Management of Merkel Cell Carcinoma

What We Know

MERKEL CELL CARCINOMA IS A GROWING health problem and the second most common cause of nonmelanoma skin cancer death. A recent review of the population-based cancer-related death registry (1994-1998) in the state of Western Australia detected 120 deaths from nonmelanoma skin cancer, including 89 from squamous cell carcinoma and 22 from Merkel cell carcinoma.[1] Incidence of Merkel cell carcinoma appears to be increasing, with the rate detected by the Surveillance, Epidemiology, and End Results (SEER) registry rising 3-fold from an age-adjusted rate of 0.15 cases per 100 000 in 1986 to 0.44 per 100 000 in 2001.[2] The estimated annual percentage change in incidence during this period was 8% per year for Merkel cell compared with 3% per year for melanoma. Factors contributing to the rise may include a higher concurrent risk of suppressed immunity, such as that associated with organ transplantation, and the share of the population represented by elderly persons, who are at highest risk for Merkel cell carcinoma.

See also pages 685 and 693

In short, it is now apparent that Merkel cell carcinoma is a major public health concern. Well-intentioned but ad hoc treatment regimens are not sufficient for approaching this dangerous but no longer rare tumor. Hence the importance of the comprehensive meta-analytic reviews by Gupta et al[3] and Lewis et al,[4] which clarify, respectively, the utility of sentinel lymph node biopsy and adjuvant local irradiation in the staging and treatment of Merkel cell carcinoma, particularly early-stage disease.

Patients with Merkel cell carcinoma can be staged using the American Joint Committee on Cancer staging system[5] for skin cancer or the technique popularized by Yieingpruksawan et al,[6] which categorizes patients into 3 categories, stage I (localized), stage II (locoregional), and stage III (distant metastasis).

Gupta et al[3] conclude that sentinel lymph node biopsy detects microscopic nodal disease in a significant proportion of patients who would otherwise have been understaged by clinical examination and computed tomography (CT) results alone. Additionally, since adjuvant treatment of sentinel lymph node–positive lesions is associated with improved prognosis, sentinel lymph node biopsy permits directed therapy, which leads to longer relapse-free survival.

Approximately 25% of the cases of sentinel lymph node biopsy examined by Gupta et al[3] were from a local cohort at Dana-Farber Cancer Institute, and the remainder were culled from a so-called case-level meta-analysis of studies larger than single case reports. That is, only reports in the literature that described individuals separately and completely, rather than as part of summary or aggregate data, were included. Further, leaving out reports of single cases reduced the likelihood of biasing the meta-analysis in favor of unusual or severe outcomes. Double-counting was avoided by detecting cases that were included in more than 1 series.

These commendable efforts notwithstanding, retrospective data pooled from a number of sources have inherent shortcomings. In the series used in the analysis, sentinel lymph node biopsy was not necessarily offered to consecutive patients. It is possible that only more sick-appearing patients were provided this option, with such selection bias contributing to the high rates of detection of disease by sentinel lymph node biopsy. In addition, not all of the contributing reports were likely of equivalent quality, with some including as few as 2 cases and others meeting only the minimum threshold of 1 month of follow-up.

Gupta et al[3] define sentinel lymph node biopsy as a diagnostic gold standard, but clearly theoretic failure is possible, and the results of a complete lymph note dissection may be more revealing. Indeed, in the Dana-Farber series, fewer than half (5/11) of sentinel lymph node biopsies were successful, suggesting that this technique is markedly operator dependent.

Staining with cytokeratin20, a histologic marker specific for Merkel cell, is highlighted by Gupta et al[3] as a key element of improved detection via sentinel lymph node biopsy. The utility of this stain is confirmed by retrospective cohort studies from the University of Michigan[7] and Memorial Sloan-Kettering Cancer Center.[8] Clinicopathologic correlation has also revealed, in other studies, a similarly high sensitivity and specificity associated with immunostaining using CAM 5.2, an antibody that reacts against low-molecular-weight cytokeratin and neurofilaments.[9]

Computed tomography was assessed by Gupta and colleagues[3] and found to be wanting as a staging test. However, at least 1 of the Dana-Farber cases of nodal involvement was detected successfully by CT but not sentinel lymph node biopsy. More generally, it is unclear that CT is the optimal imaging test for Merkel cell carcinoma in the skin and lymph nodes. Nuclear medicine with somatostatin (octreotide), positron-emission testing, and magnetic resonance imaging (MRI) have also been used by others. In particular, the superior soft-tissue resolution of MRI may render this procedure preferable to CT.

