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EDITORIAL – MELANOMAS

Should Patients Being Considered for Surgical Management in Melanoma Centers Have Their Histology Reviewed by Specialized Pathologists?

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The outlook for patients with cutaneous melanoma has substantially improved. This is attributable to a variety of factors, including enhanced patient and professional awareness of the clinical events and changes in appearance that mark the early evolution of cutaneous melanoma. This facilitates early clinical diagnosis at a time when local surgery can be curative. Increasingly, logical approaches to the extent of surgical clearance of primary tumors and new approaches to the management of the regional lymph nodes have also been contributory.[1,2] Primary care physicians and general dermatologists, while willing to undertake excision of nonmelanocytic and clinically benign melanocytic lesions, are less often willing to undertake definitive excision of diagnostically established primary melanomas, and are seldom prepared to perform lymphatic mapping and sentinel node biopsy. This has led to the evolution of highly specialized "melanoma surgeons" who work in complex multidisciplinary units that focus on surgical management of all clinical stages of cutaneous melanoma.

I have been associated with such a unit (i.e., the Division of Surgical Oncology at UCLA) for many years, and from my day-to-day experience, I strongly recommend that the histology of alleged primary melanomas is reviewed prior to any extensive surgery by a surgical pathologist or dermatopathologist who has extensive experience in the interpretation of melanocytic lesions. We usually agree with the diagnosis rendered by our colleagues in the community, but not always. Most problems relate to overdiagnosis of atypical, but benign, melanocytic lesions that represent dysplastic nevi, variants of Spitz "nevi," deep penetrating nevi, and cellular blue nevi. Most surgeons are comfortable with this extra layer of review, despite the inconvenience of procuring the original slides, the possibility of modest delay to operative plans, and a cost increase to the patient. Conversion of those who are less in favor of additional review rapidly follows their experience with cases in which a second opinion significantly changes the diagnosis, the T stage, and the predicted outcome for the patient or the evidence used to determine the need for lymphatic mapping and sentinel node biopsy. Although cumulated experience has made me (and many of my colleagues) committed supporters of specialist pathology review prior to major local or regional surgery for cutaneous melanoma (and other neoplasms), this position is derived from clinical workday experience rather than deliberately winnowed scientific evidence.

Formal evidence that emphatically supports specialist pathology review prior to surgery is provided by the excellent paper by Niebling et al.[3] in the current edition of the *Annals of Surgical Oncology*. The authors from the Melanoma Institute of Australia (MIA) evaluated 5,011 pairs of pathology reports from melanoma patients referred to their institute for further treatment between 2002 and 2011. They compared the pathology reports prepared at the referring institutes (Non-Melanoma Institute of Australia (NMIA) reports) with the findings at MIA (MIA reports): diagnosis, information needed to determine American Joint Committee on Cancer (AJCC) T staging, the extent of wide excision required,[4] and the need for lymphatic mapping and sentinel lymph node biopsy (SLNB).[5]

They found clinically significant diagnostic differences in 5.1 % of patients: 108 of 529 regarded as melanoma in situ (MIS) in the NMIA reports were upgraded to

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invasive melanoma by MIA review (20.4 %), and 8 of 529 were downgraded to a benign diagnosis (1.5 %). There were 14 of 3,753 lesions reported as invasive melanoma by the NMIA report (0.4 %) that were considered benign by MIA and 125 were downgraded to MIS (3.3 %).

These errors are less likely if a generous, oriented, uncrushed biopsy, obtained using a scalpel rather than tissue-distorting cautery is provided for analysis. This tissue should be differentially ink-marked (to maintain orientation) then extensively sampled in the pathology cutting room to determine whether the lesion is purely in situ or microinvasive. Immunohistochemistry with antibodies to tyrosinase, Mart-1, or Microphthalmia-associated transcription factor (MITF) facilitates this separation. To exclude the presence of desmoplastic melanoma, which may be dismayingly subtle in its morphology, antibodies to S-100 and Sox-10 are of real value.[6] Separation of atypical nevi and nevoid melanoma can be truly challenging, but immunohistology with antibodies to Ki67 and HMB-45 may be of real assistance.

Information necessary to assess AJCC T stage, the basis for determining optimum width of excision and predicting prognosis, was provided in 86.5 % of NMIA reports and 97.6 % of MIA reports ($P < 0.001$). In 4,269 patients, where the NMIA and MIA pathologists agreed on a diagnosis of "melanoma" specialist review changed the T classification in 22.1 % of cases. In 3,620 cases, where both groups of pathologists agreed a diagnosis of "invasive melanoma" review changed the T classification in 712 (9.7 %): T stage increased in 304 cases (8.4 %) and decreased in 408 (11.3 %). Breslow thickness should be carefully assessed for all invasive primary melanomas, using a micrometer that has been calibrated for the specific microscope that is used. The measurement is from granular layer or ulcer base to the deepest invasive contiguous melanoma cell. Melanoma cells sheathing skin appendages should not to be measured. If true microsatellites are present, they should not be included in the formal Breslow thickness, but a separate and clearly described additional measurement can be made to the satellite. Lymphoid infiltrates and subjacent pre-existing nevi should not be included in the Breslow measurement.

Criteria necessary to determine the need for lymphatic mapping and SLNB were provided in 94.5 % of NMIA reports and 99.4 % of MIA reports ($P < 0.001$). Recommendations in regard to SLNB changed after MIA rereview in 407 patients (8.6 %): in favor of SLNB in 239 patients (5.1 %) and against SLNB in 168 (3.5 %). The recent definitive report by Morton et al.[2] demonstrated that the benefits of lymphatic mapping and SLNB are greatest in patients with intermediate thickness (1.2–3.5 mm) melanomas, another argument for careful assessment of Breslow thickness in all primary melanomas. Extensive multivariable analysis investigated the characteristics of melanomas in which changes in interpretation were most common. Changes in diagnosis were most frequent in melanomas of the head and neck area that were 1 mm thick or less. Changes in T classification were most frequent in partially biopsied melanomas of the head and neck area. Changes in recommendations for extent of wide excision and SLNB were most frequent in partially biopsied melanomas of the head and neck area that were 1 mm thick or less.

The authors admit that the histopathologic diagnosis of primary melanoma can be truly difficult.[7] Their findings demonstrate that misdiagnosis and incomplete/inaccurate reporting of primary melanoma is relatively frequent. Misdiagnosis and incomplete pathological evaluation carry real risks that management strategies will be inappropriate, leading to less than optimal outcomes. Misdiagnosis of melanocytic lesions is one of the most frequent triggers for medico legal actions in the United States.

Treating surgeons remain entirely responsible for decisions regarding extent and timing of review of pathology material from their patients. They will certainly continue to recommend the course that they deem best, but will find much of interest in Niebling's salutary paper (i.e., data that will help determine the extent that they request re-review of primary melanomas).

What lessons should pathologists learn from this paper? We certainly know how difficult and treacherous it can be to interpret melanocytic lesions, and thus we should welcome additional constructive opinions as being in the patients' interests. Recent developments in regard to AJCC T staging and the criteria that determine whether or not lymphatic mapping and SLNB will be offered require that additional data be recorded to constitute an acceptably complete report of a primary melanoma. Determination of these data will represent an increase in workload for some pathologists, but this seems justified by the major contribution to enhanced patient management that such information represents.

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