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EDITORIAL

Microscopic Satellites Around a Primary Melanoma: Another Piece of the Puzzle in Melanoma Staging

Charles M. Balch, MD, FACS

Departments of Surgery, Oncology and Dermatology, Johns Hopkins Medical Institutions, Baltimore, MD

This is an important subject that is applicable to surgical treatments of the primary melanoma and the regional lymph nodes as well as melanoma prognosis and staging. The importance of cancer staging, of course, is to partition patients into risk groups based upon disease-specific survival rates. In turn, the converse of survival rates at 5 or 10 years reflects the incidence of distant microscopic metastases at the time of staging from which a patient would ultimately succumb. With respect to the nodal (N) classification in melanoma, the two most important prognostic features are number of nodal metastases (1 versus 2/3 versus $\geq$4) and tumor burden (i.e., microscopic or clinically occult versus macroscopic or clinically apparent nodal metastases).[1,2] The third criterion for defining the N category is the presence or absence of satellites or in transit metastases, regardless of the number of lesions. The clinical presence of satellites around a primary melanoma or of in-transit metastases between the primary melanoma site and the regional lymph node basin represent intralymphatic metastases that portend a relatively poor prognosis.[3–5] The available data show no substantial difference in survival outcome for these two anatomically defined entities.[3]

But what about microscopic satellites? These are defined as any discontinuous nest of intralymphatic metastatic cells >0.05 mm in diameter that are clearly separated by normal dermis (not fibrosis or inflammation) from the main invasive component of melanoma by a distance of at least 0.3 mm.[2,6] In the past, the definition of microsatellites has varied, and this may account for some of the differences in results regarding their prognostic significance. As a result, the level of evidence regarding the prognostic significance of microsatellites is less robust, but the available data indicates that this is an adverse finding associated with an increased risk of regional recurrences and a decreased disease-free survival rate similar to that of clinically detectable satellites.[7–12] Whether microsatellites represent an independent predictor of survival outcome is less clear, but at present the preponderance of evidence suggests that this feature represents an adverse prognostic factor for survival. Accordingly, the America Joint Committee on Cancer (AJCC) Melanoma Staging Committee has recommended that this feature of early lymphatic metastases, as defined above, be retained in the category of N2c melanoma.[2,6]

This issue of the *Annals of Surgical Oncology* includes a valuable contribution to our decade-long work on melanoma staging as regards microsatellites.[13] In this setting, the AJCC Melanoma Staging Database did not have direct data that could be applied to the staging rules for patients with microscopic satellitosis, except that published in the literature, much of which was published years ago.[7–12] This study by Kimsey and colleagues from Memorial Sloan–Kettering Cancer Center (MSKCC) was made possible by the commitment made through the years by MSKCC surgeons to collect prospective data on their melanoma patients, which now includes almost 4,000 prospectively followed patients.[13] Among these patients was a carefully studied cohort of 38 patients with newly diagnosed, clinically localized melanoma containing microscopic satellitosis. These primary melanomas had very aggressive features, including a median thickness of 5.4 mm and the majority (71%) being ulcerated. The 5-year overall and disease-free survival rates in these patients were 34% and 18%, respectively, and 68% had pathologically involved regional nodal metastases. They clearly constitute a high-risk group of patients for both regional and distant metastases that needs to be accounted for in our staging rules.

In the 6th edition of the *Cancer Staging Manual*, the Melanoma Staging Committee modified its staging criteria

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C. M. Balch, MD, FACS
e-mail: balchch@jhmi.edu

by incorporating both microscopic and clinically detectable satellites and/or in-transit metastases without concomitant lymph node involvement into the same nodal classification as patients with two or three metastatic lymph nodes (N2c, stage IIIB).[1,14] Patients with nodal intralymphatic metastases plus nodal metastases clearly have a worse prognosis and are therefore classified in a separate category when the regional lymph nodes contained metastatic melanoma (N3, stage IIIC). This decision was based upon the older literature cited above. As we finalized the melanoma staging criteria for the 7th edition of the *Cancer Staging Manual*, the Melanoma Staging committee debated whether or not to continue this criterion for this small, but definable group of patients with microsatellites. A decision was made to retain these staging rules, and the data from the MSKCC Melanoma Database offers contemporary results to support this decision.[2,6] In addition, their results make a compelling case for performing sentinel node biopsy in those patients with clinically negative regional nodes, since 71% of such patients had microscopic nodal metastases.

