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Surgical Management of Merkel Cell Carcinoma

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Objectives

To characterize the natural history of Merkel cell carcinoma (MCC) and to analyze the influence of patient, tumor, and treatment-related variables on survival and recurrence.

Summary Background Data

Approximately 425 cases of MCC have been described in the literature. This study represents the largest experience reported.

Methods

A review was performed of patients who had been treated at Memorial Sloan-Kettering Cancer Center for MCC between 1969 and 1996. Follow-up data were available for 102 of the 109 (94%) patients identified.

Results

The overall 5-year disease-specific survival rate was 74%. The median follow-up was 35 months. For all patients, the only independent predictor of survival was the tumor stage at presentation. For patients with stage I disease, the tumor size at presentation was also an independent predictor of survival. Recurrence of disease occurred in 55 patients (55%), and the most common site of first recurrence was within the draining lymph nodes (n = 35). Elective lymph node dissection was the only parameter independently predictive of improved relapse-free survival. The overall disease-specific survival rate after recurrence was 62%. Predictors of improved disease-specific survival after recurrence included nodal as compared to local or distant recurrence, the ability to render the patient free of disease after recurrence, and a disease-free interval of >8 months.

Conclusion

The prognosis for patients with MCC is favorable, and even after recurrence the majority of patients experience long-term survival. Incorporation of size into the staging system more accurately predicts survival in patients with stage I disease. Although elective lymph node dissection decreased the rate of recurrence, it was not associated with improved overall survival.

Merkel cell carcinoma (MCC), previously called trabecular cell carcinoma, is an uncommon cutaneous malignancy first described by Toker in 1972.[1] Merkel cells, neuroendocrine cells that reside in the basal layer of the epidermis, are the presumed cell of origin for this tumor.[2] Since the first description of this disease in 1972, approximately 425 cases have been reported in the literature.[3]

The natural history of this disease remains poorly understood. Initial case reports and small series reported excellent survival rates, with only 3 deaths from disease in the first 24 patients reported.[4] Recently, however, a more variable disease course has been described, with 5-year survival rates of 30% to 62%.[5,6] The importance of prognostic variables such as patient gender and tumor location is also uncertain. Several studies have reported improved survival in women and in patients with tumors of the head and neck region. More recent studies, however, have not confirmed these observations.[6,7]

The optimal treatment for this disease is also controversial. In the treatment of the primary tumor, the size of the surgical margin needed to minimize the risk of local recurrence has been reported to range from 2 to 3 cm.[5,8] The role of adjuvant therapy and the elective treatment of lymph nodes has also not been established. Given the propensity for regional nodal recurrence, several investigators have advocated elective treatment of the draining nodal basin with either nodal dissection or adjuvant radiotherapy.[4,9] Although these studies have shown an improvement in relapse-free survival after the elective treatment of the draining lymph nodes, a benefit in overall survival has not been demonstrated.

The purposes of the current study were to describe the natural history of this disease and to analyze the influence of patient, tumor, and treatment-related variables on survival and recurrence.

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Table 1. FREQUENCY, SIZE, AND STAGE AT PRESENTATION OF PRIMARY TUMORS ACCORDING TO LOCATION

Location	Number	Size (median)	Stage			
			I	(IA, IB)	II	III
Extremity	44	2.4	34	(17, 15)	8	2
Head and neck	29	1.0*	25	(17, 6)	4	0
Buttocks	17	4.0*	14	(1, 13)	3	0
Trunk	6	2.5	5	(1, 3)	1	0
Unknown primary	6	—	0	(0, 0)	6	0
Overall	102	2.0	78	(36, 37)	22	2

* $p = 0.0002$ (comparison of means).

PATIENTS AND METHODS

A computer search was performed of the tumor registry and of pathology department records to identify patients who had been treated at Memorial Sloan-Kettering Cancer Center for MCC between 1969 and 1996. This search identified 109 patients treated at Memorial Sloan-Kettering who had the pathologic diagnosis of MCC. Patients who were seen in consultation but who did not receive treatment at Memorial Sloan-Kettering were excluded.

Follow-up information was obtained from chart review and telephone correspondence. Adequate follow-up data were available for 102 of the 109 patients (94%) identified, and these patients form the basis for this study. The majority of these patients (53%) were treated during the last 6 years of the study period, and all but 6 patients (94%) were treated between 1980 and 1996.

Patient and tumor parameters analyzed included patient age and gender, the site and size of the primary tumor, and the stage at initial presentation. Treatment-related variables analyzed included margin status, elective treatment of the draining nodal basin, adjuvant chemotherapy, adjuvant radiotherapy, and the chemotherapeutic treatment of metastatic disease. Patient survival after the first recurrence was also evaluated. Additional parameters analyzed within this subgroup of patients included the disease-free interval, the type of recurrence, and the form of treatment rendered.

