

Radiation Monotherapy as Regional Treatment for Lymph Node-Positive Merkel Cell Carcinoma

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BACKGROUND: Merkel cell carcinoma (MCC) is an aggressive cutaneous malignancy with a high risk of lymph node involvement. To the authors' knowledge, few data have been published to date regarding the optimal regional therapy for lymph node-positive patients. This cohort study was performed to analyze the outcomes of patients with lymph node-positive MCC treated with lymph node irradiation as definitive therapy compared with completion lymphadenectomy (CLND). **METHODS:** Fifty patients with lymph node involvement of MCC at presentation and adequate follow-up data were included in this analysis. Forty-three of these patients were enrolled and followed prospectively. Twenty-six patients presented with microscopic lymph node disease, and 24 patients presented with palpable lymph node involvement. **RESULTS:** Regional control for patients with microscopically involved lymph nodes was 100% regardless of treatment modality—definitive lymph node irradiation (n = 19) or CLND ± radiotherapy (n = 7) with median follow-up of 18 months. Patients with clinically positive lymph nodes had 2-year regional recurrence-free survival rate of 78% and 73% in the definitive lymph node irradiation (n = 9) and CLND ± radiotherapy (n = 15) groups, respectively (P = .8) with a median follow-up of 16 months. **CONCLUSIONS:** To the best of the authors' knowledge, the current study is the largest series published to date of radiation monotherapy as regional treatment for lymph node-positive MCC. Lymph node irradiation alone to positive regional lymph nodes was found to confer an excellent regional control rate that was comparable to CLND for both microscopic and palpable lymph node disease. There was no difference noted with regard to overall survival. Given their similar efficacy, the choice between these lymph node therapies may be based on the clinical scenario and anticipated side effect profiles. *Cancer* 2010;116:1783-90. © 2010 American Cancer Society.

KEYWORDS: Merkel cell carcinoma, radiotherapy, lymphadenectomy, lymph node dissection.

Merkel cell carcinoma (MCC) is an aggressive cutaneous malignancy with a predilection for lymph node involvement, distant metastases, and disease recurrence. It is a disease that primarily afflicts white elderly individuals and is associated with ultraviolet exposure, immunosuppression, and a newly described Merkel cell polyomavirus.¹⁻³ The reported incidence of MCC has tripled in the past 20 years primarily due to increased detection through the development of immunohistochemical staining for cytokeratin-20, which is specific for MCC. In addition, increases in relevant risk factors (age >50 years, ultraviolet exposure, human immunodeficiency virus, solid organ transplantation) have likely resulted in true increases in the incidence of MCC.⁴

MCC is a rare disease, and therefore to the best of our knowledge no randomized controlled trials to define optimal treatment have been performed to date. Numerous retrospective studies have been performed assessing the role of radiation treatment⁵⁻¹³ with the growing consensus that radiotherapy confers local and regional control improvements. A recent population-based study suggested a survival benefit with adjuvant radiotherapy.¹⁴ Nonetheless, because of small sample sizes and heterogeneous patient populations of MCC series to date, optimal management of this malignancy continues to be controversial.

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Since its first description in 1972,¹⁵ MCC has been known to have a high risk of lymphatic metastases. Patients present with lymph node disease in 19% to 33%^{9,13,16-18} of cases. Traditional recommended practice for the regional therapy for lymph node-positive disease is completion lymphadenectomy (CLND) with or without adjuvant radiotherapy. However, given the radiosensitivity of MCC¹⁹ as well as morbidity associated with full lymph node dissection, in more recent years, radiotherapy was used as definitive treatment to the primary lymph node basin in a cohort of patients with lymph node-positive disease. As such, the present study was performed to analyze the outcomes of lymph node-positive MCC patients treated with definitive lymph node irradiation compared with CLND.

MATERIALS AND METHODS

Patient Selection Criteria

After approval by the Institutional Review Board at the Fred Hutchinson Cancer Research Center, a Repository of Data and Specimens for MCC was created. Two hundred twenty-seven patients diagnosed with MCC from 1985 to 2007 were enrolled in this repository, mostly in a prospective manner since 2002. Eighty-six of these patients were found to have lymph node-positive disease at presentation after initial workup (Fig. 1). Eleven of these patients were found to have distant metastases, 5 patients were lost to follow-up, and specific information regarding lymph node status was missing in 20 patients. Thus, the 50 patients included in this analysis met the following criteria: 1) pathologic confirmation of lymph node involvement, 2) no evidence of distant metastases at presentation, and 3) available follow-up information regarding lymph node recurrence.

