STUDY

Adjuvant Local Irradiation for Merkel Cell Carcinoma

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Objectives: To determine the effect of adjuvant local irradiation on (1) disease recurrence and (2) survival rates in Merkel cell carcinoma (MCC).

Data Sources: An Ovid MEDLINE search (January 1966–May 26, 2004) was performed using the following criteria: group 1, "Merkel cell OR trabecular OR neuroendocrine skin OR APUDoma skin OR primary small cell skin OR primary undifferentiated skin OR endocrine skin OR neuroepithelial" AND group 2, "carcinoma OR tumor OR cancer" with mapping modifiers "-title, -abstract, -keyword, -subject heading." The search yielded 843 citations.

Study Selection: The Ovid set was then searched using the following criteria: "surgery OR radiation OR radiotherapy," which yielded 242 discrete citations. Reports from all 242 citations were reviewed. For the remaining 601 citations, abstracts (when available) were reviewed to assess the level of relevance for potential inclusion; reports from 63 of these citations were reviewed. An additional 28 secondary references were reviewed, for a total of 333 reports.

Data Extraction: The following criteria for inclusion were applied to each potential patient: (1) a histopathologic diagnosis of MCC; (2) a single, primary tumor arising on the skin, for which (3) the primary treatment was surgical excision (local excision, wide excision, or Mohs surgery) with or without the use of adjuvant irradiation (to the tumor bed); (4) following surgery, negative (clear) surgical margins were obtained; (5) during the postoperative follow-up period, disease recurrence, progression, and survival and/or duration of event-free interval was documented with (6) a minimum follow-up of 1 month. A total of 1254 patients were included in the analysis.

Results: Statistically significant reductions in local (hazard ratio [HR], 0.27; $P<.001$) and regional (HR, 0.34; $P<.001$) recurrence were observed among patients treated with combination therapy compared with surgery alone. Similar rates of distant metastasis were observed between treatment groups (HR, 0.79; $P=.31$). Overall survival rates were 87% (1 year) and 49% (5 years). Cause-specific survival rates were 90% (1 year) and 62% (5 year). In general, differences in overall (HR, 0.78; $P=.16$) and cause-specific (due to MCC: HR, 0.72; $P=.14$) survival rates between treatment groups did not reach statistical significance. A subgroup analysis that excluded single-patient case reports and studies of only 1 treatment group revealed a significant overall (HR, 0.63; $P=.02$) and cause-specific (HR, 0.62; $P=.04$) survival advantage after treatment with combination therapy.

Conclusions: Surgery plus local adjuvant irradiation was associated with significantly lower rates of local and regional recurrence of MCC than surgery alone. Prospective investigation is needed to clarify the presence of a survival benefit from combination therapy.

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MERKEL CELL CARCINOMA (MCC) is an aggressive and often fatal cutaneous neoplasm. The 5-year overall survival rate has been estimated at 45% despite treatment.[1] Although the case fatality rate is striking, the incidence of MCC in the United States is low, estimated at 0.24 tumors per 100 000 person-years compared with melanoma (17.0 per 100 000 person-years), a 70-fold difference.[1,2] Merkel cell carcinoma shares with melanoma the strong propensity to recur locally, spread regionally to the lymph node basin, and disseminate widely, leading to a fatal outcome. Unlike melanoma, there is evidence that Merkel tumor cells may be highly radiosensitive. In vitro MCC tumor cell lines demonstrate a substantially lower surviving fraction (mean, 0.30) following exposure to 2 Gy (200 rad) of radiation than melanoma cell lines (0.57).[3] Several clinical studies have also suggested that the risk of local recurrence and regional (nodal) metastasis may be significantly lower in patients who undergo adjuvant radiotherapy following surgery,[4-7] although these findings have not been consistently replicated.[8]

See also pages 685 and 771

The purpose of the present investigation was to perform a comprehensive review of the literature and to assess the efficacy of adjuvant irradiation for treating MCC. Emphasis was placed on examining

the effect of local (to the tumor bed) irradiation on rate of recurrence, metastasis, and survival. Results of this investigation may have immediate and direct clinical application and can be used in the design of a randomized clinical trial to delineate more precisely the role of adjuvant irradiation in the treatment of MCC.

