Annals of Surgical Oncology, **8**(3):204–208
Published by Lippincott Williams & Wilkins

Multimodality Treatment of Merkel Cell Carcinoma: Case Series and Literature Review of 1024 Cases

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Background: Merkel cell carcinoma (MCC) is an unusual and potentially aggressive cancer of the skin. There is no consensus regarding the optimal therapeutic approach, and the relative roles of surgery, radiotherapy, and chemotherapy still are controversial The aim of this study is to analyze the roles of these therapeutic options.

Methods: The medical records of 16 patients with a diagnosis of localized, primary MCC treated at the University of Alabama at Birmingham were reviewed. An extensive review of the English-language literature also was performed. The Kaplan-Meier method was used to develop the survival curves. Comparisons were made using Fisher's exact test. Significance was defined as $P < .05$.

Results: MCC presented primarily in Caucasians (98.3%) with a median age of 69 years. Immunosuppressive therapy appeared to play a role in the development of this cancer. In the UAB experience, 3-year actuarial survival was 31%. The only factor significantly associated with overall survival was the stage of disease at presentation: median survivals were 97 vs. 15 months for stages I and II, respectively (log-rank, $P = .02$). From the literature review, adjuvant radiotherapy was associated with a reduced risk of local recurrence ($P < .00001$).

Conclusions: MCC is an aggressive cancer, with a high tendency for local recurrence and distant spread. Surgery and adjuvant radiotherapy appear to provide optimal local control. The role of chemotherapy remains to be defined.

Key Words: Merkel cell carcinoma—Surgery—Radiotherapy—Prognosis.

Merkel cell carcinoma (MCC) is an unusual and potentially aggressive cancer of the skin originally described by Toker in 1972 as trabecular cell carcinoma.[1] Merkel cells are neuroendocrine cells present in the basal layer of the epidermis and are presumed to be the cell of origin of this cancer,[2] although this theory is not held consistently in the literature.[3] Because MCC is an uncommon cancer, most published series describe a limited number of cases. There is no consensus regarding the optimal therapeutic approach, with the relative roles of surgery, radiotherapy, and chemotherapy are still controversial. Randomized, controlled studies would be very difficult to perform because of the limited number of cases available for study. We are unaware of any studies of this type for this cancer.

The purpose of this study is to describe the natural history of this cancer and to analyze the influence of patient, tumor, and treatment variables on survival and recurrence. We describe the experience with treatment of MCC at the University of Alabama at Birmingham and present an extensive review of the English-language literature.

PATIENTS AND METHODS

Sixteen patients with a diagnosis of primary MCC were identified from Tumor Registry and Radiation Oncology records at the University of Alabama at Birmingham (UAB) from January 1986 to June 2000. The medical records were reviewed, and we documented demographics, tumor characteristics, kind of treatment, and outcome. Patients referred for palliative treatment of advanced locoregional disease or distant metastases were excluded from analysis. Patients were staged according

Received August 28, 2000; accepted October 26, 2000.

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to the absence (stage I) or presence (stage II) of metastases to regional lymph nodes.[4] Disease-free and overall survival were the end points of the study and were determined from the time of diagnosis. The date of last follow-up was June 30, 2000.

The χ^2 test or Fisher's exact test, where appropriate, was used for comparisons. Actuarial survival was calculated using the Kaplan-Meier method,[5] and the curves were compared using the Cox-Mantel log-rank test. Differences were considered significant at $P < .05$.

An extensive review of the English-language literature from January 1990 to June 2000 was performed. Isolated case reports and those series that did not provide information regarding outcome were excluded. Series that focused on palliative treatment of advanced disease also were excluded. When the same institution reported its experience twice, the most recent report was taken into account. From the reviewed reports, the following information was extracted: patient age, gender and medical history (with emphasis on immunosuppressive therapy or history of previous squamous cell carcinoma [SCC] of the skin); stage at presentation; treatment; and outcome.

RESULTS

UAB Experience

There were 12 men (75%) and 4 women (25%) in the study, with a median age of 67 years (range, 37–94 years). All patients were white. Five patients (31.3%) had a history of squamous cell carcinoma (SCC) of the skin, and three patients (18.8%) were on immunosuppressive drugs because of a kidney or heart transplant. Clinicopathological characteristics of MCC are shown in Table 1. The size of the primary MCC could be determined in 11 cases; the mean MCC size was 2.73 cm (range, 0.7–7.3 cm).

All patients underwent wide local excision with a median margin of 2.0 cm (range, 0.5–2.5 cm), including one patient with partial excision of the upper lip and reconstruction with Abbe flap. Four patients presented with palpable adenopathy: three patients underwent modified radical neck dissection ipsilateral to the lesion, two of them with superficial parotidectomy, and one patient underwent an axillary lymph node dissection. Two additional patients with lesions on their forearms underwent axillary sentinel lymph node biopsy and were found to have metastasis at presentation. Both patients subsequently underwent an axillary lymph node dissection: in one patient the sentinel node was the only positive node, whereas in the second patient, 28 of the 31 lymph nodes that were removed were involved. No patient with stage I disease underwent elective lymph node dissection.