Data were collected prospectively in 43 patients and retrospective chart review was performed on the remaining 7 patients. All patients were seen at the authors' institutions for consultation and treated at a mixture of academic and private institutions as a function of geography, insurance status, and patient preference. Because the vast majority of patients did not live geographically close to the authors' institution, most or all of their treatment was provided by medical centers closer to their home. Therefore, there was no dominant institution or practitioner of surgical or radiation therapy for any particular group. Medical records were obtained from the patients' treating physicians twice yearly and at the time of analysis

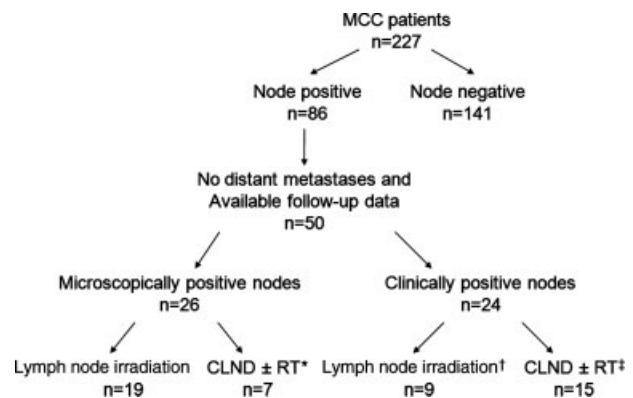


Figure 1. Patient selection is shown. MCC indicates Merkel cell carcinoma; CLND, completion lymphadenectomy; RT, radiotherapy. *3 patients received adjuvant lymph node irradiation; †3 patients underwent surgical debulking of palpable lymph node; ‡12 patients received adjuvant lymph node irradiation.

of this cohort. The treatment modality for regional lymph nodes was at the discretion of the management team.

Statistical Analysis

The endpoints of this study were regional recurrence-free survival (RRFS), disease-specific survival (DSS), and overall survival (OS). RRFS was calculated as the time from diagnosis to regional disease recurrence, defined as recurrence in the primary lymph node basin or regional in-transit lymphatics. In the case of an unknown primary tumor, regional disease recurrence was defined as recurrence within the lymph node region of initial presentation. DSS was defined as the time from diagnosis to death from MCC, and OS was defined as the time from diagnosis to death from any cause. The site of first failure was recorded as recurrence of local, regional, and/or distant disease that was the first to be detected in follow-up either by physical examination or imaging. The endpoints were calculated using Kaplan-Meier estimates. GraphPad Prism (GraphPad Software, La Jolla, Calif) was used to run statistical analyses.

RESULTS

Microscopic Cohort

Twenty-six patients meeting eligibility criteria had microscopic positive nodes as determined by sentinel lymph node biopsy (SLNB). Among these 26 patients, 16 were men and the median age was 68 years (range, 46-85 years). The median size of the primary tumor was 19 mm (range, 5-60 mm). The involved lymph node basin was in

Table 1. Kaplan-Meier Estimated 2-Year Regional Recurrence-Free Survival, Disease-Specific Survival, and Overall Survival

	2-Year RRFs	2-Year DSS	2-Year OS
Microscopic			
All (n=26)	100%	87%	81%
Lymph node irradiation (n=19)	100%	83%	75%
CLND ±RT (n=7)	100%	100%	100%
Palpable			
All (n=24)	75%	64%	61%
Lymph node irradiation (n=9)	78%	73%	63%
CLND ±RT (n=15)	73%	59%	59%

RRFS indicates regional recurrence-free survival, DSS, disease-specific survival; OS, overall survival; CLND, completion lymphadenectomy; RT, radiotherapy.

the head and neck in 3 patients, the axilla in 15 patients, and the inguinal lymph nodes in 8 patients.