METHODS

An Ovid MEDLINE search (January 1966–May 26, 2004) was performed to identify reports germane to the treatment of MCC with surgery or combination surgery plus radiation therapy using the following: group 1, "Merkel cell OR trabecular OR neuroendocrine skin OR APUDoma skin OR primary small cell skin OR primary undifferentiated skin OR endocrine skin OR neuroepithelial" AND group 2, "carcinoma OR tumor OR cancer," with mapping modifiers "-title, -abstract, -keyword, -subject heading." This search yielded 843 citations. As a sensitivity analysis, a PubMed MEDLINE search for "Merkel cell carcinoma" alone yielded 807 citations, all of which were contained in the Ovid search results. The Ovid set was then searched using the following criteria: "surgery OR radiation OR radiotherapy," which yielded 242 discrete citations. Reports from all 242 citations were reviewed. For the remaining 601 citations, abstracts (when available) were reviewed to assess the level of relevance for potential inclusion; reports from 63 of these citations were reviewed. The reference lists from all 305 reports were reviewed; reports from an additional 28 secondary references were reviewed as a result of this search strategy.

Three experts in MCC were consulted for input, although no additional reports were reviewed as a result of this search technique. Reports written in English were reviewed in their entirety. Reports in all other languages were examined for the presence of an abstract written in English and/or data presented in tabular form. Three reports written in non-English languages appearing to contain highly relevant data were translated into English. The remaining reports written in a non-English language that lacked an abstract translated into English and numerical data presented in tabular form were excluded. Reports that contained previously published data were also excluded unless the previously unpublished data could be isolated.

All study types (case reports, case series, and retrospective reviews), regardless of sample size, were reviewed. The following criteria for inclusion were applied to each potential patient: (1) a histopathologic diagnosis of MCC; (2) a single, primary tumor arising on the skin, for which (3) the primary treatment was surgical excision (local excision, wide excision, or Mohs surgery) with or without the use of adjuvant irradiation (to the tumor bed); (4) following surgery, negative (clear) surgical margins were obtained; (5) during the postoperative follow-up period, disease recurrence, progression, and survival and/or duration of event-free interval was documented with (6) a minimum follow-up of 1 month.

The following system was used to standardize the staging of patients: stage I, localized primary tumor of any size without clinical evidence of in-transit metastasis, regional lymph node involvement, or distant metastasis; stage II, clinical evidence of regional lymphadenopathy without evidence of distant metastasis (in-transit metastases, ie, nonadjacent to the primary lesion and the draining lymph node basin, were also included under the stage II rubric); and stage III, clinical or radiographic evidence of disease distant to the regional lymphatic basin.

Reports included in the analysis were further categorized by the format in which data were presented: studies reporting longitudinal data for individual patients including time-to-event intervals and duration of follow-up (individual-level studies) vs studies reporting only aggregate data for the cohort that were presented in a pooled or summary format (aggregate-level studies). No information regarding time-to-event intervals or potential effect modifiers was consistently available from aggregate-level studies. Data on study type ("comparative," referring to studies in which both treatment groups were represented, vs "noncomparative," in which only 1 treatment group was represented), sample size, patient characteristics (age and sex), clinical stage at presentation, anatomic location of primary tumor, primary treatment, recurrence (local and/or regional), distant metastasis, time-to-event intervals, survival time, duration of follow-up, cause of death, year of publication, and geographic location of the corresponding author were abstracted. Local recurrence was defined as tumor recurring within or adjacent to a scar. Discontiguous or nonadjacent recurrences were defined as in-transit metastases and were not included in the analysis of local recurrence. Patients who presented with stage I disease and later developed an in-transit metastasis were coded as having a regional recurrence and were upstaged from I to II. Metastasis to a lymph node and in-transit metastases were both classified as stage II disease and included in the analysis of regional recurrence. No attempt was made to quantify the distance from the primary surgical site of an in-transit metastasis.

Of the 333 reports reviewed, 132 met the inclusion criteria (references available on request). The remaining 201 reports were excluded for the following reasons: (1) not a treatment study (n=143); (2) non-English language publication without tabular data (n=27); (3) insufficient documentation (n=23); and (4) failure to meet other inclusion criteria (n=8). Of the 132 eligible studies, 116 reported individual-level data and 16 reported aggregate-level data. Although 1376 patients were described in these studies, 122 were excluded from the analysis for the following reasons: (1) did not have a primary cutaneous MCC (n=5); (2) were not treated with surgery or surgery plus irradiation (n=68); (3) presence of documented evidence of positive surgical margins (n=35); and (4) data were previously published (n=14). Greater latitude was required for including patients from aggregate-level studies with respect to recurrent (n=137) or unknown primary (n=21) tumors, and these patients were included as long as adequate staging information was provided. A small number of cases failed to achieve negative surgical margins (n=14) but could not be individually excluded from the cohort.

Results are based on the remaining 1254 patients from 116 individual-level (n=669) and 16 aggregate-level (n=585) studies. Of the 132 studies included in the primary end-point analysis, 38 (29%) were case reports of single patients. Of the 1254 patients included in the data set, 38 (3%) were extracted from case reports of single patients.