Recently, the first relatively large series (15 patients) in which the primary sites and metastatic foci of Merkel cell carcinoma were evaluated by MRI detected lymph node metastases in more than half of cases (n=8), and lung and bone metastases in some (n=5).[10] Diagnostic features on MRI are distinct, showing a mass with unusual multiple subcutaneous lymphatic metastases in a row formation, reticular stranding with lymphanginitis carcinomatosa, and large lymph node metastases with fine, compressed, retained fatty tissue. Magnetic resonance imaging may facilitate planning the target volume for radiation therapy and tracking tumor characteristics before and after therapy. Another diagnostic technique for Merkel cell carcinoma is fine-needle aspiration of affected lymph nodes, and the cytopathologic appearance of metastatic Merkel cell carcinoma has been described.[11] Fine-needle aspiration may be indicated when it is necessary to determine the provenance of clinical node-positive disease.

While Gupta et al[3] focused on delineating the utility of sentinel lymph node biopsy, they hazard some thoughts about the usefulness of biopsy findings in guiding adjuvant therapy, defined as total lymph node dissection, radiotherapy, or chemotherapy. The message is that when sentinel lymph node biopsy findings are positive, adjuvant therapy should be delivered because such therapy is associated with much higher relapse-free survival rates in this context. The unanswered question is what should be done when the sentinel lymph node biopsy finding is negative. Given that such biopsy may be unsuccessful, inaccurate, or simply not done, perhaps adjuvant therapy should be delivered regardless of the diagnostic outcome. Current consensus guidelines from the National Comprehensive Cancer Network (NCCN)[12] recommend adjuvant radiotherapy to nodes when sentinel lymph node biopsy has not been performed or when there is clinically evident nodal disease. Such an approach would modify the utility of sentinel lymph node biopsies: adjuvant therapy would only be withheld when nodes were clinically uninvolved and sentinel lymph node biopsy was definitively negative. Indeed, the NCCN guidelines suggest that even in some cases of sentinel node negativity, local radiation therapy to the primary site may be considered.[12]

Interestingly, Gupta et al[3] find that tumor size at the time of diagnosis is not associated with relapse-free survival. This counterintuitive finding should be of special interest to general clinical dermatologists and other first detectors. It may also be one of the few reassuring thoughts to be shared with patients who present with large lesions.

Relapse-free survival, rather than disease-free survival, is the main long-term outcome measure in the study by Gupta and colleagues.[3] As they note themselves, use of this suboptimal marker is necessitated by the dearth of long-term follow-up data on mortality. The median follow-up of 12 to 15 months is not sufficient to capture overall survival. Again, this is one of the limitations of retrospective data from a number of distinct case series. The theoretic risk is that long-term, disease-related survival, the measure patients care about most, may be minimally impacted by sentinel lymph node biopsy and subsequent adjuvant therapy.

Retrospective series from Europe appear to mostly reinforce the results of Gupta et al.[3] But the admittedly smaller cohorts of Acebo et al[9] (11 patients) and Maza et al[13] (23 patients) lead to less certain conclusions. The standard of care for stage I Merkel cell carcinoma in Europe appears essentially similar to that in the United States, beginning with surgical excision of the primary tumor with 2- to 3-cm margins and continuing to regional lymph node surgery and/or adjuvant local radiation therapy, when indicated. Maza et al[13] found 11 patients with positive lymph nodes and 12 with negative nodes; most of those with positive sentinel lymph nodes underwent elective lymph node dissection, and all patients (node positive and node negative) with primary tumors larger than 2 cm received local adjuvant radiotherapy at a dose of 40 to 60 Gy (4000-6000 rad). Median survival was 35.5 months for the patients with positive sentinel lymph nodes and 49.1 months for those with negative sentinel lymph nodes, but the difference was not statistically significant, and follow-up was incomplete.

