Merkel cell carcinoma adjuvant therapy: Current data support radiation but not chemotherapy

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Merkel cell carcinoma (MCC) is a skin cancer with 30% mortality and an incidence that has tripled in the past 15 years. There is agreement that surgical excision with negative margins is an appropriate therapeutic first step and that sentinel lymph node biopsy is a powerful prognostic indicator. After excision of detectable cancer, optimal adjuvant therapy is not well established. A role for adjuvant radiotherapy is increasingly supported by observational data. These data suggest that a regimen of surgery plus adjuvant radiotherapy is associated with both a lower loco-regional recurrence rate and longer overall survival when compared with surgery alone. In contrast, a role for adjuvant chemotherapy is not well supported. The rationale for chemotherapy in this disease is based on small-cell lung cancer, a more common neuroendocrine tumor for which chemotherapy is the primary treatment modality. Several issues call into question the routine use of adjuvant chemotherapy in MCC: lack of evidence for improved survival; the associated morbidity and mortality; important differences between small-cell lung cancer and MCC; and rapid development of resistance to chemotherapy. Importantly, chemotherapy suppresses immune function that plays an unusually large role in defending the host from the development and progression of MCC. Taken together, these arguments suggest that adjuvant radiation may be indicated for many MCC patients while adjuvant chemotherapy should largely be restricted to clinical trials. (J Am Acad Dermatol 2007;57:166-9.)

Merkel cell carcinoma (MCC) is a neuroendocrine cancer that typically presents as a rapidly growing nonspecific nodule on sun-exposed skin in people older than 65 years. The recent increase in incidence to more than 1000 cases a year in the United States has led MCC to become the second most common cause of nonmelanoma skin cancer death.[1,2] Optimal management for MCC beyond surgical excision is not agreed on, and no randomized trials have been carried out. Sentinel lymph node biopsy has been shown to be powerful in predicting subsequent recurrences and in determining whether further nodal treatment is indicated.[3,4]

DATA SUPPORT ADJUVANT RADIOTHERAPY FOR MCC

Adjuvant radiotherapy is associated with a marked decrease in local recurrences and a trend to improved survival in multiple retrospective studies. A meta-analysis was carried out on 1254 patients with MCC previously reported in the literature who met the following criteria: a single primary tumor arising on skin that was excised with negative surgical margins on whom follow-up data were included regarding recurrence and survival.[5] In this study, patients who received adjuvant radiation therapy had improved outcomes compared with those who received surgical excision only. Specifically, local recurrences at 5 years were 3 times less likely (12% vs 39%, $P < .001$) if adjuvant radiation was given, and a similar association was found for regional recurrences (23% vs 56%, $P < .001$) (Fig 1, *A*). Patients who received adjuvant radiation also had an improved overall and cause-specific survival, although this was not statistically significant.

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Although one large single institution study did not find a statistically significant improvement in outcomes if radiation therapy was given, only 13% of patients in this study received adjuvant radiation and those who received surgery monotherapy had exceptional results with only 8% experiencing local recurrences.[4]

In the most recent analysis of Surveillance Epidemiology and End Results (SEER) data, surgery plus adjuvant radiation was associated with substantially longer overall survival as compared to surgery without radiation (Fig 1, *B*).[6] Patients with MCC that received adjuvant radiation therapy (n = 477) had a median survival of 63 months, which was statistically better than the median survival of 45 months of those that received surgery alone (n = 689). Subgroup stratification according to the size of the primary lesion revealed the association of radiotherapy with improved survival to be present in tumors of all sizes, but to be particularly prominent in tumors >2 cm in diameter. Although this registry is observational, the two groups were similar for sex, race, surgical technique, and size of tumor. A potential source of bias was not addressed, as patients who were too ill to receive adjuvant radiation and died in the first few months were not deleted. Such patients would inaccurately bias the results towards benefit for radiation and this analysis was not performed. In aggregate, however, these observational studies strongly suggest improved outcomes in MCC with the addition of adjuvant radiation therapy at least in higher risk patients.