The χ^2 test, Wilcoxon rank sum test, and 2-sample *t* test were used to identify potential sources of heterogeneity in the patient characteristics between the 2 treatment groups within individual-level studies and between the individual-level and aggregate-level studies. Survivorship methods, which take into account the timing of the outcome event (disease recurrence, metastasis, and death) and the duration of follow-up, while censoring loss to follow-up and death, were applied to the set of pooled individual-level data.

For each outcome event, survivorship estimates were generated using the Kaplan-Meier method. Associations between type of treatment and each outcome were assessed using Cox proportional hazards models. The associations were summarized by calculating hazard ratios (HRs) and 95% confidence intervals (CIs). For analysis of overall survival, the end point was death due to any cause; all other patients were censored at the date of their last follow-up. For analysis of cause-specific survival, death due to MCC was the end point; all other patients, including those with unrelated deaths, were censored.

Analysis of regional recurrence, distant metastasis, and survival were restricted to patients with stage I disease in whom the effect of local treatment respecting these outcomes would most accurately be assessed. Duration of follow-up was calculated from the date of the diagnosis to either the outcome of interest or the date of last follow-up.

For each outcome tested, a small proportion of patients had a documented event but an unknown time-to-event. This subgroup of patients was excluded from the primary time-to-event analysis. A secondary analysis was also performed in which duration of follow-up or survival was imputed as the time-to-event for these patients. Without exception, results were similar for both statistical runs. Post hoc power calculations were performed for the association between treatment and distant metastasis-free, overall, and cause-specific survival using a 2-sided log rank test. The sample size required to increase the power of the observed HR to 80% is reported. Additional calculations were performed to assess study power at hypothetical HRs (results not shown).

Potential sources of confounding were investigated by separately adjusting the models for age, sex, tumor size, tumor location, stage at presentation, geographic location, study type, and year of publication and then comparing the HR for treatment group between the unadjusted and adjusted models (adjusted models not shown). To determine whether a factor was associated with a significant independent effect, its HR was calculated in a model that also included treatment group. The presence of effect modifiers was evaluated in 2 ways: (1) separate models for each level of a factor were run, and the HRs obtained from each were compared; (2) to assess for interaction effects, models that included terms for a treatment group, a factor, and the interaction between the treatment group and the factor were fit (results not shown).

Aggregate-level studies did not consistently provide adequate information to determine Kaplan-Meier rates or HRs. Survivorship estimates were calculated as the proportion of patients with an event, ignoring the timing of events and follow-up. The associations between treatment group and each outcome were summarized by calculating odds ratios (ORs) and 95% CIs.

All calculated *P* values were 2-sided, and *P* values less than .05 were considered statistically significant. Statistical analyses were performed using the SAS software package, version 8.2 (SAS Institute, Cary, NC).

RESULTS

A total of 1254 patients met the criteria for inclusion, 669 (53%) of whom were described by 116 individual-level studies (**Table 1**). Of these, more than twice as many patients were treated with surgery alone (n=465; 70%) as with combination therapy. Patients treated with surgery alone were significantly older (mean age, 71.2 years; range, 23-96 years) than those treated with combination therapy (mean age, 68.0 years; range, 27-93 years) ($P=.003$). Stage I disease was more commonly treated with surgery alone, whereas more advanced disease tended to be treated with combination therapy ($P<.001$). There was no association between anatomic location of the primary tumor or tumor size ($\leq$2 vs $>$2 cm) and treatment group.

In the United States, a significantly higher proportion of patients were treated with surgery alone (74%) than in Europe (63%) ($P=.01$), where combination therapy was used more frequently. The proportion of published cases of MCC treated with surgery alone has decreased significantly over time (from $>$90% in the 1970s to 58% in the 2000-2004 period) ($P<.001$) compared with combination therapy.

The remaining 585 (47%) of 1254 patients were described in 16 aggregate-level studies (Table 1). The average age at the time of diagnosis based on reported study means was 69 years (age range, 24-97 years). A large majority of patients presented with stage I disease (78%) compared with stage II (19%) and stage III (2%) disease. More than half of primary lesions occurred on the head and neck (53%). Among reported cases, lesions measuring 2 cm or smaller were nearly twice as numerous as those larger than 2 cm. The average lesion size based on reported study means was 2.2 cm (range, 0.2-20.0 cm). More than twice as many patients were treated with surgery alone (n=482) as with combination therapy (n=179).

The average duration of follow-up was 28.2 months (range of study means, 6-89 months). A large majority of patients were described in aggregate-level studies conducted by investigators in the United States (76%), with smaller proportions being described by European (13%) and Australian (11%) investigators, although this proportion excludes reports written in non-English languages.

LOCAL RECURRENCE

Of the 669 patients described by individual-level studies, 183 (27%) had a documented local recurrence, of which most (84%) occurred within 12 months of the initial treatment. The median time to recurrence was 5 months (range, 1-96 months).

