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CLINICAL INVESTIGATION **Skin**

EFFECT OF RADIOTHERAPY DOSE AND VOLUME ON RELAPSE IN MERKEL CELL CANCER OF THE SKIN

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Purpose: To assess the effect of radiotherapy (RT) dose and volume on relapse patterns in patients with Stage I–III Merkel cell carcinoma (MCC).
Patients and Methods: This was a retrospective analysis of 112 patients diagnosed with MCC between January 2000 and December 2005 and treated with curative-intent RT.
Results: Of the 112 evaluable patients, 88% had RT to the site of primary disease for gross (11%) or subclinical (78%) disease. Eighty-nine percent of patients had RT to the regional lymph nodes; in most cases (71%) this was for subclinical disease in the adjuvant or elective setting, whereas 21 patients (19%) were treated with RT to gross nodal disease. With a median follow-up of 3.7 years, the 2-year and 5-year overall survival rates were 72% and 53%, respectively, and the 2-year locoregional control rate was 75%. The in-field relapse rate was 3% for primary disease, and relapse was significantly lower for patients receiving ≥50Gy (hazard ratio [HR] = 0.22; 95% confidence interval [CI], 0.06–0.86). Surgical margins did not affect the local relapse rate. The in-field relapse rate was 11% for RT to the nodes, with dose being significant for nodal gross disease (HR = 0.24; 95% CI, 0.07–0.87). Patients who did not receive elective nodal RT had a much higher rate of nodal relapse compared with those who did (HR = 6.03; 95% CI, 1.34–27.10).
Conclusion: This study indicates a dose-response for subclinical and gross MCC. Doses of ≥50Gy for subclinical disease and ≥55Gy for gross disease should be considered. The draining nodal basin should be treated in all patients. © 2010 Elsevier Inc.

Merkel cell carcinoma, Radiation dose, Volume.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy with a high propensity for local recurrence, as well as regional and distant metastases (1–3). Because of its rarity, there is a lack of prospective controlled trials in these patients. Although patients are generally treated with surgery as first-line therapy (4), there is still some controversy regarding the extent of surgical intervention (5).

Merkel cell carcinoma is a highly radiosensitive tumor, and small studies have suggested an association between the use of adjuvant radiotherapy (RT) and a reduced risk of locoregional recurrence (6–11). A large study analyzing the role of adjuvant RT in patients undergoing surgical resection for MCC identified through the Surveillance, Epidemiological, and End Results (SEER) program of the National Cancer Institute showed that the use of radiation was associated with an improvement in survival for patients with all sizes of tumors (12). However, as outlined by the investigators, one of the limitations of this study was the lack of detail regarding adjuvant RT, specifically radiation doses and volumes.

At present the literature provides little data on the effect of RT dose and volume in the treatment of MCC either in the definitive setting (for gross primary and/or nodal disease) or for subclinical disease in the adjuvant and elective settings (both primary and nodal). The purpose of this study was to analyze the effect of radiation dose and volume on the relapse patterns in patients treated curatively for MCC. These data were further analyzed to establish whether a dose-response exists for primary and/or nodal RT.

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Table 1. Patient demographics

Parameter	*n*	% of total*
Total	112	100
Age (y)		
40–59	15	13
60–69	26	23
70–79	41	37
80–95	30	27
Sex		
Male	81	72
Female	31	28
Primary site		
Occult	11	10
Head and neck	60	54
Upper limb	18	16
Trunk	9	8
Lower limb	14	13
Stage, MSKCC (13)		
I	63	56
II	12	11
III	37	33
Recurrent disease		
Yes	9	8
No	103	92

Abbreviation: MSKCC = Memorial Sloan-Kettering Cancer Center.

* Percentages across subgroups do not always add to 100% due to rounding.