Tumors were staged according to their status at initial presentation. A conventional staging system was used in which stage was assigned according to the absence (stage I) or presence (stage II) of positive lymph nodes within the draining nodal basin, or by the presence of systemic metastases (stage III). Stage I patients were then further classified according to tumor size. Stage I patients who had tumors <2 cm in maximal diameter were categorized as stage IA, those with tumors ≥ 2 cm in maximal diameter as stage IB. The width of surgical margin was defined as the narrowest lateral margin as measured by pathology.

The data analyses were conducted to explore the relation between deaths from disease or disease recurrence and the patient, tumor, or treatment-related variables listed above. Parameters influencing survival and relapse were compared using the Kaplan–Meier method, with log-rank comparison.[10,11] Proportional hazards analysis was performed on all variables found significant by univariate analysis.[12] Differences were considered significant at $p \leq 0.05$.

RESULTS

Patient and Tumor Characteristics

There were 57 men (56%) and 45 women (44%) in the study; their ages ranged from 36 to 91 years (median 67 years). Initial treatment was provided to 39 patients at other hospitals before referral to Memorial Sloan-Kettering, whereas 63 patients were initially seen and treated at Memorial Sloan-Kettering. Patients initially seen at other institutions were referred to Memorial Sloan-Kettering for either additional treatment of the primary tumor or treatment of tumor recurrence.

The primary tumor was most commonly located in the skin of the extremities or of the head and neck (Table 1). Another common site of occurrence was the buttocks (17 patients). Six patients had nodal metastases and an unknown primary.

The size of the primary tumor could be determined in 89 cases. The median tumor size was 2 cm (range 0.3 to 14 cm). Tumors of the head and neck, on average, were significantly smaller at presentation than tumors of all other locations (1.6 *vs.* 3.2 cm, $p = 0.008$). Tumor size could be determined in 23 of the patients with tumors of the head and neck: 17 (74%) were <2 cm (stage IA).

At initial presentation, stage I disease was present in 78 patients, stage II disease in 22 patients, and stage III disease in 2 patients (see Table 1). The size of the primary tumor was known in 73 of the 78 stage I patients, and further division into stage IA and IB disease was possible in these cases. The primary tumor was <2 cm in 36 of these patients (stage IA) and ≥ 2 cm in the remaining 37 patients (stage IB).

Treatment of Disease at Presentation

Primary

Wide local excision was performed most often after an initial incisional or excisional biopsy had been performed. Margin status could be determined in 88 patients: the margin was negative in 81 patients and positive in 7 patients. The size of the margin could be determined in 51 cases; it averaged 1.4 cm (range 0.2 to 4 cm). Adjuvant radiotherapy was administered to the tumor bed after excision in 14 cases, with doses ranging from 38 to 61 Gy. Within this group, 2 of the 14 patients had positive margins, 11 patients had negative margins, and in a single case the margin status could not be determined.

Regional Lymph Nodes

Elective treatment of the draining nodal basin was performed in 15 patients with clinical stage I disease. Node dissection was performed in 12 of these patients; in 2 patients (17%), positive nodes were discovered. Elective radiotherapy was administered to the draining nodal basin in three patients, with two patients receiving treatment to cervical nodes and a single patient receiving treatment to inguinal lymph nodes.

Stage II disease was present in 22 patients at initial presentation. Treatment for the lymph node metastases in these patients consisted of therapeutic node dissections in 19 patients and excisional biopsy in 3 patients. Adjuvant radiotherapy was delivered to the nodal basin after complete lymph node dissection in three patients.

Treatment of Distant Disease

Adjuvant chemotherapy was administered in 25 patients. Twelve patients received adjuvant chemotherapy after the initial treatment of their disease, and 13 after tumor recurrence. Within the group of patients who received adjuvant chemotherapy after initial tumor treatment, five had stage I disease and seven had stage II disease. Chemotherapy most commonly consisted of regimens employing carboplatin and etoposide; however, cyclophosphamide-, doxorubicin-, and vincristine-based regimens were also used in several patients.

Chemotherapy was used in the treatment of 21 of 26 patients with unresectable distant metastases. In 16 of these patients, the response to chemotherapy could be determined: 12 patients had no measurable response, 2 had transient minor responses, and 2 had complete responses. The latter 2 patients were both free of disease at 2 and 29 months of follow-up.