Seven patients received adjuvant radiotherapy: four with stage II disease, one with a positive surgical margin, one with a 7-cm MCC of the scalp, and one with a tumor of the lip. Two patients with stage II disease received adjuvant chemotherapy: one patient recurred in multiple distant sites 11 months after treatment and died of disease 4 months later; the other patient is alive without evidence of disease 20 months after treatment.

Seven patients (43.7%) recurred: three presented with regional lymph node recurrence only, three with distant metastases, and one with simultaneous local recurrence and distant metastases. The mean time to recurrence was 6.9 months (range, 2–11 months).

The median survival for the entire population was 32 months (95% CI, 17–47 months). The actuarial 2- and 3-year survivals were 59% and 31%, respectively. The presence of positive nodes at presentation was found to have prognostic significance. The median survival for stage I patients was 97 months, whereas for stage II patients, median survival was only 15 months (log-rank, $P = .02$).

TABLE 1. *Clinicopathological characteristics of Merkel cell carcinoma*

Characteristic	UAB experience (n = 16) No. (%)	Literature review (n = 1024) No. (%)
Location		
Head and neck	10 (62.5%)	416 (40.6%)
Trunk	0	236 (23.0%)
Extremities	6 (37.5%)	338 (33.0%)
Unknown	0	34 (3.4%)
Stage at presentation		
I	10 (62.5%)	751 (73.4%)
II	6 (37.5%)	231 (22.6%)
III	0	41 (4.0%)

UAB, University of Alabama at Birmingham.

Literature Review

We studied 20 series (including the present one) with a total of 1024 patients.[6–24] There were 593 men (58%) and 431 women (42%), for a male:female ratio of 1.4:1. The mean patient age was 69 years (range, 18–98 years). Fifteen series reported the race of the patients: from the total of 589 patients for whom race was reported, 579 (98.3%) were white. In nine series where the incidence of SCC of the skin was reported (577 patients), the rate was 13.5% (78 patients). Seven studies, with a total of 420 patients, reported the presence of immunosuppression in their population: 61 patients (14.5%) had received or were receiving some type of immunosuppressive therapy.

The reported location of the primary MCC is shown in Table 1. The most common site of presentation was in the head and neck area (40.6%). In 3% of cases, the MCC presented as a metastatic disease of unknown primary, usually in lymph nodes. The stage of presentation was reported in all series, with 75% of patients presenting with localized disease (Table 1).

If we exclude those patients who presented with distant metastases (stage III), of the remaining 982 patients, 545 (55.5%) had lymph node metastases at presentation or developed them during follow-up. The development of distant metastases was reported in 18 series: of 895 patients included in these series, 277 (30.9%) had distant metastatic disease at presentation or during follow-up. The most common sites of distant metastasis were distant lymph nodes (60.1%), distant skin (30.3%), lung (23.4%), central nervous system (18.4%), and bone (15.2%).

The rate of local recurrence was reported in 18 series. Excluding patients with stage III disease at presentation, 279 of 926 (30.1%) patients developed local recurrence during follow-up. The average disease-free interval for local recurrence reported was 7.4 months (range, 4–10 months). Eleven series reported the local recurrence rates with and without adjuvant radiotherapy (Table 2). Of 441 patients included in these series, the local recurrence rate with radiation was 10.5% (range, 0–33%) vs. 52.6% (range, 6–100%) without radiation ($P = .00001$).

The reported survival varied from 75% at 5 years[7,10] to 35% at 3 years.[14,19] Prognostic factors associated with overall survival were reported in 12 series, including the present one. The most consistent of these was the stage of disease at presentation.[6–8,12,20] Two series[6,8] reported male gender as an adverse prognostic factor. Immunosuppressive therapy was associated with increased incidence of MCC and with poor prognosis.[11]

TABLE 2. *Effect of radiotherapy in local recurrence*

Series	LR with radiation	LR without radiation	*P*
Allen et al, 1999[7]	11%	13%	NS
Meeuwissen et al, 1995[8]	0%	21%	<.05
O'Connor et al, 1997[10]	0%	50%	<.01
Kokoska et al, 1997[14]	15%	90%	<.05
Boyle et al, 1995[15]	12%	47%	<.05
Wong et al, 1998[16]	0%	62%	<.05
Ott et al, 1999[17]	0%	32%	NS
Tennvall et al, 1990[18]	33%	55%	NS
Pergolizzi et al, 1997[21]	33%	100%	NS
Perez et al, 1998[23]	0%	100%	NS
Present	0%	6%	NS
Total	10.45%	52.63%	.00001

LR, local recurrence; NS, not significant.

