ORIGINAL ARTICLE

Merkel Cell Carcinoma of the Head and Neck

Effect of Surgical Excision and Radiation on Recurrence and Survival

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Background: Merkel cell carcinoma is a rare malignant neoplasm of the skin that most often arises in the head and neck region. Despite the innocuous appearance of the primary lesion, Merkel cell carcinoma often has an aggressive clinical course with frequent locoregional recurrences and distant metastases. We evaluated the association of the width of surgical margins and the use of postoperative radiation therapy with locoregional control and survival rates.

Methods: The medical records of 66 patients with head and neck Merkel cell carcinoma seen between 1945 and 1995 were retrospectively reviewed. The Fisher exact test was used to compare outcomes. Kaplan-Meier survival curves were constructed.

Results: Eighteen patients for whom there was adequate information were divided into the following groups according to the width of their surgical margins: smaller than 1 cm, 1 to 2 cm, and larger than 2 cm. No statistical difference in locoregional control or survival was found among these groups owing to the small patient population. In contrast, a comparison of the patients who did (n=26) and did not (n=34) receive postoperative radiation therapy revealed a significant difference in local (3 [12%] vs 15 [44%], respectively; $P<.01$) and regional (7 [27%] vs 29 [85%], respectively; $P<.01$) recurrence rates. There was, however, no significant difference in the disease-specific survival between these groups ($P=.30$). Distant disease developed in 36% of all patients regardless of therapy.

Conclusions: Any effect of the width of surgical margins on outcome was not detectable in the small number of patients analyzed. The use of postoperative radiation therapy was associated with a significant improvement in locoregional control. There was no detectable influence of the type of initial therapy on the rates of distant metastases or on survival. Future therapeutic innovations should be directed toward controlling the development of distant metastases in patients with Merkel cell carcinoma.

Arch Otolaryngol Head Neck Surg. 2001;127:149-154

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MERKEL CELL carcinoma (MCC) is an innocuous-appearing malignant neoplasm that most commonly arises in the skin of the head and neck. It usually appears as a painless, pink, solitary nodule that can be easily misdiagnosed both clinically and pathologically (**Figure 1**). The differential diagnosis is extensive, and during light microscopy, it is difficult to distinguish MCC from other small cell carcinomas. Electron microscopy and immunocytochemical studies are often required to correctly diagnose this tumor.[1-6] Merkel cell carcinoma is found almost exclusively in white patients who are usually 65 years old or older. An even sex distribution has been seen in many studies[2,4,6] and a strong male predominance in others.[5,7]

Merkel cell carcinoma often has an aggressive course, with the development of early locoregional recurrence and frequent distant metastases (DM).[4,5,8] Despite maximal surgical, radiation, and medical therapy, an estimated 25% to 35% of patients with MCC die of their disease.[4] It has been suggested that the key to increased survival is locoregional control and that the development of local or regional recurrence is directly related to the adequacy of the primary treatment.[5] Currently, standard treatment consists of wide local excision (WLE), with some authors advocating up to 2- or 3-cm margins.[4,9] With the success of radiation therapy (XRT) against this tumor, the necessity of performing extensive surgical resections needs reevaluation.[10] We therefore undertook a retrospective analysis to determine whether excision of the primary lesion with wider surgical margins affected the locoregional control rate. We also sought to determine whether postoperative XRT independently affected locoregional recurrence and survival rates.

PATIENTS AND METHODS

Through a search of the database maintained by the Department of Medical Infomatics, M. D. Anderson Cancer Center (MDACC), Houston, Tex, we identified 145 patients who were seen between 1945 and 1995 with a diagnosis of either MCC or neuroendocrine carcinoma of the skin. Sixty-nine cases were eliminated from further evaluation because the primary lesion was located in a site other than the head and neck or because the pathologic diagnosis was not MCC, leaving 76 patients with head and neck MCC. Ten of the 76 patients were excluded from further analysis for the following reasons: 2 had distant metastasis on presentation; 1 had unresectable disease and had no further treatment; 2 died of other causes during treatment of their primary lesion; 2 were unavailable for evaluation before 6 months; and 3 were seen for consultation only and had treatment elsewhere.

