Role of Radiotherapy in the Management of Merkel Cell Carcinoma of the Skin

Roy H. Decker, MD, PhD, and Lynn D. Wilson, MD, MPH, New Haven, Connecticut

Key Words
Merkel cell, carcinoma, radiotherapy, adjuvant, neuroendocrine, skin

Abstract
The role of radiotherapy in treating local and regional disease in patients with clinically localized Merkel cell carcinoma remains controversial. Given the lack of randomized evidence and patient and treatment heterogeneity in published retrospective series, sound clinical judgment is required to assess individual patient risk factors. Although many single-institution series have shown that adjuvant radiation to the primary tumor site decreases the risk for local and regional failure, evidence is emerging that there is a cohort of patients at relatively low risk for local recurrence after wide local excision alone. Node dissection, radiotherapy, and combined modality treatment may all play a role in managing occult or clinically evident nodal disease, depending on the anatomic location of draining lymphatics and the extent of microscopic or macroscopic disease. For selected patients, primary radiotherapy is a reasonable option with a low risk for local or regional recurrence. (UNCCN 2006;4:713–718)

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ozen of single-institution experiences involving hundreds of patients over several decades have documented the use of radiotherapy in the definitive or adjuvant treatment of Merkel cell carcinoma of the skin.1 However, because the patient populations and treatment algorithms are heterogeneous, conclusions about management must be made carefully when using these data. Many authors have concluded that adjuvant radiation to the tumor bed and associated undissected or dissected nodal regions improves locoregional control2–8 and survival,5,6 whereas others found no such benefit.9–11 In the absence of randomized data, patients who may benefit from adjuvant radiotherapy to the primary tumor site or draining lymph nodes should be selected based on established risk factors for recurrence and on the extent and method of primary surgical management. Clinical decision-making concerning both adjuvant radiotherapy and chemotherapy may influence the surgical approach, highlighting the importance of early multidisciplinary evaluation.

Adjuvant Treatment of the Primary Site
Many series have found adjuvant radiation to the postoperative primary tumor site to be associated with improved local control, whereas other reports have shown no benefit. Small patient numbers, differences among patient populations and treatment preferences, or the inclusion of the draining nodal basin as a local recurrence site by some authors may have caused this discrepancy.11 However, evaluating specific patient and tumor factors associated with local recurrence risk, such as tumor size, margin status, surgical approach, and anatomic location, also have important roles in selecting patients who would benefit from adjuvant local treatment.

Merkel cell carcinoma tends to have an infiltrating histologic front, resulting in a significant microscopic tumor burden within the clinically uninvolved normal tissue margin. Additionally, their propensity for spread through dermal lymphatics results in not only a high risk for occult nodal disease, but also a substantial risk for in-transit metastases and satellite lesions. Therefore, adequate local control may require sufficient surgical margins or postexcision radiation therapy.

Most published series of Merkel cell carcinoma are small and include patients with primary or recurrent disease, with close or wide margins, and with or without
radiation to the primary site. Several authors who have examined margin status independently have concluded that close margins increase the risk for recurrence at the resection site. Kokoska et al. found that margins of less than 2.5 cm predicted increased local recurrence (89% vs. 27%) and poorer survival (28% vs. 86%). Ott et al. found no local recurrences in 7 tumors excised with margins greater than 2 cm, and 7 recurrences in 24 cases with margins less than 2 cm. Intriguingly, the latter authors reported no recurrences in patients with close margins who had undergone adjuvant radiation.

