

Radiation Versus Resection for Merkel Cell Carcinoma

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The rising incidence of Merkel cell carcinoma (MCC)¹ has heightened awareness and interest in this rare and aggressive form of skin cancer. Approximately 25%²⁻⁴ of patients diagnosed with MCC have clinically apparent lymph node involvement or metastatic disease at the time of initial presentation and an additional 23% to 32%^{3,5} are found to have microscopic regional lymph node metastases with further evaluation. The stage of disease at presentation appears to be prognostic; however, optimal treatment strategies are still heavily debated.^{6,7} In this issue of *Cancer*, Fang et al report their outcomes in patients with MCC and regional lymph node metastases.⁸

Because MCC is a radiosensitive tumor, 1 of the major controversies is whether surgical resection or radiotherapy (RT) represents the optimal treatment for MCC patients with regional spread of disease. Fang et al compared patients treated with either lymph node radiation monotherapy or completion lymph node dissection (CLND) with or without RT.⁸ Another highly controversial issue, the role of systemic chemotherapy for this disease, is outside the realm of this report. From a data repository at the Fred Hutchinson Cancer Research Center, 86 patients with regional lymph node metastases at presentation were identified. Fifty patients met the inclusion criteria of pathologically confirmed regional lymph node involvement, adequate follow-up after regional therapy, and lack of distant metastasis. Lymph node involvement was classified as either clinically palpable or microscopically detected by sentinel lymph node biopsy (SLNB). Patients were seen either for treatment or for consultation only, with treatments rendered elsewhere. The authors conclude that lymph node basin RT provides regional control and survival rates that are comparable to CLND, regardless of tumor burden.

The authors describe the treatment and outcome of 2 distinct patient populations: those with microscopic tumor burden in the regional lymph node basin detected by SLNB, and those with clinically apparent lymph node disease. None of the patients with microscopic lymph node disease detected on SLNB developed regional disease recurrence regardless of the treatment modality. However, the excellent regional control rate is most likely due to the early detection of minimal tumor burden and not choice of treatment.⁹ In fact, it may even be reasonable to postulate that selective lymphadenectomy itself is therapeutic if the only focus of metastatic disease is removed during the diagnostic procedure, and that both CLND and RT represent adjuvant therapies. The authors' conclusion that CLND and RT are equally effective in this group of patients with micrometastatic disease is further confounded by the finding that greater than half of the patients who underwent CLND subsequently underwent adjuvant RT as well.

The second distinct patient population described includes patients who presented with clinically apparent lymph node disease. Drawing meaningful conclusions from this cohort of patients is challenging. Among 24 patients with palpable lymph nodes, only 6 were truly treated with radiation monotherapy because excision of the clinically apparent lymph node essentially changes the lymph node status from macroscopic to microscopic (or nil) disease. The authors observed a total of 5 patients with regional disease recurrences in this group with clinically apparent disease. Although these are extremely small numbers, 3 patients with palpable lymphadenopathy who underwent CLND alone did not develop

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disease recurrence. Is regional failure after CLND and RT due to lack of surgical control, radiation control, or tumor biology?

Prior studies addressing this issue in MCC have similarly found that stage of disease at presentation is highly prognostic. However, most prior studies examining the role of RT have included its use in the adjuvant setting, not as monotherapy, for the treatment of established regional disease. A meta-analysis comparing resection with resection plus RT found that RT improved regional recurrence rates. To the best of our knowledge, this is 1 of the few reports published to date purporting the use of radiation monotherapy as definitive treatment. In addition, in the entire cohort examined here, only 6 patients were truly treated with a single-treatment modality.

However, which treatment modality actually achieved superior regional control is impossible to determine from this retrospective review. The results presented could be viewed as a model of tumor biology: poorer survival correlates with increasing tumor burden. No patients with microscopic disease developed lymph node recurrence regardless of treatment. In the group with clinically apparent lymphadenopathy, the mean number of pathologically involved lymph nodes was 2.6 in those without lymph node recurrence, but there were an average of 6 involved lymph nodes among those who eventually failed treatment. What is not demonstrated is how patients selected for RT alone are or are not comparable to patients who undergo CLND (regardless of whether this is followed by RT). Knowledge regarding the number of positive lymph nodes, tumor burden within the dissected lymph nodes, and the presence or absence of extranodal extension certainly influenced the selection of treatment modality. The results exemplify the selection bias inherent in retrospective studies; considerations such as patient choice, comorbidities, and extent of lymph node dissection are not accounted for.

In practical terms, treatment decisions must take treatment effects into account. Although different opinions exist regarding the morbidity of RT compared with CLND, CLND followed by RT certainly carries additional risk. The authors correctly point out the short-term morbidity associated with CLND, including wound infection, pain, and the nontrivial risk of general anesthesia in an elderly or immunosuppressed population. Aside from the

sometimes challenging logistical difficulties associated with RT, it should be remembered that the side effects of RT may be significant. With head and neck radiation, xerostomia, dysphagia, dental problems, loss of appetite, and weight loss do occur.¹⁰ Lymphedema is not only a complication of axillary or inguinal lymphadenectomy, but is also a real complication of RT. A comprehensive morbidity profile will be necessary to establish a more balanced risk/benefit ratio for lymph node treatment modalities, especially given the generally elderly MCC population.

Fang et al appear to suggest that RT should be considered as monotherapy for the treatment of regional MCC.⁸ However, that conclusion may be premature. With the absence of a prospective randomized controlled trial comes the inherent inability to draw any conclusions regarding cause and effect. Because, to the best of our knowledge, no such data exist for patients with MCC in general, retrospective data must be considered. Controversy exists regarding many aspects of the management of MCC, such as the roles of resection and RT in the treatment of both the primary tumor and regional lymph node basin, the value of SLNB, and the effectiveness of adjuvant chemotherapy. Most studies reviewing therapy for MCC with regional lymph node involvement are limited by very small sample sizes and a lack of long-term follow-up. Unfortunately, larger population-based series frequently do not specifically report regional disease recurrence rates after treatment of lymph node disease.^{11,12} The current study by Fang et al⁸ certainly highlights an important controversy in MCC (ie, the role of RT in the management of both micrometastatic and macrometastatic disease to regional lymph nodes), and emphasizes once again the difficulty of defining optimal treatment pathways for uncommon diseases.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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