Thus, 66 patients with MCC of the head and neck composed the cohort for this study. Of these 66 patients, 15 presented to MDACC for primary treatment of their disease, 12 were referred to MDACC after the initial excision of the primary tumor, and 33 presented to MDACC with locoregional recurrent disease. Six patients were referred to MDACC for follow-up evaluation after receiving definitive treatment of their primary tumor elsewhere. All patients included in the study had at least 6 months of follow-up after the initial diagnosis. The surgical or biopsy specimens in all cases were reviewed by members of the pathology department of MDACC, and the diagnosis of MCC was confirmed.

There were sufficient data to determine the size of surgical margins in only 18 patients, who will be referred to as *the margin group*. The patients in the margin group were subdivided into those with margins smaller than 1 cm (n=9), 1 to 2 cm (n=6), and larger than 2 cm (n=3).

We defined *postoperative XRT* as the initiation of XRT within 1 month of the surgical excision without an intervening locoregional recurrence. This typically consisted of external beam irradiation ranging between 46 and 66 Gy to generous fields covering the primary tumor site, surgical bed, and the draining lymphatics.[9] Thirty-four patients, referred to as *group A*, did not receive postoperative XRT. The cancer stage in 4 of the 34 patients was clinically N+ at presentation; the status of the nodes was not given in 2 cases. The stage in 28 (82%) of the 34 patients was N0 at presentation. Twenty-six patients received postoperative XRT and are referred to as *group B*. Two of these 26 patients had clinically evident nodal metastases; the status of the nodes was unknown in 4 cases. The stage in 20 (77%) of the 26 patients was clinically N0 at presentation. Twenty of the 26 patients underwent elective XRT for possible microscopic disease, and 3 had definitive XRT for positive nodes; the reason for administration of XRT was not stated in 3 cases. Six patients received XRT as their definitive therapy and are referred to as *group C*. Two of these 6 patients had radiation implants at the primary site.

Patient records were retrospectively reviewed for demographic information, such as age, sex, and race. The tumor size and location; type of initial therapy; number, site, and time to onset of recurrences; and final outcome were noted for the entire study population. The date of last contact with MDACC determined the length of follow-up. The Fisher exact test was used to compare outcomes. A P value of less than .05 was considered significant. Kaplan-Meier survival curves were constructed for the different groups.

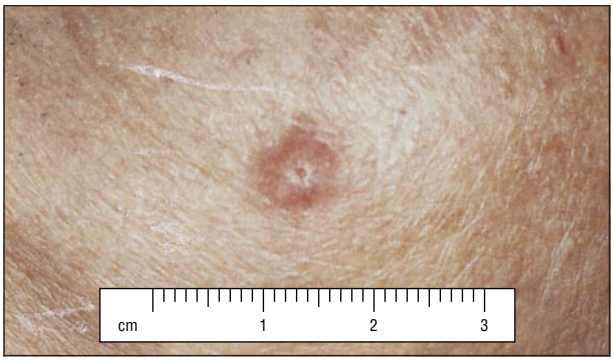

Figure 1. *Merkel cell carcinoma of the cheek. Primary Merkel cell carcinoma lesions are usually pinkish purple cutaneous nodules without ulceration.*

RESULTS

DEMOGRAPHICS

All 66 patients in this study were white (2 had Hispanic surnames). The patients ranged in age from 41 to 91 years (mean age, 68.4 years). There were 55 men and 11 women (male-female ratio, 5:1). No association was found between age or sex and outcome.

PRIMARY AND REGIONAL DISEASE

The primary tumors were located throughout the head and neck region, as shown below:

Location of Tumor	No. (%)* of Patients
Periorbital	4 (6%)
Forehead	6 (9%)
Temple	8 (12%)
Cheek	13 (20%)
Nose	9 (14%)
Mouth/chin	8 (12%)
Periauricular/ear	5 (8%)
Scalp	5 (8%)
Neck	6 (9%)
Other	2 (3%)

**The percentages add up to more than 100 because of rounding.*

The sizes of the lesions (diameter) were as follows: 43 tumors, smaller than 2 cm (67%); 10 tumors, 2 to 5 cm (15%); and 4 tumors, larger than 5 cm (6%). The diameter could not be determined in 9 cases.

Seven patients (11%) had palpable cervical lymphadenopathy at presentation (N+); 51 (77%) had no lymphadenopathy (N0); and the status of the neck could not be determined (NX) in 8 (9%). Neck dissection and/or

parotidectomy was performed as part of the initial procedure in 14 of the 66 cases: 5 of these had pathologically positive nodes, and 6 had no pathologic nodes; the status could not be determined in 3 cases. Three (43%) of the 7 patients with clinically positive neck disease and 22 (43%) of the 51 patients with clinically negative neck disease died of disease. The site and size of the primary lesion and the lymph node status at the time of presentation were not significant factors for predicting locoregional recurrence or survival rates.