Other studies, however, have failed to find higher recurrence with closer margins. Gillenwater et al. examined 1-, 2-, and 3-cm margins and found no improvement in local control with wider excision. Some patients with close margins in this and other series underwent adjuvant radiation, and this bias makes examination of pathologic risk factors more difficult. Finally, in a large, modern series from Memorial Sloan-Kettering Cancer Center, in which most patients did not undergo radiation, there was no significant increase in local recurrence after excision when margins were smaller than 1 cm. This study also reported no significant improvement in local control after adjuvant radiotherapy, although this was reported for the population as a whole rather than for those with close or positive margins. The small number of patients who underwent radiation in this population makes appropriate statistical analysis of this end point challenging. Additionally, the characteristics of patients who underwent adjuvant radiation are not reported separately, and in many series the patients who were offered adjuvant treatment represent a higher-risk cohort. Overall, however, the high rate of local control without radiotherapy in this experience has cast doubt on the paradigm that routine postoperative radiation to the tumor bed is beneficial to all patients with localized disease at diagnosis; careful evaluation of these patients may identify those at low risk for local failure. In patients who undergo resection with close margins (i.e., < 2–3 cm), the risk for local failure seems higher, and postoperative irradiation may attenuate this risk.

The size of the primary tumor has been correlated with overall survival, although not definitively with local control. The poor survival rates in patients with large tumors may indicate that size is a surrogate for an increased risk for nodal disease or metastatic spread, with or without any implications for local recurrence. The correlation of radiation use with tumor size may reflect that these lesions are excised with closer margins or have a perceived higher risk for recurrence or occult nodal disease. Overall, although primary tumor size has not been established as an independent predictor of local failure, it appears to serve as a marker of high risk that warrants aggressive treatment, including adjuvant radiation.

An alternative to wide excision is Moh's micrographic surgery, which has been shown to decrease the risk for recurrence of basal and squamous cell cancers of the skin. Retrospective reports of Moh's surgery for Merkel cell carcinoma are now emerging. In a series of 45 patients treated with Moh's surgery, with or without adjuvant radiation to the tumor bed, there was no significant benefit to radiation. In 25 patients who did not undergo any adjuvant treatment, only 1 marginal recurrence and 3 in-transit recurrences occurred. Notably, no recurrences occurred in patients who underwent radiation adjuvantly, but the study size was not sufficient to establish a local control benefit. Further evaluation of this technique will help elucidate the local recurrence risk and may establish patient and tumor risk factors. However, current evidence indicates a low risk for marginal failure after Moh's surgery when adequate normal tissue margins are obtained.

Anatomic location has also been correlated with both local recurrence and survival. In particular, lesions of the lower extremity have a high risk for local recurrence, which may be related to limited excision and compromised radiotherapy. Such compromise often results from therapeutic caution given the relatively poor vascularity inherent in distal extremities. This consideration is especially appropriate in elderly patients. For other lesions, notably those in head and neck locations, cosmesis may limit the prudent surgical margin. In these cases, planned radiotherapy is expected to result in local control equivalent to wider excision, with better functional outcomes.

Postoperative radiation has been a standard treatment after excision of clinically localized Merkel cell carcinoma and has been associated with improved local control and survival. Emerging evidence, however, suggests that when local recurrence is distinguished from nodal relapse, wide local excision alone may be sufficient to treat the primary site. Consideration of postoperative radiation to the primary tumor bed should include evaluation of the surgical margins as
The risk for clinically occult nodal metastases is also significant. In a large modern series the risk for occult nodal disease on sentinel node biopsy or nodal dissection in clinically node-negative patients was 23%, and the rate of subsequent nodal failure in clinically node-negative patients who had no nodal treatment was 44%. Because most patients who experience nodal recurrence ultimately die of disease, early definitive treatment of these regions is essential. The standard definitive therapy for patients with clinically involved nodes is nodal dissection, with or without radiotherapy. In clinically node-negative patients, data suggest that the risk for occult involvement is significant and should be addressed with sentinel node biopsy, node dissection, radiotherapy, or combined modality therapy.

Patients without clinically suspicious nodal disease at diagnosis are commonly offered surgical nodal evaluation. This approach offers prognostic information that potentially can be used to make further treatment decisions. Recent evidence suggests that sentinel node biopsy is a sensitive method of nodal staging and has become a common clinical practice. Although a negative sentinel node biopsy may obviate further adjuvant therapy directed at the nodal bed, a positive biopsy should be followed by complete nodal dissection or nodal irradiation.