Survival

The overall 5-year disease-specific survival rate was 76% (Fig. 1). At the time of last follow-up, 62 patients were free of disease, 24 patients were dead of disease, 9 were alive with disease, and 7 had died of other causes.

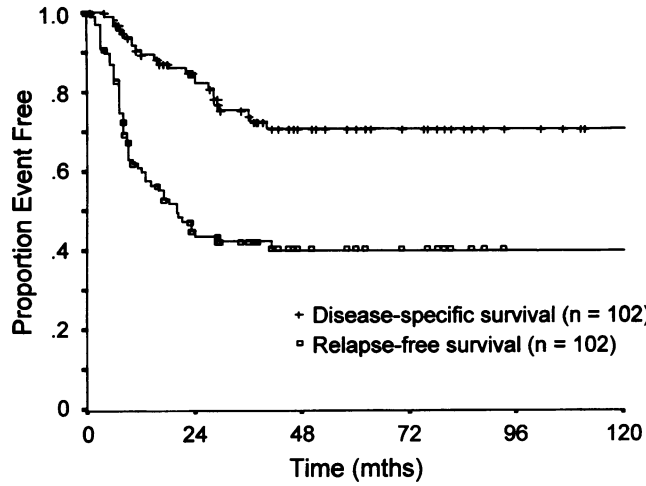


Figure 1. Ten-year survival curves of patients with Merkel cell carcinoma evaluating disease-specific and relapse-free survival for all patients.

The median time of follow-up on all patients was 35 months (mean 47 months). The median follow-up for patients free of disease at last follow-up was 47 months; follow-up exceeded 5 years in 27 of these patients. The median follow-up for patients who died of disease was 18 months.

Table 2 presents the univariate survival analysis of selected patient, tumor, and treatment-related variables and their influence on disease-specific survival. Univariate analysis predicted improved survival when the primary tumor was located in the head and neck ($p = 0.01$), when it was <2 cm ($p = 0.03$), or when it was removed with a negative margin ($p = 0.04$). By univariate analysis, patients who received adjuvant chemotherapy were more likely to die of disease than patients who did not receive chemotherapy. These variables, however, were not predictive of survival when analyzed by multivariate analysis. The only independent predictor of survival for all patients in this study was the stage of disease at presentation ($p < 0.0001$ log-rank, $p = 0.03$ Cox).

When multivariate analysis was performed and stratified by stage, the only independent predictor of survival in patients with stage I disease was the size of the primary tumor ($p = 0.04$). Size was not predictive of survival in patients with stage II or III disease. If size was removed from the analysis and incorporated into the staging system (IA, IB), then stage became a highly significant predictor of survival ($p = 0.008$, Fig. 2).

Recurrence

Location and Treatment

The most common site of recurrence was the regional lymph nodes (Table 3). This site was affected in 40 of 55 patients (73%) who had recurrence and accounted for 35

Table 2. FACTORS INFLUENCING RECURRENCE AND SURVIVAL IN PATIENTS WITH MERKEL CELL CARCINOMA

Factor	Number of Patients	Relapse-Free Survival		Disease-Specific Survival	
		Median Survival*	p value†	Median Survival*	p value†
Age					
<60 years	30	21		NR‡	
≥60 years	72	20	0.83	NR	0.26
Gender					
Male	57	17		NR	
Female	45	24	0.38	NR	0.88
Location					
Head/neck	29	NR		NR	
All other	73	20	0.24	NR	0.01
Size					
<2 cm	40	NR		NR	
≥2 cm	49	18	0.40	NR	0.03
Stage					
IA	36	NR		NR	
IB	37	17		NR	
II	22	20		NR	
III	2	—	0.65	4	<0.0001
Margin					
Negative	81	20		NR	
Positive	7	8	0.74	NR	0.04
ELND					
Yes	10	NR		NR	
No	68	13	0.005	NR	0.08
Adjuvant chemotherapy					
Yes	12	10		36	
No	88	23	0.20	NR	0.001

* Median survival in months.
† p value calculated by log–rank test.
‡ ELND = elective lymph node dissection; NR = not reached.

first recurrences (64%). Regional lymph node metastases were the most common site of recurrence in both stage I and stage II disease. Nodal recurrence within previously dissected nodal basins occurred in seven patients who had undergone therapeutic nodal dissection for stage II disease at presentation, and a single patient who had undergone a negative elective node dissection for stage I disease.