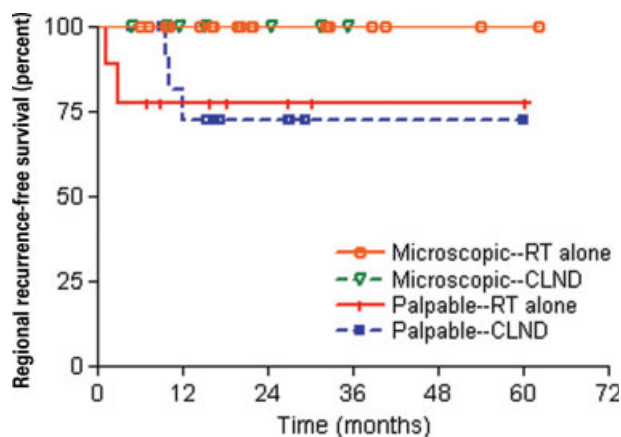
Nineteen of 26 patients received definitive lymph node irradiation, and 7 underwent CLND. Four of these 7 patients also received adjuvant lymph node irradiation. No additional positive lymph nodes obtained from CLND were found on pathology in these 7 patients. The mean number of positive SLNs was 1.4 for both patients who received lymph node irradiation and patients who underwent CLND ± radiotherapy.

All 26 patients underwent local excision to the primary site, of whom 24 patients received adjuvant radiotherapy to the primary site. Six patients in this cohort received chemotherapy: 4 with cisplatin/carboplatin and etoposide; 1 with etoposide only; and 1 with cyclophosphamide, 5-fluorouracil (5-FU), and methotrexate. The median follow-up for this cohort was 18 months (range, 5-62 months).

Clinically Palpable Cohort

Twenty-four of the 50 patients included in this analysis presented with palpable lymph nodes. Fourteen patients were men, and the median age was 59 years (range, 35-89 years). The median size of the primary tumor was 30 mm (range, 6-120 mm). The involved lymph node basin was in the head and neck in 8 patients, the axilla in 6 patients, and the inguinal lymph nodes in 10 patients. Ten patients presented with lymph node disease and no detectable primary lesion.

As regional treatment, 9 of 24 patients received definitive lymph node irradiation, of whom 3 patients underwent excisional biopsy of a clinically apparent lymph node but did not proceed to CLND. Fifteen patients underwent CLND, 12 of whom received adju-

**Figure 2.** Kaplan-Meier curves for regional recurrence-free survival are shown by lymph node presentation and treatment. RT indicates radiotherapy; CLND, completion lymphadenectomy.

vant lymph node irradiation. The mean number of dissected lymph nodes was 21, with an average of 5 positive lymph nodes.

Eleven patients underwent local excision with adjuvant radiotherapy to the primary site, 1 patient underwent local excision alone, and 2 patients received definitive radiotherapy to the primary site (the remaining 10 patients had unknown primary sites). Eight of 24 patients in this cohort received chemotherapy: 6 were treated with cisplatin/carboplatin and etoposide, 1 was treated with etoposide and doxorubicin, and the regimen was unknown in 1 patient. The median follow-up for this cohort was 16 months (range, 5-109 months).

Regional Control

For patients with microscopic lymph node involvement, the estimated 2-year RRFs was 100% regardless of treatment modality (Table 1) (Fig. 2). The 2-year RRFs for patients who presented with palpable lymph nodes was 78% and 73%, respectively, by Kaplan-Meier analysis in the definitive lymph node irradiation and CLND groups ($P = .8$).

In total, 5 patients developed regional recurrence in the primary lymph node basin, all of whom had palpable lymph nodes at the time of initial presentation. There were no in-transit recurrences. Two of these 5 patients were treated with definitive lymph node irradiation. The first patient developed a local disease recurrence and distant skin metastasis at the time of lymph node recurrence, which occurred 1 month after completion of radiation treatment; this patient died 7 months later. The other patient developed local, regional, and distant failure 3

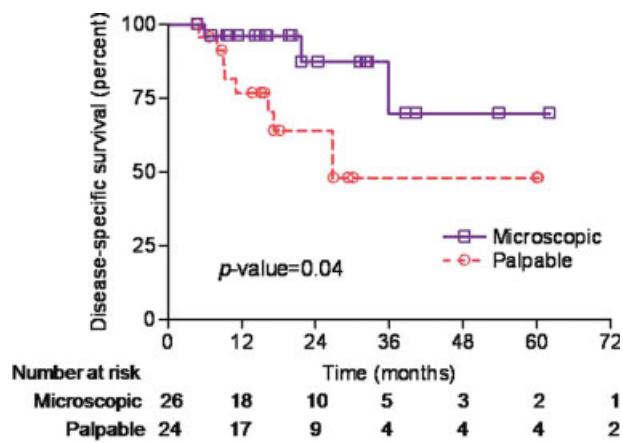


Figure 3. Kaplan-Meier curves for disease-specific survival are shown by lymph node presentation.

months after the completion of treatment and died 8 months later.