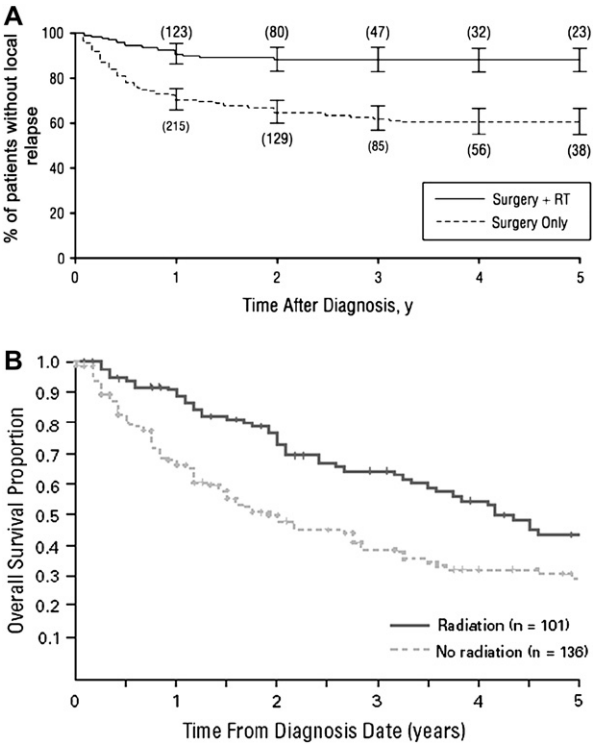

Fig 1. **A**, Adjuvant radiation therapy and local recurrence of Merkel cell carcinoma. Fraction of patients who are free of local relapse is plotted for 5 years after diagnosis. Numbers of patients (*in parentheses*) in each group who were at risk at that time point. All patients received surgery and those who also received radiation (*solid line*) are plotted separately from those who did not (*dashed line*) ($P < .001$ for difference). *Bars* represent 95% confidence limits. (Reprinted with permission, Copyright 2006 American Medical Association.[5]) **B**, Adjuvant radiation therapy and overall survival in Merkel cell carcinoma patients with primary tumor larger than 2.0 cm. The fraction of patients alive is plotted for five years after diagnosis. All patients received surgery, and those who also received radiation (*solid line*) are plotted separately from those that did not (*dashed line*) ($P = .003$ for difference). Although over 90% of MCC-associated deaths occur by three years after diagnosis[12] these "overall survival" curves continue down after three years due to deaths from non-MCC causes. (Reprinted with permission from the American Society of Clinical Oncology.[6])

ADJUVANT CHEMOTHERAPY FOR MCC IS NOT CURRENTLY SUPPORTED BY DATA

Many patients with MCC receive adjuvant chemotherapy in analogy to a more common neuroendocrine tumor, small-cell carcinoma of the lung (SCLC). However, there are several important differences between SCLC and MCC that suggest that therapy established for one disease should not automatically be extended to the other. Below are 6 issues that raise concern about the routine use of adjuvant chemotherapy in MCC.

1. Adjuvant chemotherapy for MCC has not been shown to improve survival. Several recent studies have failed to demonstrate that adjuvant chemotherapy provides a survival benefit for MCC. A 2003 Australian study appeared to show favorable outcomes for adjuvant chemotherapy in MCC.[7] However, a 2006 reanalysis of the data by the same authors using multivariate analysis to account for stage at presentation found no significant improvement in disease-specific survival.[8] Indeed, another recent study of 76 patients with stage II disease suggests that chemotherapy may actually reduce survival (Fig 2).[4] Specifically, node-positive patients who received adjuvant chemotherapy (n = 23) had a 4-year survival of 42% as compared with patients who did not receive adjuvant chemotherapy (n = 53) who had a 4-year survival of 60%. Although these node-positive patients were not randomized and this difference was not statistically significant, the 18% lower survival in the group that received adjuvant

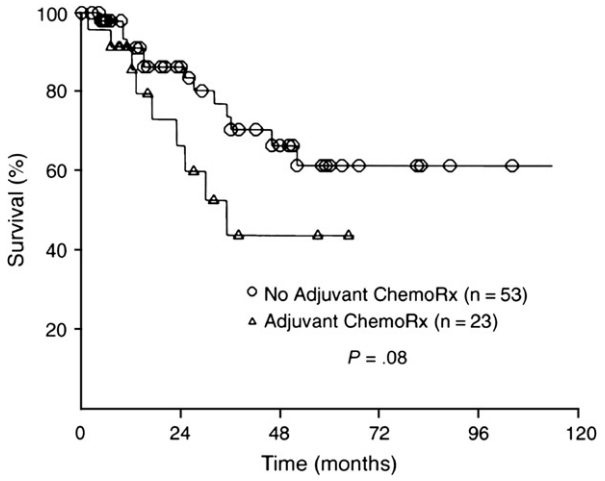

Fig 2. Adjuvant chemotherapy and survival in patients with Merkel cell carcinoma spread to lymph nodes. The group that received adjuvant chemotherapy had 20% lower survival than those who did not receive chemotherapy, although this was not statistically significant. (Reprinted with permission from the American Society of Clinical Oncology.[4])

chemotherapy does not imply a survival benefit for this treatment.

