Radiotherapy Alone for Primary Merkel Cell Carcinoma

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Background: Merkel cell carcinoma is a rare and potentially aggressive cancer of the skin. Cumulative data from small retrospective series have supported treatment by wide excision and adjuvant radiotherapy. However, wide excision may be difficult to perform in patients with tumors of the head and neck or in older populations with comorbidities that may be incompatible with general anesthesia.

Observations: Nine patients (group 1) with stage I (without lymph node involvement) Merkel cell carcinoma primary tumors were treated in our center by radiotherapy alone. The rate of recurrence was compared between this group and 17 additional patients (group 2) with stage I Merkel cell carcinoma who received conventional treatment (surgery followed by radiotherapy).

Results: The median follow-up was 3.0 years (range, 8 months to 7 years) for group 1 and 4.6 years (range, 5 months to 11 years) for group 2. During this period, we observed 1 relapse and 1 progression of disease in group 2. No statistical difference was found in overall and disease-free survival between the 2 groups of patients.

Conclusion: This study demonstrates the possibility of treating inoperable Merkel cell carcinoma by radiotherapy alone, with outcomes similar to those of classic treatment.

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MERKEL CELL carcinoma (MCC), first described in 1972 by Toker,[1] is a rare and highly malignant tumor of the skin. lt is believed to originate from the Merkel cell and comprises neuroendocrine cells in the basal layer of the epidermis. Merkel cell carcinoma most commonly arises in older white patients, with a mean age at diagnosis of 69 years.[2,3] It usually appears as a painless, red, solitary nodule that has grown rapidly over a few weeks to months. At the first consultation, 70% to 80% of patients with MCC have localized disease (stage I), 10% to 30% have regional lymph node involvement (stage II), and 1% to 4% have distant metastases (stage III).[2,3]

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Merkel cell carcinoma, once regarded as an indolent skin tumor, is considered an aggressive and often lethal malignancy, comparable to melanoma in its metastatic spread and mortality. The overall recurrence rate ranges from 55% to 79%, occurring most often locally or in regional lymph nodes within the first 6 to 12 months after initial diagnosis.[2,4]

Because of the rarity of the disease, no prospective study has assessed the management of this tumor. Cumulative data from small retrospective series have supported 2.0- to 3.0-cm-wide excision and adjuvant radiation treatment, using large fields to cover the entire surgical scar.[2,5-7] However, surgery is sometimes difficult because MCC is often found in older persons with health problems that may be incompatible with general anesthesia. Furthermore, the head and neck region is a frequent location of MCC (54% in our population), and a large excision is often difficult to perform in this topography.

Between March 1991 and November 2001, we treated in our center 9 patients with inoperable stage I MCC primary tumors by radiotherapy alone (group 1). The rate of recurrence was compared between this group and 17 patients with the same stage MCC but who received conventional treatment (surgery followed by radiotherapy) (group 2).

Characteristics of Patients With Stage I Merkel Cell Carcinoma

Patient No.	Birth Date	First Biopsy	Tumor Size, cm	Tumor Location	Tumor Margin, cm	PRN	PRT	Tumor Relapse	Cause of Death
Radiotherapy Alone (Group 1)									
1	06/20/1931	03/20/2001	1.0	Cheek	NA*	Yes	Yes	No	Alive
2	01/07/1921	04/07/1998	8.0	Leg	NA†	Yes	Yes	No	Chronic lymphoid leukemia
3	03/20/1921	12/10/1997	7.0	Leg	NA†	Yes	No	No	Chronic lymphoid leukemia
4	09/27/1920	10/15/1998	4.5	Cheek	NA*	Yes	Yes	No	Alive
5	12/31/1912	10/03/1995	2.5	Upper lip	NA*	No	No	No	Alive
6	07/30/1913	06/07/1999	4.0	Forehead	NA*†	Yes	Yes	No	Heart failure
7	04/26/1911	10/06/1999	2.0	Eyelid	NA*	Yes	No	No	Alive
8	02/26/1911	05/12/2000	3.0	Upper lip	NA*	No	No	No	Alive
9	09/12/1911	11/06/2001	1.5	Nose	NA*	No	No	No	Alive
Surgery Plus Radiotherapy (Group 2)									
1	11/05/1953	01/01/1998	NK	Cheek	3.0	Yes	Yes	No	Alive
2	03/25/1952	05/05/1999	NK	Arm	0.1	No	No	No	Alive
3	01/29/1951	10/29/1999	1.6	Elbow	0.5	Yes	No	No	Alive
4	06/28/1947	06/12/1996	2.0	Thigh	0.5	Yes	No	Yes	Alive
5	09/29/1937	02/28/1997	3.0	Thigh	0.5	Yes	No	No	Alive
6	05/09/1938	10/08/1999	1.4	Ear	0.5	Yes	Yes	No	Alive
7	05/17/1930	01/20/1999	1.0	Arm	1.0	Yes	No	No	Alive
8	04/13/1923	11/04/1992	3.0	Thigh	2.0	Yes	No	No	Alive
9	09/10/1925	09/20/1997	2.5	Thigh	2.0	Yes	No	No	Alive
10	12/26/1922	04/05/1995	1.2	Upper lip	0.5	Yes	Yes	No	Mesothelioma
11	03/11/1923	07/16/1997	2.0	Elbow	1.0	No	No	No	Alive
12	10/07/1918	04/01/1996	1.5	Cheek	1.5	Yes	Yes	No	Alive
13	11/01/1918	04/25/1998	1.0	Ankle	0.5	Yes	No	No	Alive
14	09/01/1909	03/05/1991	2.5	Neck	1.5	Yes	Yes	No	Heart failure
15	05/14/1906	08/01/1989	4.0	Cheek	NK	Yes	Yes	No	Alive
16	07/15/1909	03/15/1995	1.0	Eyebrow	0.1	Yes	Yes	No	Heart failure
17	11/25/1911	10/01/1998	3.5	Leg	1.0	Yes	No	Progression	Merkel cell carcinoma