LOCOREGIONAL RECURRENCES AND DM

Fifty-one (77%) of the 66 patients with MCC had a total of 109 recurrences. Ninety-six (88%) of these occurred within 2 years, and 104 (95%) occurred within 5 years. Of those patients who had recurrences, 31 (60%) died of disease. Nineteen patients (29%) had a single recurrence; 10 (53%) of the 19 died of disease. Multiple recurrences were common, with 32 patients having 2 or more recurrences (49% of the total population, and 63% of the patients who had a first recurrence). Twenty-one (66%) of these 32 patients died of disease.

Local recurrence was the first site of recurrence in 17 patients, 9 (53%) of whom died of disease. Regional lymphadenopathy was the first site of recurrence in 25 patients. Thirteen (52%) of the 25 patients died of disease. It was not uncommon for multiple regional recurrences to develop in a single patient. Distant metastasis occurred in 24 patients. In 9 patients (38%), DM developed as the first recurrence without locoregional recurrence; 1 of these 9 patients also had a simultaneous regional recurrence. All died of disease. Fifteen patients developed DM after a local or regional recurrence. Twenty-one patients with DM (88%) died of disease; 2 (8%) were living with disease; and 1 (4%) died of other causes with disease.

IMPACT OF SURGICAL MARGIN SIZE ON RECURRENCE AND SURVIVAL

In 18 cases, sufficient information was found in the patient records to establish the size of the surgical margins. Seven of the 18 patients remained disease free after their initial therapy. The recurrence rates for each group are given in **Table 1**. Two of the 18 patients in the margin groups had clinically evident regional disease at presentation (1 patient each in the <1- and >2-cm groups). Both patients were treated with WLE, neck dissection, and postoperative XRT and did not have a recurrence. The cancer stage was N0 in 15 patients in the margin groups at presentation; the status was unknown in 1 patient (<1-cm group) at presentation. Eight of the 15 patients were treated with WLE only; 5 (33%) were treated with WLE and postoperative XRT; and 2 (13%) were treated with WLE, neck dissection, and postoperative XRT.

In this small group of patients, there was no significant difference detected in local, regional, or distant disease control among the 3 margin groups. Furthermore, if the number of groups was reduced from 3 to 2 (margins <1 cm vs >1 cm or <2 cm vs >2 cm), significant differences in disease control still could not be detected. There was no detectable trend toward larger margins in larger sized primary lesions. Interestingly, the patients in the smaller-than-1-cm-margin group had a significantly better survival than those in the 1- to 2-cm-margin group ($P=.006$); the larger-than-2-cm-margin group was too small to make any comparisons.

Table 1. Effect of Margin Size on Recurrence

	No. (%)		
Margins	<1 cm (n = 9)	1-2 cm (n = 6)	>2 cm (n = 3)
No recurrence	5 (56)	1 (33)	1 (33)
Local recurrence	1 (11)	1 (17)	1 (33)
Regional recurrence	4 (44)	4 (67)	0
Distant recurrence	0	2 (33)	1 (33)

IMPACT OF POSTOPERATIVE XRT ON RATES OF RECURRENCE AND SURVIVAL

Of the 34 patients who were treated with WLE and no postoperative XRT (group A), only 1 patient (3%) was free of recurrence. Fifteen (44%) of these 34 patients developed a local recurrence at some point (13 of the recurrences were a first recurrence). Regional recurrence developed in 29 patients (85%). In 20 patients (59% of group A), regional disease was the first site of recurrence, without any evidence of local or distant disease. No one in group A had DM as the first recurrence, but 11 (32%) eventually developed distant disease.

Of the 26 patients who were treated with WLE and postoperative XRT (group B), 13 (50%) had no recurrences. Three patients (12%) developed a local recurrence (all recurrences were a first recurrence). Seven patients (27%) developed a regional recurrence; in 3 cases, this was the first site of recurrence. Distant metastases occurred in 11 patients (42%). In 7 patients, DM was the first recurrence.

In summary, there was a significant improvement in group B (postoperative XRT) over group A in overall disease control (50% group B vs 3% group A; $P<.001$), as well as in local recurrence rates (12% of group B vs 44% of group A; $P<.01$) and regional recurrence rates (27% of group B vs 85% of group A; $P<.001$). Interestingly, there was no significant difference between group A and group B in the development of DM (43% of group B vs 32% of group A; $P=.59$) (**Table 2**).