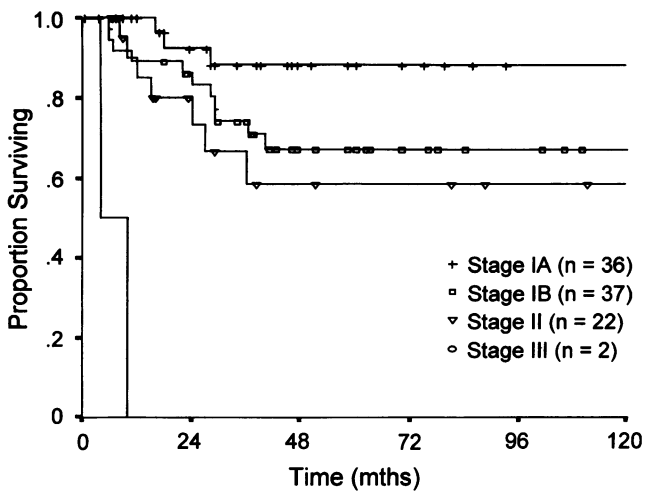


Figure 2. Ten-year survival curves evaluating disease-specific survival in patients with stage IA, stage IB, stage II, and stage III disease (p = 0.008, log-rank).

The median time to recurrence was 8 months. The median time to recurrence was 8 months for patients with nodal recurrence, 6 months for patients with local recurrence, and 9 months for patients whose initial recurrence was at distant sites. Only two patients had recurrence of disease after 24 months of follow-up.

Local recurrence was the site of first recurrence in eight cases, and an additional four patients developed local recurrence at some point during the course of their disease.

Adjuvant radiotherapy was delivered to the bed of the tumor in 15 patients. This treatment was not associated with a decrease in local recurrence. Local recurrence developed in 2 of 15 patients (13%) who received radiotherapy and in 10 of 87 patients (11%) who did not receive radiotherapy (p = 0.84). A negative surgical margin was also not predictive of local recurrence by statistical analysis. Local recurrence occurred in 2 of the 7 patients (29%) with known

Table 3. TYPE OF RECURRENCE LISTED ACCORDING TO THE TIME OF RECURRENCE AND STAGE

	Lymph Node		Locoregional		Distant	
Stage	**First**	**Other**	**First**	**Other**	**First**	**Other**
I	27	4	8	3	6	12
IA	13	1	3	2	0	6
IB	14	2	3	1	6	6
II	8	1	0	1	6	2

First = first recurrence; other = any recurrence after first recurrence.

positive margins and in 9 of 71 patients (13%) with negative margins (p = 0.19). Follow-up for the remaining five patients with positive margins was short, however: two of these patients died of distant disease within 8 months of diagnosis.

Distant metastases accounted for the first site of recurrence in 12 patients, and at some point during the course of disease an additional 14 patients developed distant metastases. The most common location for these metastases was distant nodal basins (13 patients). Other locations included distant cutaneous sites (n = 4), pancreas (n = 4), liver (n = 2), lung (n = 1), ovary (n = 1), and tongue (n = 1).

Relapse-Free Survival

The overall recurrence rate was 54% (see Fig. 1). Recurrence of disease occurred in 16 of 23 patients (44%) with stage IA disease, 23 of 37 patients (62%) with stage IB disease, and 14 of 22 patients (64%) with stage II disease. Comparisons between relapse-free survival and disease-specific survival, as stratified by stage, are illustrated in Figure 3.

Table 2 presents the survival analysis of selected patient, tumor, and treatment-related variables and their association with disease recurrence. The only factor to be associated with a significantly improved relapse-free survival rate was elective lymph node dissection (ELND; stage I patients only). Stage I patients who underwent ELND had an improved relapse-free survival rate (p = 0.005) that was significant by both univariate (p = 0.005) and multivariate (p = 0.04) analysis. ELND, however, was not associated with an improved overall survival (p = 0.08). Adjuvant radiotherapy to the draining nodal basin was given to three patients, and one of these patients suffered disease recurrence within the radiated nodes.

Survival After Recurrence

The overall survival rate for the 55 patients with recurrence was 62%, and at last follow-up, 21 of these patients had died of disease, 22 were free from disease, 9 were alive with disease, and 3 had died of other causes. The median follow-up after recurrence was 16 months (mean 31 months). The median follow-up after recurrence for patients who did not die of disease was 23 months.