Patients treated with combination therapy were significantly less likely to develop a local recurrence (HR, 0.27; $P<.001$); that is, patients treated with surgery alone were 3.7 times more likely to develop a local recurrence than patients who received combination therapy. The proportions of patients free of local recurrence (recurrence-free survival) were 71% (1 year) and 61% (5 year) after surgery compared with 90% (1 year) and 88% (5 year) after combination therapy (**Table 2** and **Figure**, A). No sources of confounding or effect modifiers were identified. However, the effect of combination treatment was stronger among patients with small lesions ($\leq$2 cm) and local disease (stage I) (**Table 3**).

Of the 585 patients described by aggregate-level studies, 120 (21%) had a documented local recurrence. Patients treated with combination therapy were significantly less likely to develop a local recurrence (OR, 0.33; $P<.001$) (**Table 4**).

REGIONAL RECURRENCES

Of the 669 patients described by individual-level studies, 566 (85%) presented with stage I disease. Of these, 219 (39%) had a documented regional recurrence. The median time to recurrence was 7 months (range, 1-192 months) and most (75%) recurred within 12 months of the initial treatment.

Patients treated with combination therapy were significantly less likely to develop a regional recurrence (HR, 0.34; $P<.001$); that is, patients treated with surgery alone were 2.9 times more likely to develop a regional recurrence than patients treated with combination therapy. The proportions of patients free of regional recurrence

Table 1. Characteristics of Patients Described by Individual-Level and Aggregate-Level Studies*

Characteristic	Individual-Level Studies: Surgery (n = 465)	Individual-Level Studies: Surgery + RT (n = 204)	Individual-Level Studies: *P* Value†	Aggregate-Level Studies‡ (n = 726)	Individual vs Aggregate *P* Value‡
Treatment			NA		.17
Surgery alone	465	NA		482 (66.4)	
Surgery + RT	NA	204		179 (24.7)	
Other	NA	NA	NA	65 (8.9)	
Sex			.62		<.001
Male	223 (48.0)	86 (42.2)		401 (55.2)	
Female	226 (48.6)	95 (46.6)		242 (33.3)	
Unknown	16 (3.4)	23 (11.3)		83 (11.4)	
Age at diagnosis, y			.003		Not calculated‖
Mean (SD)	71.2 (12.8)	68.0 (12.8)		68.6§	
Median	73	70		Not calculated‖	
Range	23-96	27-93		24-97	
Age group					
<60 y	78 (16.8)	37 (18.1)			
60-69 y	86 (18.5)	52 (25.5)			
70-79 y	152 (32.7)	58 (28.4)			
≥80 y	117 (25.2)	31 (15.2)			
Unknown	32 (6.8)	26 (12.7)			
Stage			<.001		.01
I	411 (88.4)	155 (76.0)		567 (78.1)	
II	48 (10.4)	43 (21.1)		135 (18.6)	
III	0	3 (1.5)		11 (1.5)	
Unknown	6 (1.3)	3 (1.5)		13 (1.8)	
Location			.49		.30
Head/neck	240 (51.6)	103 (50.5)		386 (53.2)	
Trunk/buttock	41 (8.8)	11 (5.4)		85 (11.7)	
Upper extremities	82 (17.6)	47 (23.0)		57 (7.8)	
Lower extremities	80 (17.2)	40 (19.6)		75 (10.3)	
Extremity unspecified	0	0		85 (11.7)	
Unknown	22 (4.7)	3 (1.5)		38 (5.2)	
Lesion size			.44		.76
≤2 cm	130 (28.0)	59 (28.9)		275 (37.9)	
>2 cm	86 (18.5)	32 (15.7)		150 (20.7)	
Not reported	249 (53.5)	113 (55.4)		301 (41.4)	
Lesion size, cm			.27		Not calculated‖
Lesions available for analysis, No.	216	91		322	
Mean (SD)	2.5 (2.1)	2.2 (1.9)		2.2†	
Median	2.0	1.6		–	
Range	0.3-15.0	0.3-15.0		0.2-20.0	
Geographic location			.02		<.001
United States	213 (45.8)	73 (35.8)		554 (76.3)	
Europe	166 (35.7)	96 (47.1)		92 (12.7)	
Australia	41 (8.8)	19 (9.3)		80 (11.0)	
Asia	12 (2.6)	5 (2.4)		0	
South America	2 (0.4)	2 (1.0)		0	
Multinational	6 (1.3)	1 (0.5)		0	
North America (not United States)	25 (5.4)	8 (3.9)		0	
Year of publication			<.001		<.001
1970s	15 (3.2)	1 (0.5)		0	
1980-1984	43 (9.3)	13 (6.4)		0	
1985-1989	109 (23.4)	20 (9.8)		0	
1990-1994	44 (9.5)	13 (6.4)		132 (18.2)	
1995-1999	95 (20.4)	40 (19.6)		397 (54.7)	
2000-2004	159 (34.2)	117 (57.4)		197 (27.1)	
Study type			<.001		<.001
Comparative	332 (71.4)	172 (84.3)		636 (87.6)	
Noncomparative	133 (28.6)	32 (15.7)		90 (12.4)	

Abbreviations: NA, not applicable; RT, radiation therapy.