Lewis et al[4] address the second half of the puzzle. Regardless of the outcome of staging procedures like sentinel lymph node biopsy, the decision must be made whether to treat local disease with adjuvant therapy and, if so, the type of therapy that is most appropriate. Specifically, Lewis and colleagues compare surgery alone with *combination therapy*, which is defined as surgery plus adjuvant radiation therapy to the local tumor bed and in some cases also other procedures, such as chemotherapy or elective lymph node dissection. Again, the method is a meta-analysis of prior reports. All included patients had a primary cutaneous Merkel cell carcinoma and most were stage I. Unlike the meta-analysis by Gupta et al,[3] studies with aggregate-level data and single case reports were not excluded from the primary analysis.

The authors compared the 2 treatment approaches with regard to local recurrence, regional recurrence, distant metastases, and survival. Local recurrence with combination therapy was almost 4 times less common than with surgery alone, and 5-year local recurrence-free survival was 88% with combination therapy and 61% with surgery alone. The benefit on local recurrence of combination therapy was greater for primary lesions smaller than 2 cm in diameter and for stage I disease. Regional recurrence was similarly less common after combination therapy, with patients treated with surgery being 3 times more likely to develop such recurrence; the rate of 5-year regional recurrence-free survival with combination therapy was nearly twice that with surgery alone (77% vs 44%).

However, rates of distant metastasis, overall survival, and cause-specific survival were similar for surgery and combination therapy. Subgroup analyses that excluded aggregate-level data and single case reports did find a difference in survival rates, with hazard ratios of 0.63 and 0.62 for overall and cause-specific survival after combination therapy, respectively, compared with surgery alone. That is, disease-associated survival was over ⅓ more likely in patients receiving combination therapy.

As in Gupta et al,[3] the significant limitation of the study by Lewis et al[4] was the lack of uniformity in the many case series from which data were extracted. The authors clarify this themselves, noting that data were inadequate to dis-

tinguish which type of surgical technique, whether it be local or wide excision or Mohs surgery, was most successful. Similarly, the dose of irradiation varied across patients, and the results do not clarify the optimal dosage. Finally, in some cases, patients also received chemotherapy and/or elective lymph node dissection, and it is unclear whether these contributed to the survival advantage associated with combination therapy.

Also, and in this too the authors are blameless, the limited size of the data set precludes definitive conclusions. While locoregional recurrences are important to patients, distant metastases and disease-related survival are doubtless more important. But these more severe outcomes are less common, particularly when patients are only observed for a few months. So the findings of Lewis et al[4] regarding distant metastases and survival are underpowered. That is, there are not enough patients experiencing these outcomes to say for sure whether surgery alone or combination therapy is better. While analyzing a larger number of patients may confirm the study's findings in this regard, the direction of the results might also change. Further, the post hoc analysis indicating that deleting aggregate data and single cases leads to a survival benefit for combination therapy is a weak result given that it was a deviation from the study's initial methods.

In defense of Lewis et al,[4] their conclusions are similar to those of recent longitudinal case series from single centers. Veness et al[14] at the University of Sydney, Westmead Hospital, describe 86 patients with Merkel cell carcinoma treated from 1980 to 2002. Those treated with surgery had a rate of nodal relapse of 37% (14/36) compared with 18% (7/38) for patients treated with surgery and adjuvant radiotherapy. Median disease-free survival was 10.5 months for the group receiving both surgery and radiotherapy and 4 months for those undergoing surgery alone. A series of 34 patients described by McAfee et al,[15] of whom 32 received surgery and radiotherapy, revealed 5-year rates of locoregional control of 80%.

A few competing studies have reached different conclusions. In a series of 251 patients treated at Memorial Sloan-Kettering Cancer Center from 1970 to 2002, Allen et al[16] did not detect any decrease in the rate of local recurrence or nodal recurrence associated with the use of adjuvant radiotherapy. Significantly, these results are less convincing given the very long time interval of this series and the dissimilar and evolving treatment strategies used over this period.