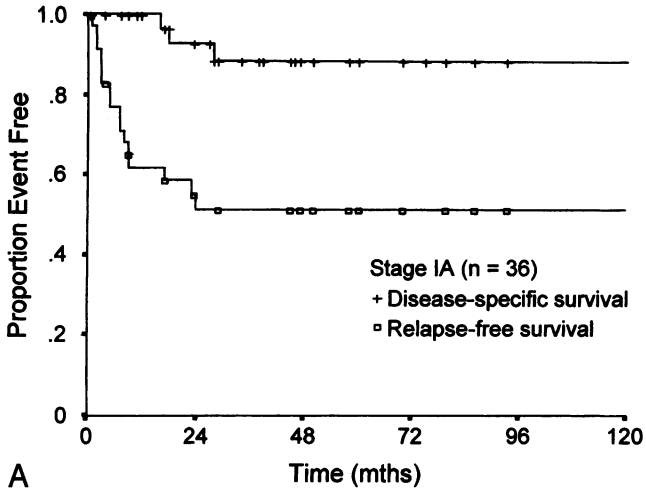
Table 4 presents the survival analysis (log-rank comparison) of selected patient, tumor, and treatment-related variables and their influence on disease-specific survival after first recurrence. Patients who had initially had tumors of the head and neck were found to have improved survival by univariate analysis. Patients who had recurrence ≥8 months after treatment of the primary tumor or patients with lymph node metastases *versus* locoregional or distant metastases (p = 0.001, log-rank, Fig. 4) were also found to have significantly improved disease-specific survival after recurrence.

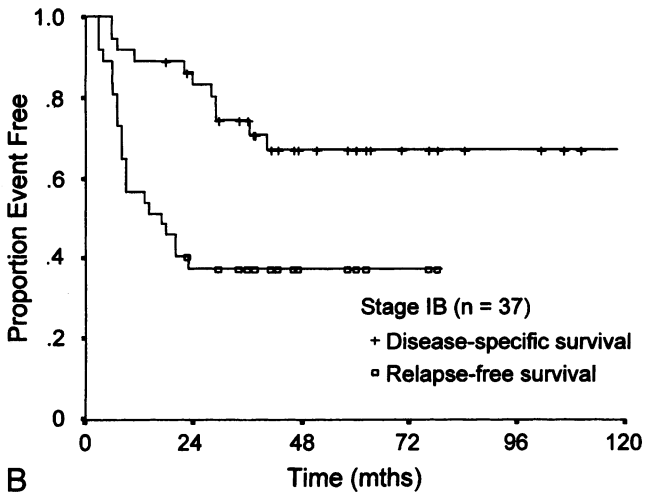
Once distant metastasis occurred, the median time to death was 5 months. At last follow-up, 19 patients were dead of disease, 6 were alive with disease, and 1 was alive without evidence of disease. Within the group of 19 patients who died of disease, 14 received chemotherapy and 5 did not. The average time to death was 7.5 months in patients who received chemotherapy and 3.7 months in patients who did not (p = 0.18).

If patients could be rendered disease-free after recurrence, however, they experienced improved survival (p = 0.01, log-rank). Two patients who had distant metastases as their first recurrence could be rendered disease-free by surgical excision. One of these patients had undergone resection of a distant nodal recurrence and was alive at 32 months of follow-up, and the other died of disease 24 months after surgical excision of a solitary ovarian metastasis.

DISCUSSION

In this study, the overall disease-specific survival for patients with MCC was 76%. For all patients, the only independent predictor of survival was the stage of disease at presentation. In the subgroup of patients with stage I dis-





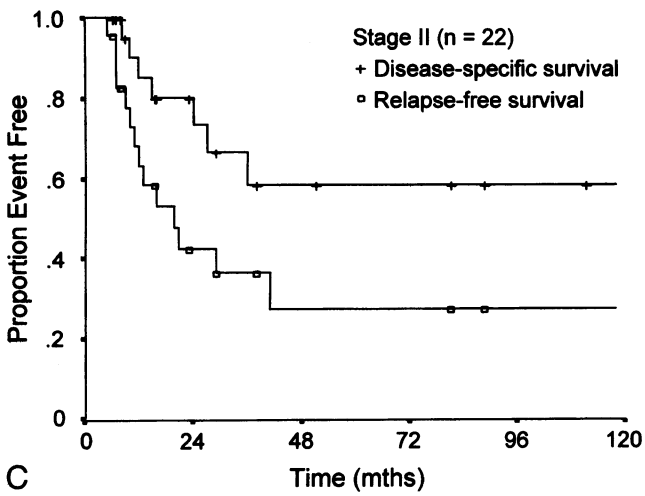


Figure 3. Ten-year survival curves evaluating disease-specific and relapse-free survival in patients with stage IA (A), stage IB (B), and stage II (C) disease.

ease, the size of the primary tumor was also independently predictive of survival. Recurrence of disease occurred in the majority of patients (55 of 100 stage I and II patients). Metastases to the draining lymph nodes accounted for the majority of recurrences, with 35 of 55 (64%) first recurrences occurring in this location. Within the group of patients with recurrence, the overall disease-specific survival rate was 62%. Predictors of survival after recurrence included the type of recurrence, the disease-free interval between the treatment of the primary and recurrence, and whether the patient could be rendered disease-free after recurrence.