*Unless otherwise indicated, all data are reported as number (percentage) of patients.

†Comparisons made using the χ^2 test for surgery alone vs surgery + RT, male vs female, stage I vs II vs III, head/neck vs all other known locations, lesion size 2 cm or larger vs smaller than 2 cm, United States vs Europe vs Australia, before 1990 vs 1990 through 1999 vs after 2000-2004, and the 2-sample *t* test for age and lesion size.

‡Since the patient characteristics were available only at the aggregate level, the results are reported for all 726 patients included in the aggregate-level studies rather than just the 585 who met the criteria for inclusion.

§For the aggregate-level studies, the mean age and lesion size were calculated by averaging (weighted for sample size) the reported means or medians.

‖Unable to calculate because estimates of the standard deviation were unavailable for the aggregate-level studies.

Table 2. Time-to-Event Analysis of Disease Recurrence, Progression, and Survival for Individual-Level Studies

Treatment Group	Patients, No.	Event-Free Survival Rate ± SE, % (No. Still at Risk) 1 y	5 y	Hazard Ratio (95% CI)	*P* Value
Local recurrence*†					
Surgery only	418	70.5 ± 2.4 (215)	60.5 ± 2.9 (38)	1.00	
Surgery ± RT	169	90.4 ± 2.4 (123)	87.9 ± 2.7 (23)	0.27 (0.17-0.44)	<.001
Regional recurrence‡§					
Surgery only	373	62.6 ± 2.6 (183)	44.4 ± 4.3 (40)	1.00	
Surgery ± RT	125	85.3 ± 3.3 (87)	77.0 ± 5.3 (15)	0.34 (0.22-0.52)	<.001
Distant metastasis‡‖					
Surgery only	383	87.3 ± 1.8 (253)	68.7 ± 3.2 (52)	1.00	
Surgery ± RT	129	87.0 ± 3.1 (93)	78.5 ± 4.0 (22)	0.79 (0.50-1.25)	.31
Overall survival‡¶					
Surgery only	381	86.3 ± 1.8 (269)	50.2 ± 3.5 (55)	1.00	
Surgery ± RT	131	89.1 ± 2.8 (103)	57.3 ± 6.1 (22)	0.78 (0.55-1.10)	.16
Cause-specific survival‡¶					
Surgery only	381	89.8 ± 1.6 (269)	61.6 ± 3.5 (55)	1.00	
Surgery ± RT	131	91.5 ± 2.6 (103)	75.0 ± 4.5 (22)	0.72 (0.47-1.11)	.14

Abbreviations: CI, confidence interval; RT, radiation therapy.

*Includes all patients, regardless of stage at presentation.

†Of the 669 patients described by individual-level studies, 183 (27%) had a documented local recurrence; of these, 153 had a reported time to recurrence (median, 5 months; range, 1-96 months). Of the 486 remaining patients without a documented recurrence, 434 had a reported duration of follow-up (median, 24 months; range, 1-192 months). The effective sample is 153 + 434 = 587 patients.

‡Includes only patients presenting with stage I disease.

§Of the 566 patients described by individual-level studies who presented with stage I disease, 219 had a documented regional recurrence. Of these 219 patients, 195 had a reported time to recurrence (median, 7 months; range, 1-192 months). Of the 347 remaining patients with stage I disease without a documented recurrence, 303 had a reported duration of follow-up (median, 24 months; range, 1-192 months). The effective sample is 195 + 303 = 498 patients.

‖Of the 566 patients who presented with stage I disease, 121 (21%) had a documented distant metastasis. Of these 121 patients, 108 had a reported time to metastasis (median, 12 months; range, 1-105 months). Among the 445 remaining patients with stage I disease without a documented metastasis, 404 had a reported duration of follow-up (median, 24 months; range, 1-216 months). The effective sample is 108 + 404 = 512 patients.

¶Of the 566 patients who presented with stage I disease, 188 deaths were reported, of which 183 had a reported time to death (median, 20 months; range, 1-160 months). Of the remaining 378 patients without documentation of death, 329 had a reported duration of follow-up (median, 25 months; range, 1-216 months). The effective sample is 183 + 329 = 512 patients.