DISCUSSION

The exact cause of MCC is not known, but it has been associated with exposure to sunlight. In our experience, all cases were localized to sun-exposed areas of the head and neck (75%) or extremities (25%). In the series reported in the literature, more than 70% of cases were localized to these areas, with 40% seen in the head and neck area and 33% in the extremities; but, more than 20% were localized to the trunk and other areas. In addition, diseases that are associated with exposure to ultraviolet radiation, such as solar keratosis or SCC, are associated with MCC. In our survey of the literature, 13% of patients for whom this data was reported had a personal history of SCC of the skin. In addition, darker skin pigmentation appears to offer some protection, based on the fact that more than 98% of reported cases occurred in Caucasians.

Immunologic aspects of this cancer are interesting because of reports of spontaneous remission.[25] In the present review, 3.3% of cases presented with metastasis from an unknown primary, suggesting regression of the primary MCC. In addition, immune compromise appears to play a role in the epidemiology of this cancer. In the UAB experience, three patients (20%) were receiving immunosuppressive drugs when they developed MCC, whereas in the literature review, 15% of patients for whom data concerning immunosuppressive therapy was reported, had or were receiving such therapy.

Merkel cell carcinoma has a high local recurrence rate (30%), which is much higher than that reported for melanoma.[26] The rate of local recurrence is affected favorably by radiotherapy. Like other neuroendocrine tumors, MCC is considered a radiosensitive cancer, although variation in radiosensitivity has been reported in small cell carcinoma cell lines.[27] Several series suggest that radiation alone can achieve local control in some patients with gross disease. Our review of the literature suggests that in the adjuvant setting, radiotherapy will improve local control,[8,12] but patients still are at high risk for distant recurrence. Radiation doses of approximately 46 to 50 Gy, at 2 Gy per fraction to the tumor bed and draining lymphatics, have been recommended following gross resection.[28] Whether this radiation dose could be reduced if concurrent chemotherapy is utilized remains unproven. Although radiation produces excellent local control in the adjuvant setting, marginal recurrences have been described. Of 31 patients treated at The MD Anderson Cancer Center, only one patient developed an in-field recurrence, but three patients developed marginal recurrences.[28] It has been suggested that radiation ports

also include nodal basins that are at risk, but clinically uninvolved, should be considered.

Not all studies, however, have found benefit in adjuvant radiation. In the series from Memorial Sloan-Kettering Cancer Center,[7] local recurrence developed in 13% of MCC patients who received radiotherapy and in 11% of patients who did not ($P = .84$). This result is weakened by the fact that only 15 of the 102 patients included in the report received radiation. In the UAB experience, of the seven patients who received radiotherapy, all had adverse prognostic factors: four had stage II disease; two had positive or narrow margins; and one patient had a very large tumor of the scalp. No patient who received radiotherapy developed local recurrence. There is no evidence in the literature that radiotherapy prolongs survival in the MCC patient, but retrospective analysis of clinical data strongly suggests that locoregional control of disease is improved.

Lymphatic dissemination occurs often and early in the course of MCC. More than 20% of patients presented with stage II disease, but during follow-up, more than 50% of patients developed lymph node metastases. Almost all authors agree that the presence of lymphatic disease is an adverse prognostic factor,[6–8,12,20] but the role of prophylactic regional node dissection in determining prognosis is more controversial. Victor et al.[20] reported that the rate of regional recurrence is nil with prophylactic regional lymph node dissection, whereas with observation, 50% of patients developed lymph node metastasis. In the series from Memorial Sloan-Kettering,[7] elective lymph node dissection was the only parameter independently predictive of improved relapse-free survival, but it was not associated with overall survival.

An alternative to elective regional lymph node dissection is selective lymphadenectomy or sentinel lymph node biopsy, a technique well established for melanoma[29] and previously reported in MCC.[30] At UAB, recent MCC sentinel lymph node biopsy has been attempted in three patients: two patients with upper extremity MCC and one with a forehead cancer. Localization of the sentinel node was successful in the patients with extremity MCC. We propose that sentinel lymph node biopsy be used to select those patients who will benefit from lymphadenectomy for regional control. However, this approach should be considered investigational, because there are no data concerning patterns of lymph node metastases in MCC. In the presence of metastatic disease to the sentinel node, we recommend complete dissection of the nodal basin, radiotherapy being reserved for patients who are not surgical candidates or those who refuse further surgical intervention.

The reported survival for MCC has been variable. In our experience and that of others,[14,19] the outcome is dismal, with 3-year overall survival of only 31%. Because most patients die from distant metastatic disease, effective adjuvant systemic treatment is necessary to improve survival. A recent review[31] reported response rates to chemotherapy of between 60% and 75%; however, the chemotherapeutic regimens used were toxic and were not shown to affect survival.

In conclusion, MCC is an aggressive cancer, with high rates of local recurrence and distant metastasis. Sentinel lymph node biopsy may be useful in selecting those patients who will benefit from elective node dissection for regional control. Radiotherapy seems to offer an advantage for local control of this disease.

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