Table 2. Patient treatment details

Parameter	*n*	% of total*
Total	112	100
Treatment		
RT only	4	4
Surgery + RT	93	83
Surgery + RT + chemotherapy	15	13
Surgery to primary		
None	11	10
Biopsy (positive margin)	21	19
Excision (negative margin)	69	62
Wide excision	11	10
Surgery to nodes		
None	94	84
En-bloc resection	10	9
Excisional/SLN biopsy	3	3
Limited resection	5	4
RT volume		
Local RT only		
Gross disease	1	1
Subclinical disease	11	10
Nodal RT only		
Gross disease	5	4
Subclinical disease	8	7
Both local and nodal RT		
Local:gross + nodal:gross	4	4
Local:subclinical + nodal:subclinical	64	57
Local:gross + nodal:subclinical	7	6
Local:subclinical + nodal:gross	12	11
Chemotherapy		
None	97	87
Adjuvant	2	2
Concurrent	2	2
Concurrent + adjuvant	11	10

Abbreviations: RT = radiotherapy; SLN = sentinel lymph node.

* Percentages across subgroups do not always add to 100% due to rounding.

PATIENTS AND METHODS

Patients and design

Eligibility for this study included a diagnosis of MCC between 2000 and 2005 treated with curative RT at three public radiation treatment centers in Queensland, Australia. Patients were identified using the Queensland Oncology Repository, an integrated database on all cancer patients in the region. The Queensland Oncology Repository was searched for patients who had an ICD-10 diagnosis code of C44 and a morphology code of 8247/3 (Merkel cell carcinoma). All diagnoses were then verified through examination of clinical records. The patients were all classified as Stage I–III by clinical examination, computed tomography, and/or positron emission tomography scans, according to the Memorial Sloan-Kettering Cancer Centre (MSKCC) staging system (13). Of the 145 patients identified, 33 were excluded: 27 patients were treated palliatively, and 6 had insufficient RT or follow-up information. Demographics, tumor characteristics, and pathology reports were reviewed for the 112 eligible patients.

Radiotherapy treatment plans were studied to define the dose and the volume treated. All RT dose prescriptions were translated into 2-Gy equivalent doses (for $\alpha/\beta = 10$), with no correction for overall treatment time. Follow-up notes, radiology, and registries were reviewed to determine patient relapse data. The closeout date for the study was November 30, 2008.

Statistical analysis

All statistical analyses were performed using Stata software (StataCorp, College Station, TX). Kaplan-Meier plots were used to summarize time to event, measured from the date of RT. Overall survival considered any death as an event, whereas disease-specific survival censored deaths from intercurrent causes. Locoregional control was defined as the proportion of patients who did not develop relapse at a treated primary and/or nodal site. The relapse rate was compared across demographic and clinical characteristics using Cox proportional hazards regression.

For the dose–response analysis, local and nodal disease were analyzed separately and categorized as local and nodal (gross and subclinical). This was justified because often the primary and nodal regions were treated differently (*e.g.,* adjuvant for primary and radical for nodes). Both continuous and categoric forms of age and radiation dose were evaluated; the continuous form was used if the response seemed sufficiently linear. Where sufficient patient numbers were available, multivariate adjustments were performed for age, gender, clinical stage (I/II vs. III), site (lower limb vs. other), recurrence, chemotherapy, and excision margin.

RESULTS

Patient characteristics

The median age at MCC diagnosis was 74 years (range, 30–95 years), and 81 patients (72%) were male. The most common primary site of disease was the head and neck (54%), followed by upper limb (16%), lower limb (13%), and trunk (8%), with 11 patients (10%) having occult primary disease. According to the MSKCC staging system, more than half of patients had clinical Stage I disease (56%), 12 patients (11%) had Stage II, and 37 patients (33%) had Stage III

