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EDITORIAL – MELANOMAS

Is a "Merkel" Just Like a Melanoma? The Pathologic Analysis of Merkel Cell Carcinoma Specimens

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I remember being presented my first pathology report for a patient with Merkel cell carcinoma (MCC). What caught my attention the most was the absolute lack of detail in the report, which was generated from a leading academic medical center. Were treatment decisions really being made on such rudimentary variables, such as tumor *diameter*? At the time, however, a busy clinic and the multiple obligations of a surgical fellow pushed the thoughts to the back of my head. Yet that experience was brought back to the forefront of my mind once again only a few days later when our internal review of that Merkel cell cancer specimen was completed. I was now staring at a pathology report with a wealth of descriptive information similar to what a standard melanoma pathology report would include: tumor *thickness*, ulceration, mitotic count, etc. Now I was thoroughly engaged because I was completely confused—what was the important primary tumor data that a clinician should use to make subsequent treatment recommendations in this rare cutaneous malignancy? Do the same variables that are associated with outcomes in melanoma apply *a priori* to MCC? The idea seems logical enough, given that they are both "skin cancers." However, there also are many differences (cell of origin, growth pattern, proliferative index/growth rate, etc.) that might make using the melanoma prognostic factors to risk stratify MCC, such as placing the proverbial "square peg in a round hole"; it is entirely possible that the most significant similarity between melanoma and MCC is that they both start with "m."

In melanoma, the American Joint Committee on Cancer (AJCC) stage classification and determination of the prognostic significance of tumor thickness, mitotic rate, and ulceration is based on an exhaustive analysis of more than 30,000 patients with stage1–3 melanoma with excellent clinical, pathologic, and follow-up data.[1] In contrast, the AJCC staging system in MCC is based on a population-based analysis (utilizing data from the National Cancer Database [NCDB]) of 5,823 patients.[2] However, unlike the melanoma dataset, the NCDB data is quite limited. For example, detailed pathology data and long-term follow-up are missing. Also, cause of death is not recorded, and thus it is not possible to determine associations between clinical and pathologic variables and death from MCC. In rare diseases like MCC, where large, prospective, randomized, clinical trials will almost certainly never occur, detailed reports of natural history provide excellent insight into the disease and form the best foundation to guide treatment recommendations.

Our 2010 report on 412 patients represents the largest single-institution experience in MCC.[3] Although this analysis provides a comprehensive analysis (similar to the AJCC melanoma database) of the natural history of MCC at a tertiary referral center, it is still limited by the rarity of the disease and the biases of any single-institution study. For example, as a stand-alone cancer center, we did not have a large number of immunosuppressed solid organ transplant patients with MCC in our data set, which differs from many other single-institution series of MCC. Despite these limitations, strong attention to detail in data collection and excellent follow-up in some single-institution series represent the best strategy to study patients with rare diseases, such as MCC. For example, we clearly

Editorial regarding "Increasing tumor thickness is associated with more frequent recurrence and poorer survival in Merkel cell carcinoma patients," by Lim & Thompson, et al. (Manuscript ID ASO-2011-12-2319.R1).

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demonstrated the weakness of overall survival (OS), the endpoint from the NCDB data used to formulate the AJCC staging system for this rare tumor, as a relevant endpoint in MCC; because MCC is a disease of elderly patients, more than half of the patients die of something other than MCC.

In this issue of *Annals of Surgical Oncology*, Lim et al. utilize their high-caliber institutional data from the Sydney (Australia) South West Area Health Service to determine whether a more extensive (melanoma-like) analysis of primary MCCs is associated with disease-free and disease-specific survival (DFS and DSS, respectively). Most notably, in their analysis of 104 MCC specimens, increasing primary tumor *thickness* was significantly associated with poorer DFS (hazard ratio = 1.12, $p = 0.002$). Patients with thin primary tumors (≤10 mm) had improved 5-year DFS and DSS compared with those with thick (>10 mm) tumors (69 vs. 18%; $p = 0.002$ and 97 vs. 74%; $p = 0.006$, respectively).

Analyzing MCC specimens in a fashion analogous to melanoma (including variables such as tumor thickness, tumor-infiltrating lymphocytes, and solar elastosis) is not new. The current results are in agreement with a 2008 study by Busam on 156 patients where increasing tumor thickness also was associated with worse DSS.[4] The current study also found a moderate positive correlation between Ki-67 staining and tumor thickness and a strong positive correlation between Ki-67 staining and mitotic rate. However, in their thorough analysis, there were no other clinical or pathologic variables associated with DFS or DSS, including ulceration, mitotic rate, lymphovascular space invasion (LVSI), perineural invasion, presence of tumor infiltrating lymphocytes (TILs), and immunohistochemical staining for p53, p63, and Ki-67.