There does not, however, appear much dispute that chemotherapy, whether for adjuvant treatment or advanced disease, is ineffective in the treatment of Merkel cell carcinoma. Systemic agents that have been used as adjuvant therapy in node-positive disease include cisplatin or carboplatin, etoposide, and vincristine; doxorubicin has been used for treatment of metastatic disease. Initial response rates have been reported to be as high as 75%, but the median survival time for patients with distant metastatic disease remains a dismal 9 months. Protein kinase inhibitors may be promising therapies for the future, with a phase 2 trial of imatinib in process for the treatment of metastatic or inoperable Merkel cell carcinoma. Imatinib's activity includes inhibition of the expression of the proto-oncogene c-kit, which is frequently expressed in Merkel cell carcinoma.[17]

In summary, the 2 articles in this issue, by Gupta et al[3] and Lewis et al,[4] are a major contribution to clinical management of early-stage, locoregional Merkel cell carcinoma. Gupta et al sift through the best available data to conclude that sentinel lymph node biopsy is a valuable prognostic indicator in the staging of Merkel cell carcinoma. After excluding suboptimal case reports, Lewis and colleagues find that patients receiving adjuvant radiation treatment with surgical excision have lower disease-associated mortality than those undergoing surgery alone. Neither of these results is conclusive, but both derive from thorough, methodologically rigorous analyses of the extant literature. Additionally, both results provide clinicians with valuable advice about how to approach this challenging and worrisome tumor.

Given that Merkel cell carcinoma is still uncommon relative to other nonmelanoma skin cancers, randomized clinical trials of diagnosis and therapy are difficult to perform and as yet have not been done. Unfortunately, single-institution, open-label trials and retrospective chart reviews are inherently subject to bias. This bias may be somewhat mitigated by pooling the results of many centers, as done by Lewis et al[4] and Gupta et al,[3] but this does not really solve the problem. A meta-analysis of potentially biased reports is likely to be biased as well. Selection bias occurs since included subjects may be sicker, easier to find, or more recently seen than those who are omitted; if, in turn, the analysis is not based on all the cases in a given population over a certain time period, the results may not be generalizable to this population.

Another relevant form of bias is information bias, which occurs when the methods of gathering information about the subjects are inadequate. In the case of the meta-analyses discussed, each of the centers contributing case series may have had biased methods for abstracting records and interviewing subjects. Idiosyncratic methods of record keeping may have systematically excluded certain types of patients with Merkel cell carcinoma. If, in some cases, case reports were derived from interviews with patients or health care workers, recall bias may have led to interviewees reporting information differently depending on how they were prompted. Indeed, even the rising incidence of Merkel cell carcinoma may be partially attributed to surveillance bias, with disease ascertainment now improving in areas like Australia where there is increased vigilance for nonmelanoma skin cancer.

Assuming that the general conclusions in the meta-analyses by Gupta et al[3] and Lewis et al[4] are confirmed by future randomized control trials, the effect sizes are likely to be smaller than they suggest. Even when randomized controlled trials confirm the quality of relationships described previously, the reduction of bias is associated with less dramatic associations than previously hypothesized.

In conclusion, the NCCN guidelines on Merkel cell carcinoma reflect the stark observation that the mean time to locoregional recurrence is 8 months, and the mean time to develop distant metastases is 18 months. Thus, regardless of the utility of additional staging tests and targeted adjuvant therapy, prompt extirpation of the pri-

mary lesion with clear margins should be performed whenever possible. The efforts and insights of Gupta et al[3] and Lewis et al[4] do not change the fact that Merkel cell carcinoma should first and foremost be removed surgically. If sentinel lymph node biopsy is performed, definitive excision should be delayed until after such biopsy. Thereafter, the results of the studies in this issue can be used to guide therapy and offer patients hope.

Murad Alam, MD

Correspondence: Dr Alam, Department of Dermatology, 675 N St Clair St, Suite 19-150, Chicago, IL 60611 (m-alam@northwestern.edu).
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