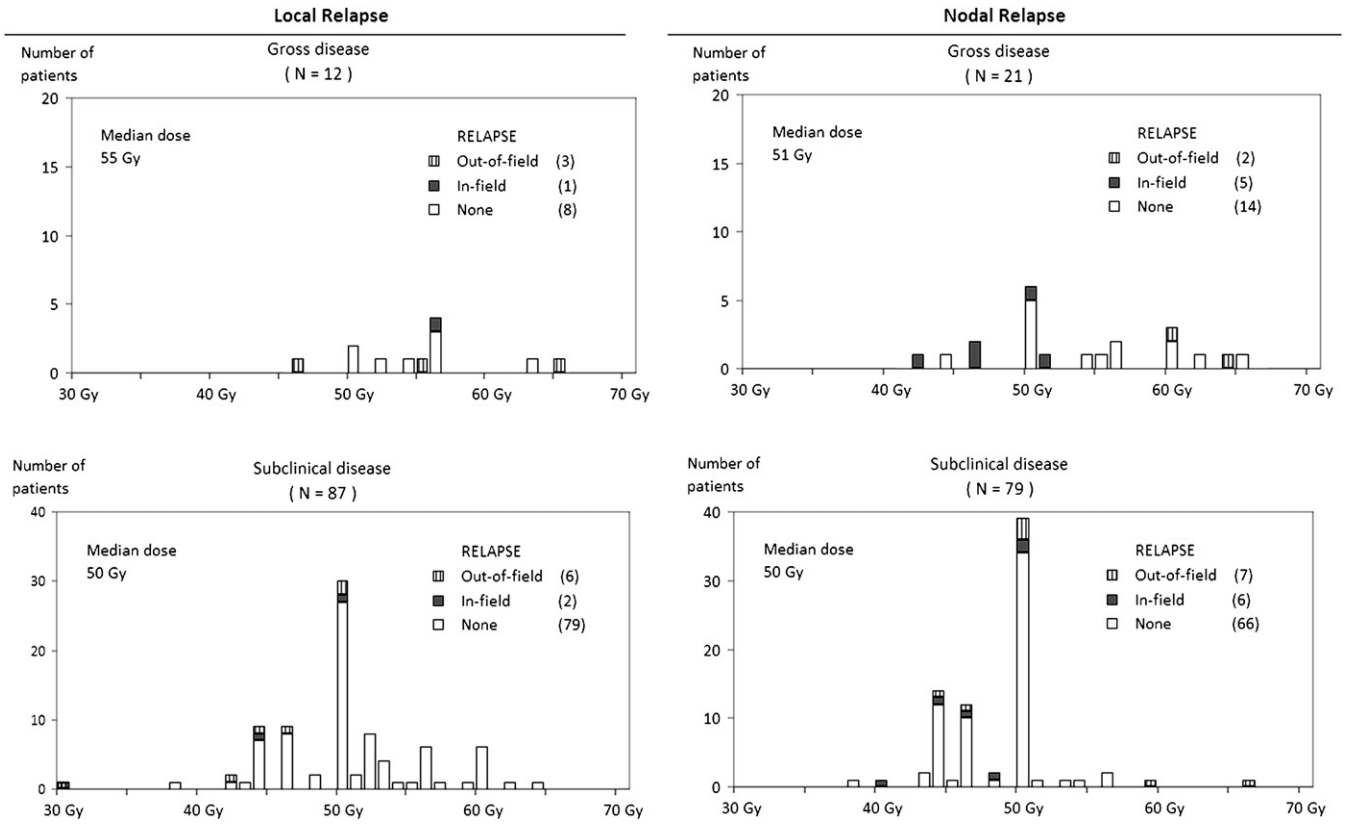

Fig. 1. Dose distribution and relapse.

disease. Nine patients (8%) presented with recurrent MCC. Patient demographic data are detailed in Table 1.

Treatment

Surgery. Of the 112 evaluable patients, 101 (90%) had surgery to the primary disease; the 11 patients without surgery to the primary disease all had occult primary disease. Eleven patients (10%) had a wide local excision, defined clinically by the surgeon as an excision with a minimum of a 2-cm radial margin around the primary disease. Excisional biopsy was performed on 90 patients (80%); more than two thirds of these had a histologic negative margin. Although 37 patients (33%) had clinical Stage III disease, only 18 patients (16%) had surgery to the draining lymph nodes, which included an en-bloc resection, a limited resection, sentinel lymph node biopsy, or excisional biopsy (Table 2).