So, it seems that MCC is *sort of* like melanoma with respect to pathologic analysis, in that patients with thicker (or bigger) tumors fare worse. Single institution studies of patients with MCC are always limited by factors of selection bias and inadequate patient numbers. With that in mind, when the association between tumor *depth* and outcomes is reported by several authors from different institutions, it may have clinical relevance. A negative result, however, could very easily be a false negative reflecting these limitations. For example, contrary to other reports, the failure by Lim et al. to show an association between p63 and outcomes in MCC should be viewed in this context.[5,6] This is highlighted by their low rate of p63 positivity (9 %) compared with other studies (53 %), reflecting inherent differences between the study populations.

Importantly, and in contrast to the present study, we also found that LVSI was critically important in predicting recurrence and DSS in MCC.[3,7] It is logical that depth and LVSI should have a relationship, because deeper tumors will have access to the lymphovascular spaces. It may be that LVSI, which can be somewhat represented by depth, is a critical variable in predicting outcomes in MCC. As a variable, LVSI is often not included in MCC pathology reports. Furthermore, the determination of LVSI is a product of how hard the pathologist looks for it, including the use of immunohistochemical methods to stain the lymphovascular channels, which increases the yield of LVSI. This is certainly reflected in the large differences in LVSI reported in series of MCC.[3,8]

What then, if anything, is to be done with primary tumor variables for which conflicting reports exist in the literature with respect to their association with outcomes in MCC? Once again, some perspective from melanoma is helpful. If we examine how mitotic rate became incorporated into the AJCC staging system for melanoma, the difficulty in characterizing a rare disease like MCC become clearer. Through the herculean efforts of the AJCC Melanoma Staging Committee, more than 30,000 patients from 17 participating institutions have been analyzed *prospectively* to group patients into stages that were associated with outcomes.[1] In 2009, the 7th edition of the AJCC melanoma staging system included mitotic rate for the first time, and it was found to be associated with survival. One can thus appreciate the chasm that exists between melanoma and MCC—the largest discrepancy lies in an order of magnitude difference in numbers of patients included in such analyses.

In the present study, the authors also comment that, in their experience, SLNB does not accurately predict recurrence in MCC.[9] Based on this, they conclude that SLNB is not a useful staging tool in MCC, which is reflected in the low percentage of patients that underwent SLNB in this study (7 %). Our report of SLNB in MCC had similar findings with respect to recurrence, but we came to a very different conclusion.[7] Patients with a positive SLNB nearly always underwent further treatment (and even if they did not, removal of the SLN is a form of intervention with potential therapeutic benefit), whereas those with a −SLNB rarely underwent further treatment. Thus, selection bias in treatment decisions based on SLN status makes it impossible to determine a causal relationship between SLNB status and outcome. Supporting this observation, we also found a substantially higher rate of nodal recurrences in patients who did not undergo SLNB (stage IB and IIB) compared with those who underwent the SLNB procedure (stage IA, IIA, and IIIA).[10] So, where do we go from here? As was mentioned above, the key to making progress in rare diseases, such as MCC, is maintaining high-quality, prospectively collected data related to the diagnosis, treatment, and follow-up of patients. This includes standardizing the manner in which MCC specimens are analyzed by pathologists. We would advocate that institutions with a substantial interest in and volume of MCC patients prospectively collect uniform data and report them

in a synoptic fashion. Other variables, exemplified by the growing literature regarding associations between the Merkel cell polyoma virus and outcomes in MCC, should be included.[11] Whenever possible, tissue banking of fresh tumor specimens is to be strongly supported. With regard to treatment, we continue to advocate offering SLNB to all patients with clinically localized MCC, as the implications of nodal basin microstaging are as yet not completely understood in this nodotrophic tumor. Treatment decisions should be made based on available evidence and also should be diligently recorded. Importantly, complete follow-up with diligent recording of patterns of recurrence and cause of death are imperative if we are to fully understand the natural history of this enigmatic disease. The study by Lim et al. is clearly a significant contribution in this regard.

One could envision a time in the not-too-distant future where data could more effectively be compared across institutions to have something akin to the best of both worlds—a large data set of patients with high-quality data containing the variables of interest to the MCC community. Such a scenario would be exceptionally helpful in guiding treatment recommendations and designing future clinical trials in this rare disease.

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