(recurrence-free survival) were 63% (1 year) and 44% (5 year) after surgery compared with 85% (1 year) and 77% (5 year) after combination therapy (Table 2, Figure, B). No sources of confounding or effect modifiers were identified. However, the effect of combination treatment was stronger among patients with small lesions (≤2 cm) (Table 3).

Of the 326 patients described by aggregate-level studies who presented with stage I disease, 122 (37%) developed a regional recurrence. Patients treated with combination therapy were significantly less likely to develop a regional recurrence (OR, 0.19; $P<.001$) (Table 4).

DISTANT METASTASES

Of the 566 patients described in individual-level studies who presented with stage I disease, 121 (21%) developed a documented distant metastasis. The median time to metastasis was 12 months (range, 1-105 months), and a majority (54%) developed a metastasis within 12 months of initial treatment.

Among patients who presented with stage I disease, the rate of distant metastasis was similar between treatment groups (HR, 0.79; $P=.31$), although 7 times as many patients would be required to adequately (80%) power this calculation. In this group, the proportions of patients free of distant metastasis (metastasis-free sur-

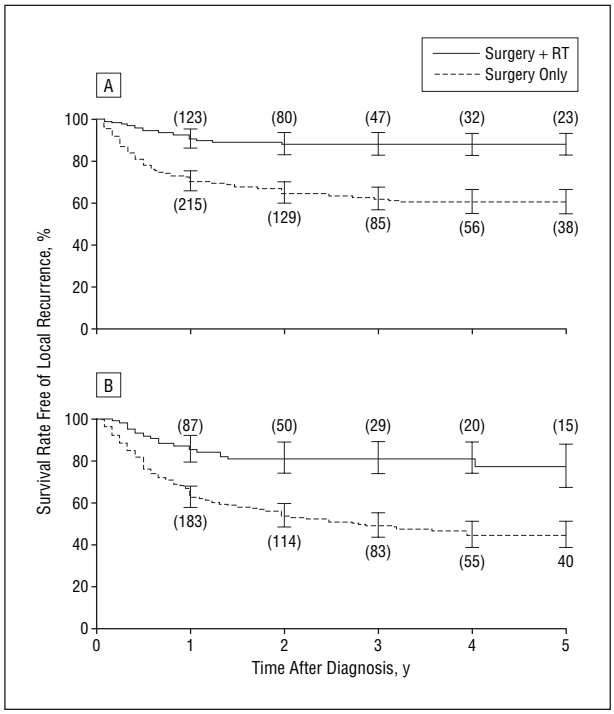

Figure. Survival curves for patients free of local (A) and regional (B) recurrence shown with 95% confidence limits and, parenthetically, numbers of patients still at risk. Panel A includes all stages of disease; panel B, stage I only. RT indicates radiation therapy.

Table 3. Time-to-Event Analysis of Patient Characteristics as Potential Effect Modifiers of the Relationship Between Treatment Group and Outcome From Individual-Level Studies Only