Radiotherapy. All patients had RT as part of their curative treatment. In most cases CT planning was used, except in those situations in which only the primary disease was treated and clinical mark-up was appropriate. Local RT to the primary disease consisted of wide-field RT with a minimum 3-cm margin around the surgical bed or gross disease where practical. Either electrons or megavoltage photons were used, and in all cases a tissue equivalent bolus was used to ensure full dose on the skin. Nodal RT was given to the next echelon of nodes adjacent to the primary site. This was CT planned, and the volume was at the discretion of the treating radiation oncologist.

Ninety-nine patients (88%) received RT to the primary for either gross or subclinical disease (Table 2). Of the 13 patients who did not receive RT to the primary, 11 had occult disease. The other 2 patients were referred for RT after developing nodal relapse, and it was decided that the patient did not warrant adjuvant RT to the primary.

One hundred patients (89%) had RT to the regional lymph nodes. In most cases (71%) this was for subclinical disease in either the adjuvant or elective setting. However, there were 21 patients (19%) who were treated with RT to gross nodal disease. Table 2 outlines the extent of RT in all patients.

Although a range of dose fractionation schedules was used, 50 Gy in 25 fractions was the most common schedule for subclinical disease. Of the 199 schedules delivered for both subclinical and gross disease (local and nodal), 137 (69%) were at 2 Gy per fraction, 18 (9%) were at 1.8 Gy per fraction, and the remainder had doses of >2 Gy per fraction. Of the hypofractionated schedules, the doses ranged from 25 Gy in 6 fractions to 62 Gy in 25 fractions.

Chemotherapy. Fifteen patients (14%) received chemotherapy as part of their treatment, and in most cases (13 patients) this involved concurrent platinum-based chemotherapy with or without adjuvant chemotherapy, as per the Trans-Tasman Radiation Oncology Group 96.07 protocol (14).

Radiotherapy volume and locoregional relapse

Of the 99 patients (88%) receiving local RT for either subclinical (87 patients) or gross disease (12 patients), the

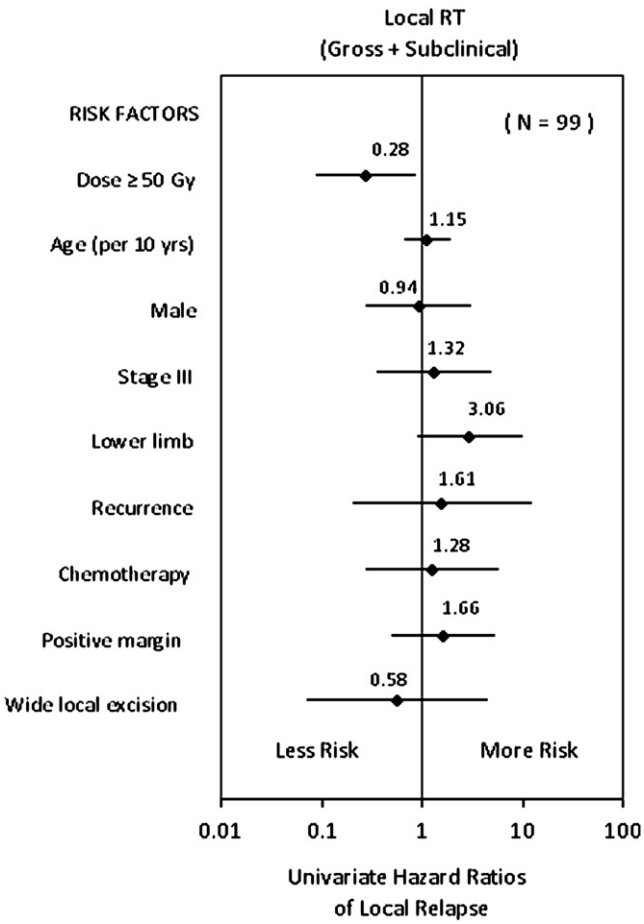

Fig. 2. Univariate Cox proportional hazard ratios with 95% confidence intervals of local radiotherapy (RT) (gross and subclinical) for any relapse (in-field and out-of-field) as outcome.

local relapse rate was 12%; three relapses were in-field and nine out-of-field. Of the nine out-of-field local relapses, RT fields with a minimum of a 3-cm margin around the surgical bed (6 patients) or gross disease (3 patients) were used. Relapses were immediately adjacent or in close proximity to the field edge. Head-and-neck primary disease accounted for five of these relapses; the remaining four (two each) were for upper and lower limb primary disease. On univariate analysis neither gross disease, positive margins, negative margins, nor wide local excision had an effect on local relapse.