Survival curves for the patients in groups A and B are shown in **Figure 2**. As illustrated, there was no significant difference in disease-specific survival between these 2 groups ($P>.30$). Among those patients who were treated with surgical excision and postoperative XRT, there was no difference in recurrence or survival rates for those who received XRT at MDACC compared with those who were treated elsewhere ($P=.11$).

Table 2. Effect of Radiation Therapy on Recurrence

Group*	No. (%)						
	Local Recurrence		Regional Recurrence		Distant Metastasis		
	First	Total	First	Total	First	Total	No Recurrence
WLE ± ND and no XRT (n = 34)	13 (32)	15 (44)	20 (56)	29 (85)	0	11 (32)	1 (3)
WLE ± ND + XRT (n = 26)	3 (12)	3 (12)	3 (12)	7 (27)	7 (27)	11 (42)	13 (50)
XRT only (n = 6)	1 (17)	1 (17)	2 (33)	4 (44)	2 (33)	2 (33)	1 (17)
P (XRT vs no XRT)	.04	.01	<.001	<.001	.002	.59	<.001

**WLE indicates wide local excision; ND, neck dissection; and XRT, radiation therapy.*

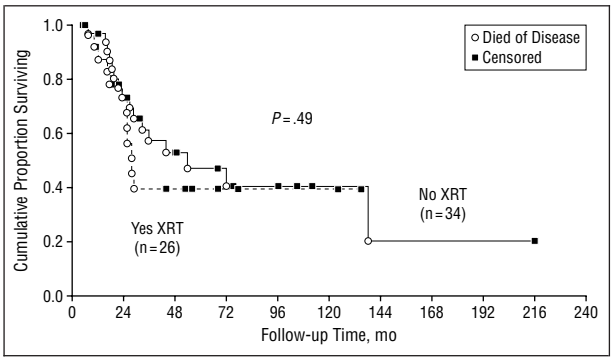

Figure 2. *Comparison of survival in patients treated with or without postoperative radiation therapy (XRT).*

IMPACT OF NODAL STATUS AND REGIONAL THERAPY ON RECURRENCE AND SURVIVAL

There were 51 patients who presented with no clinical evidence of nodal metastases. Of these patients, 24 underwent WLE only and did not receive elective treatment to the draining lymphatics. In this group, 19 patients (79%) had a regional recurrence (in 14 cases [58%], this was the first recurrence). Only 1 (4%) of the 24 patients remained free of disease, and 10 patients (42%) died of disease.

Only 2 (4%) of the patients with N0 disease underwent WLE and prophylactic neck dissection. Both eventually developed a regional recurrence (1 had regional disease as the first recurrence), and 1 died of disease. Sixteen patients (31%) underwent WLE with elective postoperative XRT. Only 3 patients (19%) had a regional recurrence, 1 of which was the first recurrence. Eleven patients (69%) remained free of disease, and 5 patients (31%) died of disease. Four patients (8%) underwent WLE and both elective neck dissection and postoperative XRT; none of these 4 patients developed a regional recurrence. However, all 4 developed DM, and all 4 died of disease (**Table 3**).

Among the patients with N0 disease, statistical analysis could be performed only on the WLE-only group (n=24) and the WLE-with-postoperative-XRT group (n=16) because of the insufficient patient numbers in the other treatment subsets. A significant decrease in first regional recurrence ($P=.001$), overall regional recurrence ($P=.003$), and all recurrences ($P<.001$) was found in the patients who were treated with WLE and postoperative XRT compared with those who were treated with WLE only. However, there was no difference in the percentage of patients in these 2 treatment groups who died of disease ($P=.74$).

There were only 7 patients (11%) who had clinically evident neck disease at the time of presentation. One of these patients had XRT as the definitive treatment, developed DM, and died of disease. For reasons not disclosed in the medical record, 1 patient underwent WLE only, without recorded treatment of the neck. The patient developed a regional recurrence as well as DM and died of disease. Three of these 7 patients underwent WLE and neck dissection. All 3 patients eventually developed a regional recurrence (1 of which was a first recurrence), and 2 of these patients died of disease. Two patients underwent WLE with neck dissection and postoperative XRT. Neither patient developed recurrence or died of disease.