In this rather small sample of patients with microscopic satellites, the impact of nodal status was profound. Thus, patients with microsatellites around the primary melanoma and pathologically negative sentinel node had 5-year survival of 60%, while none of those patients with microsatellites and nodal metastases lived more than 5 years ($p = 0.02$). These survival results are similar to that in a larger sample size from the 2008 AJCC Melanoma Staging Database which contained new information about 399 patients with intralymphatic metastases and negative nodes (N2c).[2] The 5-year survival rate was 69%, similar to that reported in the MSKCC study. These are somewhat more favorable survival rates than previously reported in the literature, and higher than for the remaining cohort of stage IIIB patients (54% at 5 years).[3] Nonetheless, the AJCC Melanoma Staging Committee noted that the category of stage IIIB was presently the closest fit and recommended that the 6th edition staging definition be retained.[2,6]

Finally, the authors make comparisons of a very small number of patients with metastases in the sentinel node but who, for reason not explained, did not have completion lymphadenectomy. The survival rate of these patients was no different from those who did have completion lymphadenectomy. Since most all of these patients eventually died of distant metastases, the lack of survival differences is not surprising. In a retrospective analysis like this, and without knowing more about the clinical decision making that led to some patients not having completion lymphadenectomy, it would be difficult to make any conclusions about any survival benefit of lymphadenectomy in these high-risk patients. Even in those circumstances where survival rates are not increased, there may still be a justification for completion lymphadenectomy to achieve regional disease control, although the benefit–risk indications should be higher in this circumstance.[15] The issue of completion lymphadenectomy is still a debated subject, as evidenced by the results from the National Cancer Database that only 50% of patients with biopsy-proven metastases in the USA have completion lymphadenectomy as recommended in national melanoma guidelines.[16]

What are the implications for surgical excision of primary melanoma? Our present approach is to excise a margin of normal skin and underlying subcutaneous tissues to incorporate the primary melanoma and lymphatics immediately surrounding the melanoma to prevent subsequent development of a local recurrence, defined as tumor within 2 cm of the surgical scar. The appearance of a local recurrence after appropriate wide excision of a melanoma is usually associated with aggressive tumor biology of the primary melanoma (i.e., increased thickness and mitotic rate, ulceration) and is a harbinger of fatal metastases in the majority of such patients. An interesting speculation is that intralymphatic satellites around a primary melanoma have a role in the subsequent development of "local recurrences." The survival rates of such patients with local recurrences are virtually the same as those with intralymphatic metastases.[17] One could hypothesize that local recurrences are, in fact, a manifestation of intralymphatic disease, not of retained primary melanoma cells that grow back with an unusually aggressive biological capacity for metastases. This explanation is a much more logical rationale for why we perform a wide excision of normal-appearing skin surrounding a primary melanoma, that is, to excise microsatellite metastases that are usually not detected without serial sectioning of the primary melanoma. It is interesting that, in the entire MSKCC database of 3,753 patients, there were 162 (4.3%) with microscopic satellitosis in their primary melanoma, most of whom had clinically evident regional or distant metastases. The results of this study clearly demonstrates the importance of performing sentinel node biopsy in those patients without clinical or radiological evidence of nodal metastases, since about 70% of such patients will, in fact, harbor clinically occult nodal metastases. More knowledge about the true incidence of microsatellites and their distance from primary melanomas of varying T stage might help in the design of future clinical trials to determine what width of surgical margins will prevent the development of a fatal local recurrence later on.

Finally, the melanoma surgeons at MSKCC, like others who have maintained prospective cancer databases through the years, are to be commended for their continued investment in this valuable resource. These prospective databases enable us to examine specific details of patient management that are useful in the staging, prognosis, and treatment outcomes of our patients.

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