The results of completion nodal dissection in these patients are instructive. In one of the largest series of surgically staged patients, Allen et al. reported that only 25% of patients with a positive sentinel node who underwent dissection had further involved lymph nodes, and that following dissection, the risk for subsequent nodal recurrence was only 11%. Patients who underwent radiotherapy after dissection experienced no significant decrease in nodal recurrence, although only a small number underwent radiation. Additionally, because most patients had a single positive node, the series size limited analysis of recurrence and the effect of adjuvant therapy in those with multiple involved nodes.

The authors did conclude that the absolute risk for recurrence after dissection in the entire cohort was low, and therefore any potential benefit of nodal irradiation should be balanced against potential toxicity. Although other authors have reported a decreased risk for nodal relapse after combined modality treatment, these studies included patients who did not universally undergo nodal dissection before radiation. The benefit of radiotherapy in this context remains unclear, and because the anatomic location of the draining lymph nodes determines the potential toxicity of multimodality therapy, these patients should be evaluated individually. If radiation to the nodal basin is planned, dissection might be omitted to minimize late toxicity. Series that applied radiotherapy alone to clinically uninvolved draining lymph nodes reported encouraging regional control rates of 79% to 100% (%); however, the efficacy of single-modality radiation after positive sentinel node biopsy is unclear.

Combined modality therapy often is recommended for patients presenting with clinically evident lymph node involvement. Because of the presumed increased risk for multiple node involvement and extracapsular extension, node dissection alone may be associated with a significant risk for regional failure. In the surgical series from Memorial Sloan-Kettering Cancer Center, the risk for nodal failure after dissection of a clinically involved nodal bed was 26%. In patients treated with radiation after dissection, the failure rate was only 13%, a decrease which did not reach statistical significance. Similarly, in a series reported by Veness et al., the nodal failure rate of clinically node-positive patients after dissection alone was 43% versus 14% after dissection and adjuvant radiation. Furthermore, 5 patients with clinically evident nodes were treated with radiation alone, with only 1 nodal relapse (20% crude recurrence). In a series from the University of Florida, 7 of 8 patients with clinically positive nodes treated with radiation alone experienced a complete response. Although data are derived from relatively small numbers of patients, evidence suggests that multimodality treatment of clinically involved lymph nodes offers improved control compared with either nodal dissection or radiotherapy alone.

**Primary Radiotherapy**

Because Merkel cell carcinoma is a highly radiosensitive tumor, radiation alone may be used for...
relatively bulky disease with a reasonable expectation of complete response and durable locoregional control. In patients who are not surgical candidates, radiation has been used as the primary treatment with acceptable local control and survival, although the number of patients treated is notably smaller compared with surgical series. Ashby et al.\textsuperscript{24} reported that 3 patients treated with radiation alone experienced control within the treatment field and were disease-free at follow-up. Bischof et al.\textsuperscript{25} reported on a single patient treated with primary radiation who experienced local control, Morrison et al.\textsuperscript{8} reported on 10 patients who experienced long-term local control, and Mortier et al.\textsuperscript{26} reported on 9. In a relatively large series of primary radiotherapy from the Peter MacCallum Cancer Centre, 22 of 23 sites of clinically evident disease showed complete clinical response to radiation therapy, with only one local failure.

One of the only prospective trials of Merkel cell carcinoma examined definitive chemoradiotherapy in high-risk patients. In the TROG 96:0728 trial, 53 patients with locally advanced disease (large primary, in-transit metastases, nodal disease, or recurrent disease in the absence of distant metastases) were treated with concurrent radiation and carboplatin/etoposide. Although only 4 patients underwent node dissection, the actuarial locoregional control of 75% compares favorably with high-risk historic controls treated with surgery and adjuvant radiation.\textsuperscript{5,21} Although 38 patients underwent excision of the primary tumor before chemoradiation, locoregional control was not significantly different after surgical excision (77% vs. 71%). Although these results are promising, the use of chemotherapy in patients without metastatic disease has not been demonstrated to confer a survival benefit, and is therefore somewhat controversial.\textsuperscript{29}

Overall, the results of primary radiotherapy appear comparable to those seen after wide local excision,\textsuperscript{26} although the published experience is smaller. Additionally, patient selection in these retrospective reports may bias results because patients more likely to die of comorbid illness, or those with metastatic or recurrent disease, may have been chosen for nonsurgical management. Although surgical resection of the primary lesion remains the best approach based on current evidence, primary radiation can be considered an option with a reasonable expectation of local control.