Abbreviations: NA, not applicable; NK, not known; PRN, prophylactic radiotherapy of the draining lymph nodes; PRT, prophylactic radiotherapy of the area between the primary tumor site and the draining lymph nodes.

*Tumor location precluded surgery.

†Patient health precluded surgery.

METHODS

PATIENTS

Among the patients with stage I MCC treated in our center between 1991 and 2001, 26 patients were selected who had been treated by radiotherapy alone or by conventional surgery followed by radiotherapy. There were 18 women (69%) and 8 men (31%), for a female-male ratio of 2.2:1. The mean age was 81 years (range, 49-94 years). The primary tumor was located in the head and neck area in 14 patients (54%) and in the extremities in 12 (46%). The histological diagnosis of MCC was established by immunohistochemical staining of skin biopsy specimens in all cases.

The mean diameter of the tumors was 3.7 cm (range, 1.0-8.0 cm) in group 1 and 2.1 cm (range, 1.0-3.5 cm) in group 2. The diameters of the tumors in the 2 groups were comparable, except for 2 patients in group 1 who had 7.0- and 8.0-cm-wide tumors. The stage I status of the patients in the study was established by physical examination, chest x-ray films, and ultrasound examination of the draining lymph nodes.

TREATMENT

Surgical Treatment

In group 2, excision with 0.1- to 3.0-cm-wide margins was performed. Margins were less than 1.0 cm in 8 patients, between 1.0 and less than 2.0 cm in 5 patients, and 2.0 cm or greater in 3 patients. Margins for 1 patient were not known (**Table**).

Radiotherapy

All 26 patients received radiotherapy on the primary tumor site, as the exclusive treatment in group 1 and as adjuvant treatment after surgery in group 2. In each case, large fields were used to cover the tumor site, with margins greater than 2.0 cm.

The median dose used was 6000 rad (60 Gy) (range, 5000-7800 rad [50-78 Gy]), with a standard regimen of 5 irradiations per week totaling 1000 rad (10 Gy) per week in both groups.

Recently, because of the poor prognosis of patients with MCC at stage II and the radiosensitivity of this tumor, prophylactic irradiation of the draining lymph nodes has been proposed. The efficacy of this treatment has not been evaluated in the literature.

We performed prophylactic irradiation of the draining lymph nodes in 21 patients. Three patients in group 1 and 2 in group 2 did not receive this treatment. Additional irradiation of the area between the primary tumor site and the draining lymph nodes was performed in 4 patients in group 1 and in 7 in group 2; the site in 10 of these patients was the head and neck region. This was not considered a treatment of in-transit metastases but a prophylactic irradiation of in-transit tumor cells.

STATISTICAL ANALYSIS

The overall survival and disease-free survival were analyzed using the nonparametric Kaplan-Meier method. The log-rank test was used to compare the data, with the significance level fixed at $P = .05$.

RESULTS

Follow-up data were available in all 26 patients, with a median follow-up of 4 years (range, 5 months to 11 years) from the date of the first biopsy confirming the diagnosis. The median follow-up for group 1 was 3.0 years (range, 8 months to 7 years) and for group 2 was 4.6 years (range, 5 months to 11 years).

Among the entire population, 1 recurrence was observed, a precocious skin relapse 6 months after treatment distant from the primary tumor site in a patient in group 2. This skin relapse was treated by radiotherapy alone, and the patient is alive 5 years after treatment. In another group 2 patient, metastasis occurred after treatment of an MCC tumor that was 3.5 cm in diameter, with relapse around the surgical scar 3 weeks after treatment and resistance to irradiation. This patient died 5 months after the relapse as a result of metastasis.

During the follow-up, 7 patients died, 3 in group 1 and 4 in group 2. Heart failure was the cause of most of the deaths (6 patients); the patient in group 2 with metastasis was the sole death from the MCC.

