more likely—and more likely to be severe and/or permanent—than they would have been if a completion lymphadenectomy had been done soon after the sentinel node biopsy. While this is just a single case, it is by no means a unique case in our experience and it also recapitulates the findings of MSLT-1 wherein more positive nodes were found at therapeutic lymphadenectomy upon nodal relapse than at completion lymphadenectomy following sentinel node biopsy.[11] Cases such as these have strengthened our resolve to urge patients not to forego completion node dissection outside the setting of a prospective clinical trial, and to continue to pursue strategies to minimize the morbidity of completion lymphadenectomy.[12]

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