Merkel Cell Carcinoma Treatment With Radiation

A Good Case Despite No Prospective Studies

DERMATOLOGIC SURGERY

WITH A MORTALITY rate of roughly 25%, Merkel cell carcinoma (MCC) is significantly more dangerous than melanoma (roughly 15% mortality). Although precise numbers do not exist, its incidence of approximately 400 cases per year in the United States[1,2] is likely to be on the rise.[3] Factors that are likely contributing to this include the aging population (mean age of MCC onset is about 70 years), greater numbers of immunocompromised organ transplant recipients (a greater incidence and severity of MCC in this population over the general public has been reported[4]), and, of course, the increased sun exposure habits of the past few decades. Despite a great need for the best possible care for patients with this dangerous malignancy, significant confusion persists in the literature regarding optimal management of MCC.

Specifically, despite an extensive body of literature that supports a role for radiation therapy, there persist statements that suggest radiation therapy is unproven or unnecessary in managing this disease.[5,6] The accompanying report in this issue of the ARCHIVES by Mortier and colleagues[7] uses radiation therapy alone in managing MCC and underlines the unusual radiation sensitivity of this challenging tumor.

WHY IS THERE A LACK OF CONSENSUS IN THE TREATMENT OF MCC?

We believe there are several factors that have conspired to make the current treatment recommendations for MCC quite controversial. One is its rarity. Given only about 400 cases per year in the United States in 1997, it is about 100 times less common than melanoma (roughly 40 000 cases per year). With such low numbers, there are no prospective studies to provide us with high-quality data on

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which to base clinical decisions. Another reason for confusion is that no single specialty has taken a leadership role in managing this disease. This lack of a clear "owner" of MCC among its various caregivers (dermatology, medical oncology, radiation oncology, and surgery) has meant that the literature is distributed through these disciplines and is subject to the different biases that each field brings with it. A further problem is that the case reports and case series on which our current treatment recommendations are based are often unclear in important regards—lacking information such as the criteria for deciding which patients undergo adjuvant therapy and the outcomes based on therapies used for each patient. Given such handicaps, it is not surprising that uniform guidelines have not been established for MCC.

INADEQUACY OF SURGERY ALONE AND IMPROVED OUTCOMES WITH ADJUVANT RADIATION

Merkel cell carcinoma can be associated with very high recurrence rates—up to 100% for surgery alone (in 38 of 38 cases[8]). Even wide excision (>2.5 cm) has not been successful in controlling local recurrence, indeed providing no statistically significant improvement in outcomes compared with narrower excision in several studies.[9-11] These high rates of local persistence, and nodal metastasis may be due to rapid lymphatic spread. Indeed, roughly 33% of clinically uninvolved lymph node beds harbor metastasis as shown by positive sentinel lymph node biopsy results, suggesting early movement out of the primary lesion into the lymphatic system.[12]

Mohs micrographic surgery appears to be as good or better than wide excision, but limitations of these studies include relatively short follow-up times. In the largest series of MCC patients treated with Mohs surgery, Boyer and colleagues[6] stated that adjuvant radiation may not be required for control of MCC. We disagree with this assessment. Indeed, all 4 recurrences in their study occurred in patients treated only with Mohs surgery and no radiation. Their argument that this difference was not statistically significant does not justify the conclusion that radiation provides no utility as an adjuvant to Mohs surgery. When taken together, the global experience for MCC treated with Mohs surgery (70 patients) suggests that radiation therapy is associated with diminishing local and regional recurrence rates by roughly 50% (**Table 1**), although the small numbers again mean this is not statistically significant.

Compared with Mohs surgery, more extensive data are available on the efficacy of adjuvant radiation therapy for traditional excision of MCC. Numerous prior studies have suggested that adjuvant radiation improves local and nodal control in MCC.[8,10,11,14-20] In one of these reports, the addition of radiation reduced the rate of recurrence from 100% of 38 patients treated only with surgery to 30% of 34 patients treated with surgery and radiation.[8] Moreover, the median time to relapse in this study was increased from 6 months to 17 months by the addition of radiation therapy. We have summarized several studies in **Table 2** showing a statistically signifi-

cant improvement in local and nodal recurrences, although not in survival. It is important to mention that merging patients from multiple studies introduces biases likely to be hidden within each study, so such aggregate data must of course be interpreted with caution. Based in part on these data, we present a proposed treatment algorithm for MCC in the **Figure**.

Although it is beyond the scope of this editorial to compare lymphadenectomy with radiation therapy as adjunct therapies, their efficacy appears to be similar in controlling nodal disease while radiation has less severe side effects (such as pain and lymphedema) than completion lymphadenectomy. We therefore favor radiation therapy over lymphadenectomy in most situations for nodal control. In some cases, the possible (but undocumented) additional benefit of using both lymphadenectomy and radiation may outweigh the considerable risk of pain and lymphedema from this combined approach.

NEW INSIGHTS INTO RADIATION AS MONOTHERAPY

In this issue of the ARCHIVES, Mortier and colleagues[7] report surprising efficacy for radiation therapy when used as monotherapy for MCC. They describe 9 patients treated exclusively with radiation and 17 patients treated with both surgery and radiation. All patients in their study had stage I/early disease (nodes clinically uninvolved on presentation) with no stage II (nodes clinically enlarged) or stage III (distant metastases on presentation) disease. The median follow-up periods were 3 years (radiation only) and 4.5 years (surgery plus radiation). These follow-up periods are reasonable for this disease in which most recurrences occur within 2 years of presentation.[9] Surprisingly, none of the 9 patients treated with radiation alone had recurrence and only 2 of the 17 in the surgery plus radiation group had recurrence or had progressive disease. This study essentially doubles the total number of reported patients with stage I MCC treated with radiation as monotherapy.