In the comparison of overall survival and disease-free survival between the 2 groups of patients, no statistically significant difference was found (**Figure 1**).

COMMENT

Merkel cell carcinoma was initially described as an indolent skin tumor of low malignant potential. However, subsequent investigations revealed that the tumor often has an aggressive course.[8] This tumor has traditionally been managed with surgery alone, and 2.0- to 3.0-cm margins have been generally recommended.[9,10] However, Gillenwater et al[11] recently reported no difference in outcome among 18 patients with margins less than 1.0 cm, 1.0 to 2.0 cm, or greater than 2.0 cm.

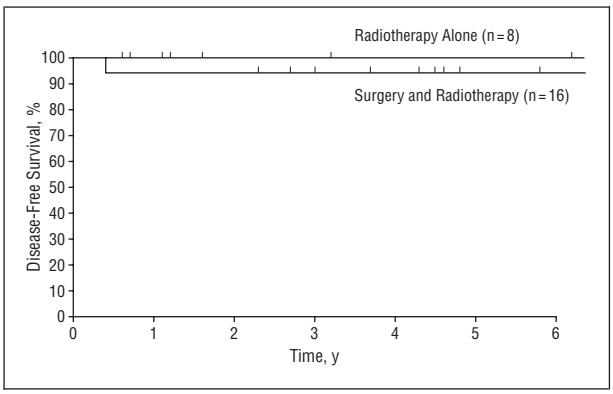

Figure 1. Disease-specific, relapse-free Kaplan-Meier survival of the 2 groups of patients (P=.48, log-rank test).

Several authors reported improved local control by using postoperative irradiation to the primary site.[5,6] Recently, Boyer et al[12] compared survival and recurrence rates between patients with MCC treated with Mohs surgery alone and those treated with Mohs surgery and adjuvant postoperative radiation and did not find a significant difference between the treatment groups. However, all of the recurrences were in the Mohs surgery–only group, 1 of them marginal and 3 of them in transit.

Radiotherapy has also been proposed in the prophylactic management of draining lymph nodes,[2] but no study has evaluated the survival rates using this modality of treatment. The data presented herein support the use of radiotherapy in the management of MCC, as 21 patients in the cohort received this prophylactic treatment.

Merkel cell carcinoma affects the sun-exposed areas of the skin, with approximately 50% of all tumors occurring in the face and neck. In this region, wide excision is often difficult to obtain. Furthermore, the need for general anesthesia for wide excision often presents difficulties in older patients. In these situations, radiotherapy alone should be considered, as it produces similar results (**Figure 2** and Table).

Although no dose-response curve has been established for the treatment of MCC, most authors agree that doses of 4000 to 6000 rad (40-60 Gy) with standard fractionation are appropriate.[5,6] In the present study, 6000 rad (60 Gy) was successfully used in both patient groups.

Other results of treating primary MCC by radiotherapy alone have been published in case reports,[13,14] as Ott et al, who showed a prolonged remission in 4 patients with MCC of the head and neck, but the study did not evaluate the outcome of this treatment compared with standard treatment.

In conclusion, this study demonstrates the possibility of treating inoperable MCC by radiotherapy alone, with outcomes similar to those of classic treatment with surgery and radiotherapy.

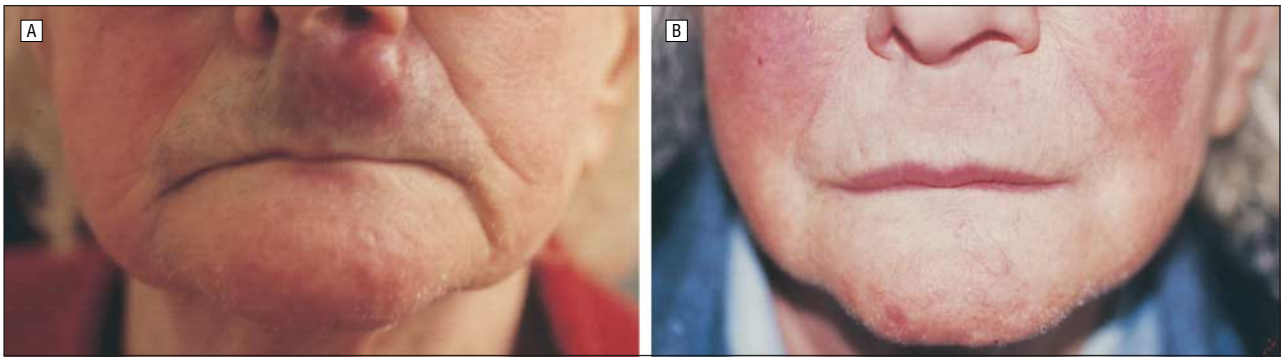

Figure 2. Results of Merkel cell carcinoma treated by radiotherapy alone (patient 5 in the Table) before (A) and 5 months after (B) irradiation. This patient is alive 7 years after treatment.

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