Three patients with palpable lymph node disease who underwent CLND developed lymph node recurrence. All 3 patients received adjuvant radiotherapy to the regional lymph nodes at the time of initial treatment. One patient had local, regional, and distant disease recurrences at 12 months and died 5 months later. One patient developed local and regional disease recurrences at 10 months, followed by distant metastasis at 14 months. The third patient developed a regional disease recurrence at 10 months and distant metastasis at 11 months.

Among patients treated with CLND, the mean number of pathologically involved lymph nodes identified at the time of dissection was 6 in those that developed a regional disease recurrence versus 2.6 in patients that did not develop a regional disease recurrence.

Survival

The 2-year DSS rate was 87% and 64% in patients with microscopic lymph node involvement versus clinically positive lymph nodes ($P = .04$) as shown in Figure 3. Among patients with microscopic lymph node involvement, the 2-year DSS rate was 83% and 100% in the lymph node irradiation group and CLND group, respectively ($P = .7$). The 2-year DSS rate for patients who presented with palpable lymph nodes was 73% and 59% in the lymph node irradiation group and CLND group, respectively ($P = .9$). Among patients who received CLND, the mean number of pathologically positive lymph nodes was 4.3 in patients who died of MCC versus 2.6 in patients who died of other causes.

Table 2. Patterns of First Disease Recurrence

Site of First Disease Recurrence	Microscopic (n=26) No. of Patients	Palpable (n=24) No. of Patients
No recurrence	22 (85%)	9 (38%)
Any recurrence	4 (15%)	15 (62%)
Local alone	2 (8%)	0
Regional alone	0	1 (4%)
Local and regional	0	2 (8%)
Local, regional, and distant	0	2 (8%)
Distant alone	2 (8%)	10 (42%)
Total	26 (100%)	24 (100%)

The estimated 2-year OS rate was 81% in patients with microscopic lymph node disease compared with 61% in patients who presented with palpable lymph nodes (P -value = .05) as shown in Table 1.

Patterns of First Failure

Distant metastasis was the most common site of first failure for all patients. Distant metastasis occurred in 8% (2 of 26) of patients with microscopic lymph node involvement and 50% (12 of 24) of patients with palpable lymph node involvement (Table 2). Regional failure occurred exclusively in patients with palpable lymph nodes at diagnosis (5 of 24).

DISCUSSION

To date, the current study is the largest published series of lymph node-positive MCC patients treated definitively with lymph node irradiation without CLND (Table 3). There was a clear selection bias favoring CLND in the presence of palpable lymph node disease and for radiotherapy without CLND if lymph node involvement was identified solely by SLNB. Subgroup analysis revealed that there were no regional failures in any patient who presented with microscopic lymph node involvement. Among patients who presented with palpable lymph node disease, the 2-year RRFS rate was comparable at 78% in the lymph node irradiation group and 73% in the CLND group (P -value 0.8). It is interesting to note that the time to lymph node recurrence was shorter for the 2 patients in the radiation monotherapy group, neither of whom underwent surgical debulking. Although no conclusions

Table 3. Selected Series of Lymph Node-Positive Patients, Treatment, and Outcomes

	No. of Patients Studied	Regional Treatment			Lymph Node Involvement Detected by and No. of Patients	Crude Regional Recurrence Rate
		XRT	CLND	CLND+XRT		
Current study	50	28	7	15	Clinical: 24 SLNB: 26	10% (5/50)
Pectasides 2007 ²⁰	5	0	1	4	Clinical: 5	0% (0/5)
Jabbour 2007 ^{8a}	29	2	8	17	Clinical: 29	Not reported
Senchenkov 2007 ²¹	11	2	5	3	Clinical: 5 SLNB: 6	18% (2/11)
Maza 2006 ²⁸	11	2	8	0	SLNB: 11	0% (0/11)
Allen 2005 ^{5b}	76	4	46	11	Clinical: 60 SLNB: 12 ELND: 4	14% (10/73 ^c)
Veness 2005 ⁵¹	35	5	9	17	Clinical: 35	Not reported
Veness 2005 ¹³	8	0	1	7	Clinical: 8	25% (2/8)
Schmalbach 2005 ³⁰	2	2	0	0	SLNB: 2	0% (0/2)
McAfee 2005 ^{10d}	11	1	0	9	Clinical: 8 ELND: 3	20% (2/10)
Gillenwater 2001 ^{7e}	7	1	3	2	Clinical: 7	57% (4/7)
Meeuwissen 1995 ^{18f}	26	13	5	7	Clinical: 26	Not reported
Boyle 1995 ^{32g}	10	4	2	2	Clinical: 10	Not reported
Morrison 1990 ¹²	9	1	3	5	Clinical: 4 ELND: 5	Not reported
Shaw 1972-1990 ^{52h}	23	5	11	5	Clinical 23	Not reported