The overall survival witnessed in this study confirms earlier reports that the majority of patients with MCC will survive.[2,4] The majority of our patients had stage I disease (76%); the overall survival rate was 81% for these patients. Once distant disease developed, however, almost all patients had a rapid progression of disease and death: the median survival after the development of distant metastases was 5 months. There was only a single death from disease

Table 4. FACTORS INFLUENCING SURVIVAL AFTER RECURRENCE OF MERKEL CELL CARCINOMA

Factor	Number of Patients	Survival After Recurrence: Median Survival*	Survival After Recurrence: p value†
Age			
<60 years	16	21	
≥60 years	39	NR‡	0.24
Gender			
Male	33	34	
Female	22	NR	0.94
Location of primary			
Head/neck	13	NR	
All other	42	20	0.03
Size of primary			
<2 cm	17	NR	
≥2 cm	28	21	0.20
Stage at presentation			
IA	16	NR	
IB	23	34	
II	14	16	
III	—	—	0.16
Disease-free interval			
<8 months	26	21	
≥8 months	29	NR	0.04
Type of recurrence			
Local	8	20	
Regional LN	35	NR	
Distant	12	14	0.001
Rendered disease-free			
Yes	42	NR	
No	13	14	0.01
Adjuvant chemotherapy			
Yes	13	NR	
No	30	NR	0.72

* Median survival in months.
† p value calculated by log-rank test.
‡ NR = not reached.

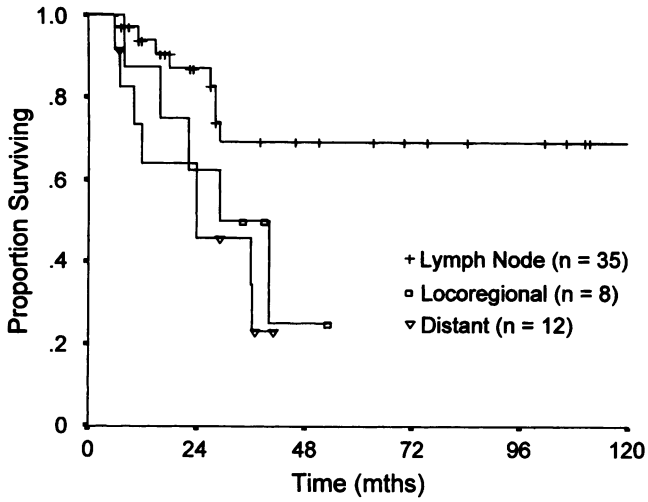


Figure 4. Ten-year survival curves evaluating disease-specific survival after recurrence in patients with regional nodal recurrence, locoregional recurrence, and distant recurrence (p = 0.001, log-rank).

after 3 years of follow-up, however, and this occurred 41 months after the initial diagnosis.

Although previously reported as predictors of survival, patient gender and location of the primary tumor were not independent predictors of survival in our analysis.[6,7] In this study, patients with tumors of the head and neck had significantly smaller lesions than patients with tumors at other locations (p = 0.008). Because of the significance of size in overall survival, these patients most likely have an improved survival rate secondary to the small size of their tumors rather than a difference in behavior because of location alone.

The size of the primary tumor was an independent predictor of survival for stage I patients. Patients with stage I disease who had tumors ≥2 cm in diameter had a survival rate similar to that of patients with stage II disease (p = 0.48). The traditional staging system for MCC does not incorporate size as a criterion. Patients with localized disease have been classified as stage I, those with node-positive disease as stage II, and those with distant disease as stage III. Because of the importance of size in the prognosis of stage I patients, we propose that size should be incorporated into the staging system as noted above. This system further divides stage I patients into those with IA (<2 cm in maximal diameter) and IB (≥2 cm in diameter) disease.

The most common site for recurrence was within the draining lymph nodes, with 35 of 55 first recurrences occurring in this location. This site was the most common site of recurrence even in stage II patients who had previously undergone therapeutic node dissection. The tendency for nodal metastases to occur before distant metastases has been observed in several studies and has led to the conclusion that Merkel cell tumors might spread in an orderly fashion from the site of the primary first to draining lymph nodes and then to distant locations.[5,7] Although our study confirms the high incidence of nodal metastasis, 12 of 55 patients (22%) with recurrence had distant recurrence as their first site of detectable recurrence; this challenges the theory of an orderly "cascade" pattern of spread. The site of distant metastasis was also highly variable. Remote nodal basins were the most common site of recurrence; however, other sites, including the pancreas, liver, tongue, and ovary, were observed.