COMMENT

Merkel cell carcinoma is a rare, aggressive skin malignancy; only approximately 600 cases have been documented in the literature since MCC was first described by Toker[1] in 1972. The annual age-adjusted incidence of MCC per 100 000 is estimated to be 0.23 for whites.[11] The etiology of MCC remains unclear. Miller and Rabkin[11] found an increased incidence of MCC with an increase in the solar UV-B index, similar to that of melanoma, suggesting an etiologic role for sun exposure in MCC carcinogenesis. This finding is in agreement with clinical series that have reported an association of MCC with UV exposure and other skin neoplasms.[6,12] Merkel cell carcinoma has also been reported to occur more frequently in persons with immunosuppression as a result of B-cell malignancies or after transplantation.[11,13]

The histogenesis of MCC also has not been clearly elucidated. Tang and Toker[3] first postulated that MCC arose from neural crest cells, whereas other investigations have suggested an epidermal origin with subsequent neuroendocrine differentiation.[14,15] Molecular analyses have implicated genetic alterations at 1p36,[16,17] a site of frequent genetic changes in other neuroendocrine tumors, including neuroblastomas, pheochromocytomas, and melanomas.

Few authors see sufficient numbers of patients with this disease to publish comparative analyses of treat-

Table 3. Outcome of Patients Based on Nodal Status and Treatment

Treatment*	No. (%)				
	Patients	Regional First Recurrence	Total Regional Recurrence	Any Recurrence	Died of Disease
All N0	51 (77)	18 (35)	27 (53)	38 (74)	22 (43)
XRT only	5 (10)	2 (40)	3 (60)	4 (80)	2 (40)
WLE only	24 (47)	14 (58)	19 (79)	23 (96)	10 (42)
WLE + ND	2 (4)	1 (50)	2 (100)	2 (100)	1 (50)
WLE + XRT	16 (31)	1 (6)	3 (19)	5 (31)	5 (31)
WLE + ND + XRT	4 (8)	0	0	4 (100)†	4 (100)
All N+	7 (11)	2 (29)	4 (57)	5 (71)	3 (43)
XRT only	1 (14)	0	0	1 (100)†	1 (100)
WLE only	1 (14)	1 (100)	1 (100)	1 (100)	1 (100)
WLE + ND	3 (43)	1 (33)	3 (100)	3 (100)	0
WLE + XRT	0	0	0	0	0
WLE + ND + XRT	2 (29)	0	0	0	0

*XRT indicates radiation therapy; WLE, wide local excision; and ND, neck dissection.
†All distant metastases.

ment outcomes.[5,10,18] We therefore analyzed our series of patients with head and neck MCC to determine the impact of surgical and XRT on locoregional disease control and survival.

Merkel cell carcinoma has a propensity for recurrence and metastasis.[19] Our overall 29% local recurrence rate, 59% regional recurrence rate, and 36% DM rate are comparable to those in previous series.[9,18] It has been suggested that inadequate excision of primary MCC lesions will lead to locoregional recurrence and eventually DM. Bourne and O'Rourke[20] recommend that 3-cm margins be performed but comment that it is impractical in all sites. Thus, what constitutes an adequate surgical margin in the head and neck has not been assessed. Our evaluation of the impact of surgical margin width on outcome was hindered by the retrospective nature of the data collection, which produced only a small population with enough information to determine margin size. In the 18 evaluable patients, no statistically significant difference in locoregional control or outcome could be detected. Unfortunately, the small patient numbers do not give sufficient statistical power to detect any small incremental advantage to wide surgical margins. Although we found no evidence that wider margins were taken around larger, more "malignant-appearing" lesions, this also would mask a small improvement in disease control associated with wider surgical margins. From our analysis, we conclude that the width of surgical margin around the primary site does not have a major impact on recurrence or survival rates, but we were unable to definitively determine the effect of margin size on locoregional control. Allen et al,[21] in a retrospective analysis of 102 patients with MCC in all sites, also found no specific size of surgical margin that correlated with a decrease in local recurrence.

The treatment of the draining lymphatics has evolved over the years. In 1984, Goepfert et al[5] recommended elective treatment to the draining lymphatics after finding a 75% failure rate in patients with untreated necks. In 1988, it was suggested that outcome improves when both the primary and the draining lymphatics are treated regardless of the initial neck stage.[20] In 1991, Shaw and Rumball[22] noted that the combination of elective neck dissection and XRT was associated with a significant drop in locoregional recurrence rates. Morrison et al[10] and Meeuwissen et al[18] demonstrated the efficacy of elective XRT alone for controlling the regional lymphatics. Our findings also confirmed the importance of electively treating the draining lymphatics with XRT. We found a 19% regional recurrence rate among those patients who received postoperative XRT compared with 79% among those who underwent WLE only ($P<.001$). Only 2 patients underwent elective neck dissections without XRT, so we could not assess the effectiveness of elective surgical management of the neck. There were also an insufficient number of patients to compare the combination of elective neck dissection plus XRT with elective XRT alone.