**Recurrent Disease**

Patients with locally recurrent disease in the absence of distant metastases may benefit from aggressive therapy directed at the site of disease. Although these patients seem to be at high risk for ultimate metastatic failure,\textsuperscript{22} several series have also reported that they have increased risk for further local failure compared with primary lesions.\textsuperscript{5,8,26} Local or regional disease in patients who undergo aggressive therapy may be managed initially with surgery or radiotherapy. Many single-institution series include recurrent disease, and adjuvant radiotherapy is associated with improved local control.\textsuperscript{23} In appropriate patients, radiotherapy alone would also be expected to control local disease.

**Radiotherapy Technique**

Radiation field design should allow for the microscopically infiltrating tumor margin and the prediction for dermal lymphatic spread. Therefore, traditional margins include 5 cm or more of normal tissue surrounding gross disease or a surgical tumor bed. When feasible, nodal fields should be treated contiguously with the primary site so that potential in-transit metastases may be included.

Compared with epithelial skin malignancies, Merkel cell carcinoma is a relatively radiosensitive tumor.\textsuperscript{23} Historically, radiation doses of between 45 and 60 Gy have been used to treat both microscopic and gross tumors with excellent response rates and durable local control.\textsuperscript{5,27} Our own practice is to treat areas of microscopic disease (e.g., surgical beds, clinically negative or dissected nodal areas) to 50 Gy in 2 Gy fractions, and gross disease to 60 Gy or greater. Some anatomic areas, such as distal extremities and inguinal, axillary, and supraclavicular fields, may not tolerate higher doses without a significant risk for late effects. In these cases, a multimodality approach of limited excision and lower dose radiation may offer the best balance of local control and limited toxicity.

**Conclusions**

The optimal management of Merkel cell carcinoma with respect to radiotherapy remains controversial. The lack of randomized trials, small experiences spanning decades, heterogeneity of treatment paradigms, and patient selection have provided evidence that can be difficult to interpret. For this reason, patients should...
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be evaluated prospectively in a multidisciplinary setting. While the complex interaction of patient and tumor factors must be considered individually, Figures 1 and 2 contain simplified algorithms for treating local and nodal regions.

The addition of adjuvant radiotherapy after surgery has been associated with improved local control of primary tumors, but strong evidence now shows that small, widely excised tumors have a relatively low risk for recurrence at the tumor bed without adjuvant treatment. When anatomic location, tumor size, or cosmesis limit excision margins, adjuvant radiotherapy offers excellent local control. Because locally recurrent lesions also present a higher risk for further recurrence after resection, adjuvant radiation is indicated. Additional clinical factors associated with increased risk of local recurrence include large tumor size, in-transit or satellite metastasis, and immunosuppressed host status. In this context, multimodality treatment should be considered. Alternately, primary radiation has been used in small numbers of patients with reasonable outcomes.

The risk for clinically evident or occult nodal involvement is high, regardless of tumor size, and elective management of nodal regions should be initiated in all patients treated with curative intent. Clinically node-negative patients should be offered sentinel node biopsy, followed by complete dissection or nodal irradiation where appropriate. Routine postoperative radiotherapy to dissected lymph nodes seems to have no benefit when minimal microscopic disease is present. When multiple nodes are involved or extracapsular extension is present, adjuvant treatment should be considered, extrapolating from a well-documented increased risk for failure after dissection alone in epithelial tumors. Combined modality therapy with nodal dissection and adjuvant radiation offers the best regional control in patients with clinically apparent nodal disease, although the relative toxicity in certain nodal basins should be considered. Radiation alone also has been used to definitively manage undissected nodal regions with reasonable control rates in these patients.
References