There are, however, a number of surprising and confusing aspects in this study by Mortier et al. The major issue is the low recurrence rate in both treatment groups (0% for radiation alone and 12% for radiation plus surgery). What may account for these rates that are well below most of the typical reported recurrence rates? Indeed, based on the prior literature of 10 patients treated with radiation alone for MCC,[16,19-22] one might conclude that radiation as monotherapy for MCC is not very effective because 5 of the 10 patients experienced recurrence.[16] Importantly, however, 3 of the 5 recurrences reported in the prior literature were nodal recurrences in patients who did not receive radiation to the lymph nodes as they did in the Mortier et al study. A further factor may have been the use of a higher dose of radiation therapy in this study than is typical—6000 rad (60 Gy) delivered in 30 treatments, compared with the more typical 5000 rad (50 Gy) in 25 treatments. Also, most patients in the Mortier et al series received wide-field radiotherapy (in addition to the primary site, the majority also received prophylactic therapy to the lymph nodes and roughly 40% of patients from both groups received radiation to the in-transit regions). This study was unusual in that it was based solely on patients with stage I disease (nodes clinically uninvolved), and these patients typically have 2-year survival that is better than that of patients with stage II disease (56% vs 33% for stage II).[23] It is also possible that some further factor that remains unknown separates this French cohort from a more typical population of MCC patients with higher recurrence rates, suggesting caution in its interpretation.

Nevertheless, the report by Mortier and colleagues does underline the impressive efficacy that radiation therapy can have in treating MCC, sometimes even as monotherapy. The single most common site for MCC to occur is the head and neck region where complete excision may be difficult, impossible, or refused by elderly patients not eager for aggressive surgery. In such cases it is reassuring that radiation monotherapy may offer effective control. Indeed, other studies support the efficacy of radiation in incompletely excised primary lesions. In the largest of these, local control was successfully achieved in 6 of 7 cases of incompletely excised primary lesions.[8]

Table 1. Treatment Outcomes for Mohs Surgery Alone vs Mohs Plus Radiation Therapy (RT)*

	No. (%)			
Treatment (n)	Local Recurrence	Nodal Recurrence	Follow-up, mo†	References
Mohs only (39)	5 (13)	9 (23)	24	6, 13-15
Mohs + RT (31)	2 (6)	4 (13)	17	6, 13-15

*Recurrence rates in the group that also received RT were lower, but the differences were not statistically significant (Fisher exact test). Inclusion criteria for this analysis of studies: treatment modalities were specified with each patient and their outcome.

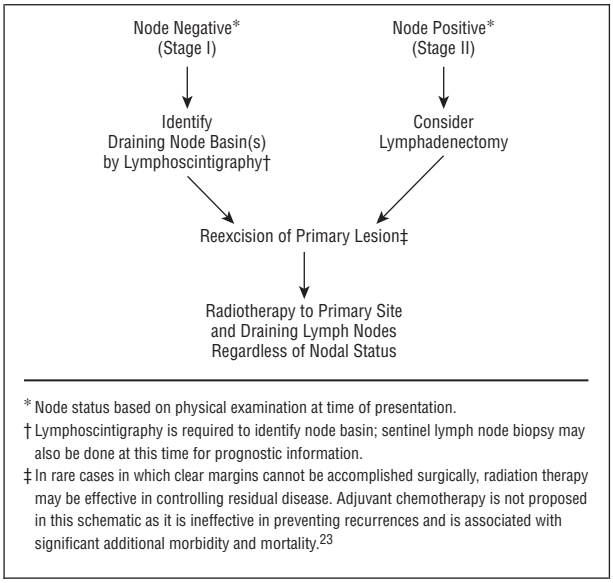
†Follow-up: weighted mean (based on number of patients in each study) of median follow-up periods from the 4 studies.

Table 2. Outcomes for Stage I Merkel Cell Carcinoma Treated With Surgery Alone vs Surgery Plus Radiation Therapy (RT)*

	No. (%)				
Treatment (n)	Local Recurrence	Nodal Recurrence	Distant Recurrence	Follow-up, mo†	References
Surgery only (63)	15 (25)	26 (42)	13 (21)	32	6, 17, 18
Surgery + RT (37)	1 (3)	8 (22)	4 (11)	23	6, 17, 18
P value	.005	.045	.27		

*Inclusion criteria for this analysis: at least 10 patients in the study in which the stage at presentation and treatment modalities were specified with each patient and their outcome.

†Follow-up: weighted mean (based on number of patients in each study) of median follow-up periods from the 3 studies.



* Node status based on physical examination at time of presentation.

† Lymphoscintigraphy is required to identify node basin; sentinel lymph node biopsy may also be done at this time for prognostic information.

‡ In rare cases in which clear margins cannot be accomplished surgically, radiation therapy may be effective in controlling residual disease. Adjuvant chemotherapy is not proposed in this schematic as it is ineffective in preventing recurrences and is associated with significant additional morbidity and mortality.[23]

Schematic for Merkel cell carcinoma therapy.

In summary, the lack of prospective, randomized data on which to make decisions in this very dangerous cutaneous malignancy is deeply frustrating and concerning. Despite this, there is evidence from many studies that radiation therapy is important in preventing the frequent local and nodal recurrences of MCC treated with surgery alone. Indeed, as described by Mortier and colleagues, radiation therapy has significant efficacy in selected cases of MCC even in the absence of surgery.

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