XRT indicates radiotherapy; CLND, completion lymphadenectomy; SLNB, sentinel lymph node biopsy; ELND, elective lymph node dissection.

^aTwo patients did not receive treatment to the regional lymph nodes.

^bTen patients underwent excisional biopsy alone, 1 patient did not receive lymph node treatment, and in 4 patients the lymph node treatment was not reported.

^cExcluded 3 patients who presented with clinically positive lymph nodes but these lymph nodes were not pathologically assessed.

^dIn 1 patient, the treatment was unknown and patient was lost to follow-up.

^eOne patient did not receive lymph node treatment.

^fOne patient underwent excisional biopsy alone.

^gOne patient received chemotherapy alone, and 1 patient underwent biopsy alone.

^hTwo patients did not receive directed lymph node treatment.

can be drawn based on 2 cases, it is plausible that such a trend represents inferior short-term regional control of bulky lymph node disease by lymph node irradiation alone. Conversely, these data may be interpreted as CLND merely delaying lymph node recurrence.

There is a lack of randomized controlled trials to guide management of this aggressive disease, as is the case with other rare malignancies. Surgery, typically CLND with or without radiotherapy, has been accepted as standard therapy for regional lymphatics in patients with lymph node-positive MCC. Published regional outcomes are sparse, but available data report crude regional recurrence rates of 0% to 25% (Table 3).^{5,10,13,20,21} A series from The University of Texas M. D. Anderson Cancer Center reported a lymph node failure rate of 16% (2 of 12) in lymph node-positive patients treated with therapeutic dissections with or without radiotherapy.²² Allen et al published a single institution experience from Memorial Sloan-Kettering Cancer Center⁵ including 252 patients and reported a 14% (8 of 57) regional recurrence rate in pathologically lymph node-positive patients treated with

surgery alone and a similar 13% rate (2 of 16) in patients treated with surgery and adjuvant radiotherapy. In the current series, the crude rate of regional recurrence in patients treated with CLND with or without radiotherapy was 14% (3 of 22) and thus similar to published outcomes.

In historic series of patients presenting with lymph node-positive MCC, the vast majority of reported patients were lymph node-positive by clinical examination. More recently, SLNB has become standard of care for MCC based on several reports and meta-analyses.²³⁻²⁵ It is particularly appropriate in this disease given its predilection for occult lymph node involvement. SLNB is now recommended in the National Comprehensive Cancer Network guidelines.²⁶ Mehrany et al compiled all published cases of MCC patients who underwent SLNB and reported the grouped results of 60 patients.²⁵ Approximately 33% (20 of 60) had a positive biopsy result and of these patients, only 1 had an isolated regional disease recurrence that occurred in the untreated contralateral neck.²⁷ A series of previously unpublished cases from the Dana-Farber

Cancer Institute of 30 patients who underwent SLNB reported a 30% (9 of 30) lymph node positivity rate,²⁴ and there was 1 lymph node recurrence in this group. Maza et al reported on 11 patients with microscopic lymph node involvement by positive SLNB²⁸; 3 patients developed recurrence, however, none of them were lymph node recurrences. Similarly, in this study, no patients with microscopic lymph node involvement found on SLNB developed a regional recurrence regardless of treatment modality. These data together suggest that patients with microscopic lymph node involvement have low regional failure rates when treated with radiation or surgery to the involved lymph node bed.