	Recurrence						Survival			
	Local*		Regional†		Distant†		Overall†		Cause-Specific†	
Characteristic	Patients, No.	HR‡ (95% CI)	Patients, No.	HR‡ (95% CI)	Patients, No.	HR‡ (95% CI)	Patients, No.	HR‡ (95% CI)	Patients, No.	HR‡ (95% CI)
Overall	587	0.27 (0.17-0.44)	498	0.34 (0.22-0.52)	512	0.79 (0.50-1.25)	512	0.78 (0.55-1.10)	512	0.72 (0.47-1.11)
Sex										
Male	278	0.34 (0.17-0.66)	234	0.30 (0.16-0.56)	239	1.10 (0.61-1.97)	239	1.05 (0.66-1.67)	239	0.99 (0.57-1.70)
Female	285	0.21 (0.09-0.45)	243	0.33 (0.17-0.64)	253	0.53 (0.25-1.13)	252	0.59 (0.34-1.02)	252	0.49 (0.23-1.05)
Age§										
<60 y	115	0.07 (0.01-0.51)	94	0.19 (0.07-0.52)	92	0.43 (0.16-1.15)	96	0.53 (0.21-1.30)	96	0.46 (0.17-1.24)
60-69 y	131	0.42 (0.19-0.93)	107	0.28 (0.13-0.62)	111	0.61 (0.26-1.44)	112	0.79 (0.40-1.58)	112	0.65 (0.29-1.46)
70-79 y	201	0.31 (0.13-0.72)	177	0.41 (0.20-0.87)	180	1.12 (0.53-2.39)	180	0.91 (0.50-1.65)	180	1.00 (0.48-2.10)
80+ y	140	0.25 (0.08-0.81)	120	0.51 (0.18-1.44)	129	0.93 (0.26-3.26)	124	1.06 (0.53-2.14)	124	0.73 (0.25-2.14)
Lesion size‖										
≤2 cm	166	0.08 (0.01-0.59)	143	0.28 (0.10-0.79)	149	0.47 (0.14-1.61)	149	0.49 (0.21-1.19)	149	0.27 (0.06-1.18)
>2 cm	103	0.70 (0.30-1.60)	83	0.52 (0.16-1.73)	82	2.27 (0.73-7.07)	84	2.41 (0.94-6.19)	84	3.00 (1.14-7.90)
Stage										
I	503	0.30 (0.18-0.50)	498	0.34 (0.22-0.52)	512	0.79 (0.50-1.25)	512	0.78 (0.55-1.10)	512	0.72 (0.47-1.11)
II	76	0.42 (0.08-2.29)	NA	NA	NA	NA	NA	NA	NA	NA
Lesion location										
Head/neck	312	0.27 (0.14-0.53)	265	0.36 (0.19-0.67)	268	1.04 (0.52-2.07)	272	0.81 (0.50-1.32)	272	0.87 (0.47-1.63)
Other	272	0.27 (0.13-0.57)	233	0.31 (0.17-0.58)	233	0.61 (0.33-1.12)	240	0.76 (0.46-1.25)	240	0.62 (0.34-1.14)
Geography¶										
United States	267	0.44 (0.21-0.94)	220	0.27 (0.12-0.61)	222	0.60 (0.28-1.29)	226	0.61 (0.33-1.13)	226	0.72 (0.35-1.48)
Europe	227	0.18 (0.08-0.40)	191	0.35 (0.18-0.68)	193	0.91 (0.40-2.06)	199	0.80 (0.46-1.37)	199	0.58 (0.27-1.26)
Australia	55	No recurrences	53	0.61 (0.25-1.51)	52	0.85 (0.33-2.15)	53	1.06 (0.46-2.42)	53	0.89 (0.35-2.27)
Study type										
Comparative	442	0.32 (0.19-0.54)	369	0.34 (0.22-0.54)	387	0.72 (0.43-1.20)	382	0.63 (0.34-0.92)	382	0.62 (0.38-0.99)
Noncomparative	145	0.14 (0.02-1.02)	129	0.22 (0.03-1.62)	125	3.2 (1.10-9.45)	130	2.33 (0.82-6.66)	130	2.22 (0.66-7.42)

Abbreviation: CI, confidence interval; HR, hazard ratio; NA, not applicable.
*Includes all stages.
†Includes stage I disease only.
‡Hazard ratio for the association between treatment group (surgery and irradiation combined vs surgery only) and each outcome.
§Age was handled as a continuously scaled variable in the Cox regression model.
‖Lesion size was handled using 2 indicator variables for the 3 levels: 2 cm or smaller, larger than 2 cm, and unknown size.
¶Geography was handled using 2 indicator variables for the 3 main regions, United States, Europe, and Australia.

vival) were 87% (1 year) and 69% (5 year) after surgery compared with 87% (1 year) and 79% (5 year) after combination therapy (Table 2). No sources of confounding or effect modifiers were identified.

Of the 174 patients described by aggregate-level studies who presented with stage I disease, 15 (9%) developed a documented distant metastasis. Treatment with surgery alone was associated with a similar risk of distant metastasis compared with combination therapy (OR, 0.72; $P = .62$) (Table 4).

SURVIVAL

Of the 669 patients described in individual-level studies, 229 deaths were reported. Of these, 153 deaths (67%) were attributed to MCC. The median time to death from MCC

Table 4. Analysis of Disease Recurrence, Progression, and Survival for Aggregate-Level Studies

Treatment Group	Total Patients, No.	Patients With Event, No. (%)	Odds Ratio* (95% CI)	*P* Value
Local recurrence†				
Surgery only	429	105 (24.5)	1.00	<.001
Surgery ± RT	156	15 (9.6)	0.33 (0.18-0.58)	
Regional recurrence‡				
Surgery only	250	112 (44.8)	1.00	<.001
Surgery ± RT	76	10 (13.2)	0.19 (0.09-0.38)	
Distant metastasis‡				
Surgery only	130	12 (9.2)	1.00	.62
Surgery ± RT	44	3 (6.8)	0.72 (0.19-2.68)	
Overall survival‡				
Surgery only	72	27 (37.5)	1.00	.11
Surgery ± RT	25	5 (20.0)	0.42 (0.14-1.24)	
Cause-specific survival‡				
Surgery only	71	17 (23.9)	1.00	.56
Surgery ± RT	32	6 (18.8)	0.73 (0.26-2.08)	