The treatment of the draining nodal basin in patients with clinically negative lymph nodes remains controversial. Both surgical dissection and adjuvant radiotherapy to the draining nodal basin have been advocated.[9,13,14] In this study, ELND was an independent predictor of relapse-free survival. In addition, none of our patients who had undergone ELND died of disease. Because of the limited number of patients in this group, as well as the overall good prognosis of stage I patients, this did not correlate with an overall survival advantage. The group of stage I patients who underwent ELND, however, did not all have favorable-sized tumors: five patients had stage IB lesions.

An aggressive approach toward the treatment of clinically negative lymph nodes would seem reasonable for two reasons. First, in this study 40% of patients developed regional nodal recurrence at some point during the course of their disease, and patients who had undergone ELND had a significant improvement in relapse-free survival and excellent overall survival. Second, the presence of nodal disease was found to be a strong predictor of survival and therefore may identify patients who would be most suitable for current protocols evaluating the benefits of adjuvant therapies. Lymphatic mapping, as used at present in the treatment of patients with clinically localized melanoma, has recently been described in the treatment of MCC. This form of nodal investigation may be a reasonable alternative to routine ELND in patients with clinically localized Merkel cell tumors; it is under clinical investigation.[15,16]

The optimal form and extent of treatment for the primary tumor also remain controversial. The size of margin required to reduce the incidence of local recurrence has been reported to be as large as 3 cm. Analysis of the size of surgical margin in this study did not reveal any specific size of margin to be associated with a decrease in local recurrence. Local recurrence, however, was uncommon in this study: only 8 of 55 patients had local recurrence as their first recurrence. However, a negative surgical margin should be obtained whenever possible. Several studies have argued that adjuvant locoregional radiotherapy is also required to reduce the incidence of local recurrence.[17,18] We were unable to demonstrate the value of adjuvant radiotherapy in this series secondary to the low incidence of local recurrence and the infrequent use of adjuvant radiotherapy.

Survival after the first recurrence of disease was associated with three factors: the disease-free interval between treatment of the primary and the time of first recurrence, the type of first recurrence, and the ability to render the patient disease-free after recurrence. Patients who had nodal recurrence as their first type of failure had a disease-specific survival rate after recurrence that was significantly better than that of patients with local or distant failure. At last follow-up, 8 of the 35 patients (23%) who had nodal recurrence as their first recurrence had died of disease, compared with 12 of 20 patients (60%) who had either local or distant failure. The treatment of patients with locoregional and distant metastases was also predictive of survival. Patients who could be rendered free of disease by surgical excision had a better survival rate than patients who could only undergo palliative treatment. Because of this, attempts should be made to resect isolated metastases whenever complete resection is possible.

The role of chemotherapy in the treatment of MCC, both in the adjuvant setting and in the treatment of metastatic disease, remains controversial.[19,20] Some have advocated the use of adjuvant chemotherapy in the treatment of patients at high risk for recurrence, although there are no data to support this in routine clinical practice. The majority of studies have evaluated the use of chemotherapy in patients with advanced disease.[21–23] Most of the agents selected for the treatment of MCC have been ones used in the treatment of small-cell lung carcinoma, and most recently carboplatin and etoposide have shown the most promising results.[24]

Our data have not shown a benefit in the use of chemotherapy in the adjuvant setting. Patients who received adjuvant chemotherapy, both after the initial treatment of disease and after disease recurrence, did not show an improvement in either relapse-free or disease-specific survival. The most common regimen used was carboplatin and etoposide, but a wide range of other agents were used. Further investigation into the benefits of chemotherapy will require standardization of treatment regimens and prospective evaluation.

Once distant disease occurred, patients did poorly whether or not they received chemotherapy. The average length of survival in patients after the development of distant disease was 3.7 months for the 5 patients who did not receive chemotherapy and 7.5 months for the 14 patients who did. In two patients, however, a complete response was achieved; these two patients were alive at 2 and 29 months of follow-up. These results are similar to other reports describing the chemotherapeutic treatment of advanced MCC.[22,23,25,26]

In summary, the overall prognosis for patients with MCC is favorable, and even after recurrence the majority of patients may have long-term survival. Almost all patients who have recurrence of disease will do so within the first 2 years after initial treatment. The prognosis for patients with this disease depends on the stage at presentation, and incorporating tumor size into the staging system more accurately predicts survival for patients with stage I disease. Elective nodal evaluation should be considered in stage I patients: none of these patients in this study went on to die of disease, and an improvement in relapse-free survival in this group was observed. Resection of nodal recurrence, and other recurrence when localized, did improve survival after recurrence and should be considered even when distant recurrence develops. The role of adjuvant chemotherapy remains undetermined; the systemic treatment of established metastatic disease may produce a response in a minority of patients.