Although surgery with or without adjuvant radiotherapy is the mainstay of locoregional treatment, there is only a small body of literature regarding the management of MCC with radiotherapy alone. Mortier et al published a series of 9 patients with medically inoperable lymph node-negative MCC who were treated with radiotherapy alone to a median dose of 60 Gray (Gy).²⁹ With a median follow-up of 3 years, there were no disease recurrences or deaths reported. The authors concluded that radiotherapy alone produced acceptable outcomes in these patients. Schmalbach et al reported on 10 patients with MCC of the head and neck evaluated with SLNB.³⁰ Two patients were found to have micrometastatic disease; they refused surgery and were treated with radiation alone to the lymph node basin. Both patients were free of disease at 38 months and 45 months, respectively. Other case reports of patients treated with radiation as monotherapy have been published with varying results,^{12,30-34} and small numbers have precluded the ability to draw any conclusions. In this series, 28 patients who received lymph node irradiation without CLND had control rates comparable to the surgical cohort for both microscopic and palpable lymph node presentations.

If lymph node irradiation without CLND can be effectively used as definitive regional treatment for lymph node-positive MCC, the potential morbidities of therapeutic lymph node dissection such as wound infection, lymphedema, pain, numbness, decreased range of motion, and nerve injury can be mitigated. The incidence of lymphedema after lymphadenectomy has been well-described in the literature, particularly for breast cancer and melanoma, and is in the range of 10% to 25%.^{35,36} The addition of radiotherapy to lymph node dissection can substantially increase the risk to as high as 38% to 77%³⁷⁻⁴⁰ and has been shown to negatively impact quality

of life.^{41,42} In this series, 7 patients developed lymphedema (3 patients were treated with CLND and 4 patients with CLND followed by adjuvant radiation). No patients who received lymph node irradiation alone developed lymphedema, despite a similar distribution of affected lymph node basins. Because toxicity data were not collected in a systematic manner, robust conclusions cannot be drawn; however, the incidence is consistent with that reported in the lymphedema literature cited above. Lower rates of complications have been reported with SLNB or lymph node sampling plus radiotherapy compared with full dissections performed in breast cancer patients.^{43,44} Radiotherapy is not without its toxicities such as tissue fibrosis, brachial plexopathy, and lymphedema; however, long-term toxicity rates are expected to be low, particularly with doses of 50 to 55 Gy. Daily radiation treatment for 5 to 6 weeks is an inconvenience to the patient compared with surgery, although this may be an acceptable alternative if the risk of late toxicities are lowered.

The major limitations of the current study are its small sample size and nonrandomized nature leading to unidentified biases. Such is the difficulty with investigations of rare entities. Another shortfall is the absence of systematically collected information regarding toxicities; however, these data are consistent with what would be anticipated based on experience in melanoma and breast cancer. The median follow-up was 16 to 18 months, but the literature suggests that the majority of lymph node recurrences appear within 1 year of diagnosis.^{17,22,45-47} In the largest published MCC meta-analysis, it was found that the median time to lymph node recurrence was 7 months, with 75% of these events occurring within 12 months of initial treatment.⁹ Nevertheless, with longer follow-up, an increase in recurrence rates may be reported.

As we continue to refine regional management for lymph node-positive MCC, systemic failure remains a significant challenge, as is demonstrated in this series with distant failure as the most common site of first disease recurrence. Chemotherapy has been evaluated with disappointing results. A phase 2 study of concurrent and adjuvant cisplatin and etoposide in high-risk MCC patients initially reported favorable outcomes⁴⁸; however, an update with further analyses demonstrated no significant improvement in OS or DSS when compared with historical controls.⁴⁹ Given the known chemotherapy-related morbidity and mortality in conjunction with no clear evidence of improved outcomes, adjuvant chemotherapy is currently not routinely recommended.⁵⁰

Because metastatic disease will dictate the survival and ultimate outcomes of these patients, future investigations will have to be directed at improving systemic control.

Conclusions

It is imperative to define the optimal therapy for lymph node-positive MCC as the use of immunohistochemical staining and SLNB will increasingly identify patients with lymph node-positive disease. In addition, it is estimated that 30% to 50% of MCC patients will develop lymph node involvement over the disease course. This study found that lymph node irradiation to the primary lymph node basin in lymph node-positive disease confers an excellent regional control rate that is comparable to surgical outcomes with no detectable difference in OS. Definitive lymph node irradiation can thus be considered as a treatment option in patients with positive lymph nodes.

CONFLICT OF INTEREST DISCLOSURES

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