2. Chemotherapy for MCC is associated with significant treatment-related mortality. The largest single report of 204 patients with MCC treated with chemotherapy observed a toxic death rate of 3.4%.[9] A separate analysis of patients older than 65 years found that 16% of older patients with MCC died of complications of chemotherapy.[10] Given that the median age of MCC presentation is older than 70 years, and that the most commonly used regimen (cisplatin and etoposide) is identical for both adjuvant and therapeutic regimens, this death rate is significant. Although this mortality risk is similar to other cancers, it is more troubling in MCC given a lack of evidence for improved outcomes.

3. Adjuvant chemotherapy adds significant morbidity. In the largest clinical trial of patients with MCC who were given adjuvant chemotherapy, 63% experienced serious skin toxicities with moist desquamation in areas that were also irradiated.[11] More importantly, 40% of patients were hospitalized with neutropenia.[11] Patients who receive adjuvant chemotherapy routinely experience substantial hair loss and fatigue. Although tolerable if necessary, these morbidities negatively impact quality of life, increase infection risk, and are especially difficult to tolerate for elderly patients with MCC.

4. The rationale for adjuvant chemotherapy is based on a tumor that is biologically different from MCC. The more common neuroendocrine tumor, small cell lung carcinoma (SCLC), is routinely treated with chemotherapy as the primary modality. Although MCC and SCLC share striking histologic similarity, these tumors have distinct presentations, prognoses, and biological behavior. Accessibility of the primary lesion is one fundamental difference: SCLC is visceral with more than 75% of patients presenting with advanced disease that is not amenable to cure with surgery and radiation. In contrast, MCC originates in the skin often allowing earlier detection when surgery and radiation can be curative.[3,12,13] Given the >90% cure rate for node-negative MCC using locoregional therapy only[4], exposing patients at low risk to the known toxicities of adjuvant chemotherapy is not indicated. Even among patients with MCC at high risk (node-positive) there is approximately a 50% chance of cure by surgery and radiation and no evidence for improved survival by adjuvant chemotherapy as noted above. In contrast, chemotherapy in SCLC is better justified as a result of a proven survival benefit and the low chance of cure by surgery and radiation.[13] Furthermore, the biology of these cancers may be distinct. Specifically, the Ras/Raf/MEK/Map kinase pathway has been shown to be active in fewer than 5% of MCC and active in approximately 50% of SCLC.[14,15] As discussed below, MCC is highly sensitive to immune function in terms of incidence and survival. In contrast, SCLC appears to be less related to immune function. Although SCLC incidence is 2.1-fold increased in patients with HIV as compared with the general population, this is far less than the 13.4-fold increase in MCC in HIV and the lung cancer finding has been partly attributed to risk factors such as smoking.[16] Given these diverse differences, a role for chemotherapy in patients with MCC should be based on data from that disease rather than extrapolated from SCLC.

5. Resistance to chemotherapy develops frequently. Initially 40% to 70% of MCC is sensitive to chemotherapy with partial or complete responses.[10] In contrast, there are no good salvage mechanisms for recurrent disease initially treated with chemotherapy. As with many other malignancies, MCC seems to gain broad resistance to chemotherapeutic agents after an initial course of chemotherapy. Because there are no data to suggest adjuvant chemotherapy is beneficial in MCC it may make sense to withhold chemotherapy for palliation when surgery and radiation are no longer an option.

6. The immune system is unusually important in controlling MCC. MCC is distinct from many cancers because its incidence and prognosis are strongly related to immune function. This cancer occurs more frequently and behaves more aggressively in diverse immune-compromised populations.

There is about a 10-fold increase in incidence in solid organ transplant recipients and a 13.4-fold increase among patients with HIV.[17,18] Immune-compromised patients present with MCC at a more advanced stage (68% have nodal disease vs 39% of immune-competent patients with MCC) and at a younger age (53 vs 74 years).[3,12,17] Finally, MCC is more deadly in immune-compromised patients (56% disease specific mortality vs 25%-35%).[17] These data suggest that a healthy immune system is critical in both preventing the development and halting the progression of MCC. We speculate that the negative impact of chemotherapy on immune function may counteract benefits that come from reducing tumor cell burden in this unusually immune-sensitive disease.

In summary, there is a growing consensus that surgical excision, sentinel lymph-node biopsy, and radiation therapy are important components in managing MCC. When the biological underpinnings of this cancer are better understood, it is hoped this will lead to more effective molecularly targeted therapies. However, regarding currently available adjuvant chemotherapy, current data do not support its routine use in MCC due to its known morbidity, mortality, immune suppression, and lack of evidence of survival benefit.

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