Abbreviations: CI, confidence interval; RT, radiation therapy.
*Odds ratios ignore time-to-event methods.
†Includes all patients regardless of stage at presentation.
‡Includes patients presenting with stage I disease only.

was 17 months (range, 1-114 months). Overall survival rates among patients described by individual-level studies were 87% (1 year) and 49% (5 year). Survival rates were similar (HR, 0.78; *P*=.16) among patients with stage I disease treated with combination therapy (89% at 1 year, 57% at 5 years) vs surgery alone (86% at 1 year, 50% at 5 years) (Table 2). However, more than 3 times as many patients would be required to adequately (80%) power this calculation. A subgroup analysis excluding single-patient case reports and noncomparative studies demonstrated a significant overall survival advantage after treatment with combination therapy (HR, 0.63; *P*=.02) (Table 3).

Cause-specific survival rates among patients described by individual-level studies were 90% (1 year) and 62% (5 year). Cause-specific survival rates were similar (HR, 0.72; *P*=.14) among patients with stage I disease treated with combination therapy (92% at 1 year, 75% at 5 years) vs surgery alone (90% at 1 year, 62% at 5 years) (Table 2). However, more than 3 times as many patients would be required to adequately (80%) power this calculation as well. A subgroup analysis that excluded single-patient case reports and noncomparative studies again revealed a significant cause-specific survival advantage after treatment with combination therapy (HR, 0.62; *P*=.04) (Table 3). No sources of confounding or effect modifiers were identified in either survival analysis, although smaller lesions were independently associated with a cause-specific survival advantage following combination therapy (Table 3).

Of the 118 deaths reported by aggregate level studies, 83 (70%) were attributed to MCC. No significant survival benefit was observed across treatment groups (Table 4).

COMMENT

Merkel cell carcinoma is an aggressive cutaneous neoplasm with a propensity to recur and metastasize despite treatment. Results of this meta-analysis suggest that overall survival rates approach 87% at 1 year and 49% at 5 years. The data also suggest that combination treatment with surgery and adjuvant irradiation may significantly reduce the risk of local recurrence. As well, the rate of progression from stage I to stage II was significantly lower following treatment with surgery and adjuvant irradiation compared with surgery alone. By contrast, the overall rates of distant metastasis and of any-cause and cause-specific survival were not significantly different between treatment groups. A subgroup analysis of comparative individual-level studies showed statistically significant overall and cause-specific survival advantages among patients with stage 1 disease treated with combination therapy. In this analysis, case reports of single patients and noncomparative studies were excluded from consideration.

There are several limitations to this study. None of the reports included was a prospective, randomized study. As well, several factors were inconsistently documented and could not be addressed in the analysis, including (1) the type of surgery (local excision vs wide local excision vs Mohs surgery) and width of surgical margins; (2) the dose or field of radiation therapy beyond the tumor bed (which may have included in-transit lymphatic vessels and/or lymph node basins); and (3) any independent effect that additional treatment (lymph node dissection and/or chemotherapy) may have had.

Several issues arose when we considered how to analyze aggregate-level studies in which important data points including time-to-event, duration of follow-up, and summary measures (HRs) were inconsistently documented. As a result, it was not possible to pool patients from individual- and aggregate-level studies. Because the number of cases (585 of 1254) and the collective clinical experience proffered by the institutions reporting aggregate-level data are substantial, these studies warranted a degree of statistical consideration in this meta-

analysis. Appropriate caution in the interpretation of these is warranted, however. Of note, the proportion of patients who presented with stage I disease was significantly lower among aggregate-level studies ($P = .01$), which supports an anecdotal observation that many of these reports were published by tertiary referral centers, where patient acuity might be higher. Despite this possibility, significant reductions in local and regional recurrence were also observed in this group of studies suggesting that the treatment effect was consistent. In addition, choice of treatment was similarly divided within each study type, highlighting the lack of consensus on use of radiation therapy for MCC even among large institutions.

Despite its limitations, the present study represents the largest collective evidence regarding the efficacy of local adjuvant irradiation in the management of MCC. The results of this investigation potentially have direct clinical application and are germane to the practices of many medical and surgical specialists who manage patients with MCC. Geographic differences and chronologic trends indicate discordant and evolving practice patterns that have not been reported previously. Recent opinions in the literature document controversy regarding the role of radiation therapy based on relatively small case series and incomplete literature reviews. The results of the present study support strong consideration of local adjuvant radiation therapy after complete surgical excision of MCC to lower the risk of local and regional recurrence. Suggestion of a potential survival benefit emphasizes the need for a prospective randomized controlled study. After more than 30 years of treating this aggressive and often fatal tumor without prospective data, the time has come for a multicenter collaborative effort to characterize more definitively indicators of prognosis and effective therapeutic interventions for MCC.

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