References

1. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972; 105:107–110.
2. Tang CK, Toker C. Trabecular carcinoma of the skin: an ultrastructural study. Cancer 1978; 42:2311–2321.
3. Pitale M, Sessions RB, Husain S. An analysis of prognostic factors in cutaneous neuroendocrine carcinoma. Laryngoscope 1992; 102:244–249.
4. Raaf JH, Urmacher C, Knapper WK, et al. Trabecular (Merkel cell) carcinoma of the skin. Cancer 1986; 57:178–182.
5. Yiengpruksawan A, Coit DG, Thaler TT, et al. Merkel cell carcinoma: prognosis and management. Arch Surg 1991; 126: 1514–1519.
6. Smith DE, Bielamowicz S, Kagan AR, et al. Cutaneous neuroendocrine (Merkel cell) carcinoma: a report of 35 cases. Am J Clin Oncol 1995; 18:199–203.
7. Shaw J, Rumball E. Merkel cell tumour: clinical behaviour and treatment. Br J Surg 1991; 78:138–142.
8. Gould V, Moll R, Moll I, et al. Biology of disease: neuroendocrine (Merkel) cells of the skin: hyperplasias, dysplasias, and neoplasms. Lab Invest 1985; 52:334–353.
9. Meeuwissen JA, Bourne RG, Kearsley JH. The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. Int J Radiat Oncol Biol Phys 1995; 31:325–331.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–457.
11. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977; 35:1–39.
12. Cox DR. Regression models and life tables (with discussion). J R Stat Soc 1972; B34:187–187.
13. Pilotti S, Rilke F, Bartoli C, Grisotti A. Clinicopathologic correlations of cutaneous neuroendocrine Merkel cell carcinoma. J Clin Oncol 1988; 6:1863–1873.
14. Hitchcock CL, Bland KI, Lahey RG, et al. Neuroendocrine (Merkel cell) carcinoma of the skin: its natural history, diagnosis, and treatment. Ann Surg 1988; 207:201–207.
15. Choe W, Housini I, Mello AM. Lymphoscintigraphy in a case of Merkel cell tumor. Clin Nuclear Med 1995; 20:922–924.
16. Messina JL, Reintgen DS, Cruse CW, et al. Selective lymphadenectomy in patients with Merkel cell (cutaneous neuroendocrine) carcinoma. Ann Surg Oncol 1997; 4:389–395.
17. Shack RB, Barton RM, DeLozier J, et al. Is aggressive surgical management justified in the treatment of Merkel cell carcinoma? Plast Reconstr Surg 1994; 94:970–975.
18. Boyle F, Pendlebury S, Bell D. Further insights into the natural history and management of primary cutaneous neuroendocrine

(Merkel cell) carcinoma. Int J Radiat Oncol Biol Phys 1995; 31:315–323.
19. Ratner D, Nelson BR, Brown MD, Johnson TM. Merkel cell carcinoma. J Am Acad Dermatol 1993; 29:143–156.
20. Wynne CJ, Kearsley JH. Merkel cell tumor: a chemosensitive skin cancer. Cancer 1988; 62:28–31.
21. Feun LG, Savaraj N, Legha SS, et al. Chemotherapy for metastatic Merkel cell carcinoma: review of the M.D. Anderson Hospital's experience. Cancer 1988; 62:683–685.
22. Azagury M, Chevallier B, Atlan D, et al. VP-16, cisplatin, doxorubicin, and bleomycin in metastatic Merkel cell carcinoma. Am J Clin Oncol 1993; 16:102–104.
23. Crown J, Lipzstein R, Cohen S, et al. Chemotherapy of metastatic Merkel cell cancer. Cancer Invest 1991; 9:129–132.
24. Pectasides D, Moutzourides G, Dimitriadis M, et al. Chemotherapy for Merkel cell carcinoma with carboplatin and etoposide. Am J Clin Oncol 1995; 18:418–420.
25. Sharma D, Flora G, Grunberg SM. Chemotherapy of metastatic Merkel cell carcinoma: case report and review of the literature. Am J Clin Oncol 1991; 14:166–169.
26. Tennvall J, Bioklund A, Johansson L, Ackerman M. Merkel cell carcinoma: management of primary, recurrent and metastatic disease. Eur J Surg Oncol 1989; 15:1–9.