An investigation of the use of intraoperative lymphatic mapping and sentinel lymph node biopsy in 18 patients with MCC (including 1 patient with MCC in the head and neck region) was conducted by Hill et al.[23] Two patients were found to have metastatic disease in the sentinel nodes and no further involved nodes on subsequent nodal dissections, suggesting the possibility that the concept of a "sentinel node" as a predictor of the disease status of the entire nodal basin may be applicable for MCC. The 16 patients who were negative for sentinel nodes in this study and who received no further elective treatment to the draining lymphatics have not developed locoregional recurrence. However, the follow-up period (median length of follow-up, 7 months) is too short to assess any effect on locoregional control. Without further studies in patients with MCC of the head and neck, it is difficult to know what future role lymphatic mapping and sentinel lymph node biopsy may play in the treatment of these patients.

Merkel cell carcinoma is a very radiosensitive tumor.[24] Several series have demonstrated increased rates of locoregional recurrence in patients treated with surgery alone compared with those treated with surgery and XRT.[10,18,19] However, the few patients who were treated with XRT alone had high rates of locoregional recurrence and DM, possibly because of a selection bias.[10] In our study, there were 6 patients who received XRT as definitive therapy.

One of the 6 had no recurrences and remained free of disease. Of the 5 patients who had recurrences (1 locoregional, 2 regional, and 2 distant), 4 died of disease and 1 died with disease. For the present, it seems that complete surgical excision is warranted before postoperative XRT.

In the current study, the use of postoperative XRT significantly improved locoregional control rates, yet there was no improvement in DM rate or disease-specific survival. The development of DM was the most important factor for predicting survival; 88% of those who developed DM died of disease. A multimodality management approach incorporating adjuvant systemic therapy that can maintain locoregional control and prevent DM needs to be developed. Studies of chemotherapeutic agents that are active against small cell carcinoma of the lung, such as etoposide and cisplatin or cyclophosphamide, methotrexate, and fluorouracil, have shown promising short-term results in patients with established DM.[25] Fenig et al[25] showed that chemotherapy used in a palliative setting had complete responses in 69% of patients, most remarkable for locoregional disease and less for visceral metastases. They noted that the response was short-lived unless the chemotherapy was followed by consolidation XRT. Voog et al,[7] through a review of the literature, found a 60% response rate (57% for DM and 69% for locoregional disease) to chemotherapy in patients with MCC. The median overall survival after starting chemotherapy was 9 months for patients with DM and 24 months for patients with locoregional disease. The conclusion reached by the investigators was that recurrent and metastatic MCC is chemosensitive but not chemocurable. The use of chemotherapy in the adjuvant setting has not been thoroughly investigated. In the current study, the role of chemotherapy could not be evaluated.

CONCLUSIONS

We evaluated the effectiveness of surgical resection margin width and use of postoperative XRT for locoregional control and survival in this retrospective analysis of 66 patients with head and neck MCC seen at a single institution. The number of patients in whom margin size could be accurately determined was too small to enable us to detect any effect of the width of surgical margins on outcome. Postoperative XRT to the primary tumor site and draining lymphatics did have a significant impact on locoregional control, but not on the incidence of DM or on long-term survival rates. The only factor affecting survival in this study was the development of DM.

Merkel cell carcinoma of the head and neck region has proved to be an aggressive skin cancer with a poor prognosis. Like that of melanoma, the incidence of MCC may be on the rise, possibly owing to greater UV exposure in the population or to the increased numbers of patients surviving with immunodeficiency disorders. Unfortunately, the optimal treatment for this disease continues to elude us. The currently recommended treatment at MDACC is conservative surgical excision of the primary tumor with microscopically negative margins on frozen section, followed by postoperative XRT to the primary and draining lymphatics. While we found that XRT improved locoregional disease control, survival rates remained poor: almost 50% of patients died of their disease within 3 years of diagnosis. Further therapeutic innovations incorporating systemic therapy are needed to reduce the development of DM and to increase survival rates.

Accepted for publication June 28, 2000.

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