Of the 100 patients (89%) receiving nodal RT for subclinical (79 patients) or gross nodal disease (21 patients), the rate of nodal relapse was 20%, of which 11% were in-field. The nodal in-field relapse rate was only slightly lower (8%) in the subset of 63 Stage I/II patients. Among the 12 Stage I/II patients who did not receive nodal treatment, 4 (33%) had nodal relapses, all of which occurred adjacent to the primary (and would therefore have been in-field if treated). This rate is much higher than the nodal in-field relapse rate among node-treated Stage I/II patients (8 of 63 patients), even after adjustments for age, gender, site, and chemotherapy (multivariate hazard ratio [HR] = 6.03; 95% confidence interval [CI], 1.34–27.10).

Radiotherapy dose and locoregional relapse

Dose was translated into 2-Gy equivalent doses (for α/β = 10), and this was the most significant predictor of relapse at both primary and nodal sites (Figs. 2 and 3). The median dose for local subclinical disease was 50 Gy (range, 30–64 Gy), whereas the median dose for local gross disease was 55 Gy (range, 46–65 Gy). Because of the low rate of in-field local relapse it was not possible to perform a dose–response analysis for in-field relapse. However, for local gross disease there were no in-field relapses at a dose >56 Gy and for local subclinical disease there were no in-field relapses at a dose >50 Gy.

For local RT (gross and subclinical) we performed a univariate analysis on any local relapse (in- and out-of-field), and dose ≥50 Gy (the median) was significant for relapse (HR = 0.28; 95% CI, 0.09–0.88). This response remained significant (p = 0.03) after multivariate adjustment for site, stage, and excision margin. Positive surgical margins (including gross disease) had no effect on the risk of local relapse when compared with wide excision or negative margins in both univariate and multivariate analyses (p > 0.20).

The median dose for nodal subclinical disease was 50 Gy (range, 38–66 Gy), whereas the median dose for nodal gross disease was 51 Gy (range, 42–65 Gy). Among the 21 patients who received nodal RT for gross disease, the rate of in-field relapse showed a marked decline with every increase of 5 Gy over the range of doses (univariate HR = 0.24; 95% CI, 0.07–0.87). The effect remained significant (p = 0.02) after controlling for site (lower limb vs. other), the next-most significant factor in the analysis. The in-field relapse response to increasing dose was much less pronounced in the 79 patients given nodal treatment for subclinical disease (univariate HR = 0.44; 95% CI, 0.14–1.42). Nonetheless, dose was numerically the strongest predictor of in-field relapse for subclinical disease in both univariate and multivariate regressions.

The proportion of nodal in-field relapse respective to RT dose among MCC patients given nodal RT is shown in Fig. 4.

Survival and locoregional control

The median length of follow-up from start of RT to either death or date last seen was 3.7 years (range, 0.3–8.3 years), and 43 patients (38%) had developed relapse. The median overall survival was 6.4 years, with 2-year and 5-year rates of 72% and 53%, respectively (Fig. 5). The disease-specific survival rate at 2 and 5 years was 80% and 68%, respectively, and the locoregional control rate stabilized at approximately 75% after 2 years (Fig. 5).

DISCUSSION

The optimum treatment for MCC of the skin remains controversial because there is a lack of data on which to base treatment algorithms. With the mounting evidence that RT improves locoregional control (6–11) and survival (12), it is important that the appropriate radiation doses and volumes are defined in the curative management of these patients. This

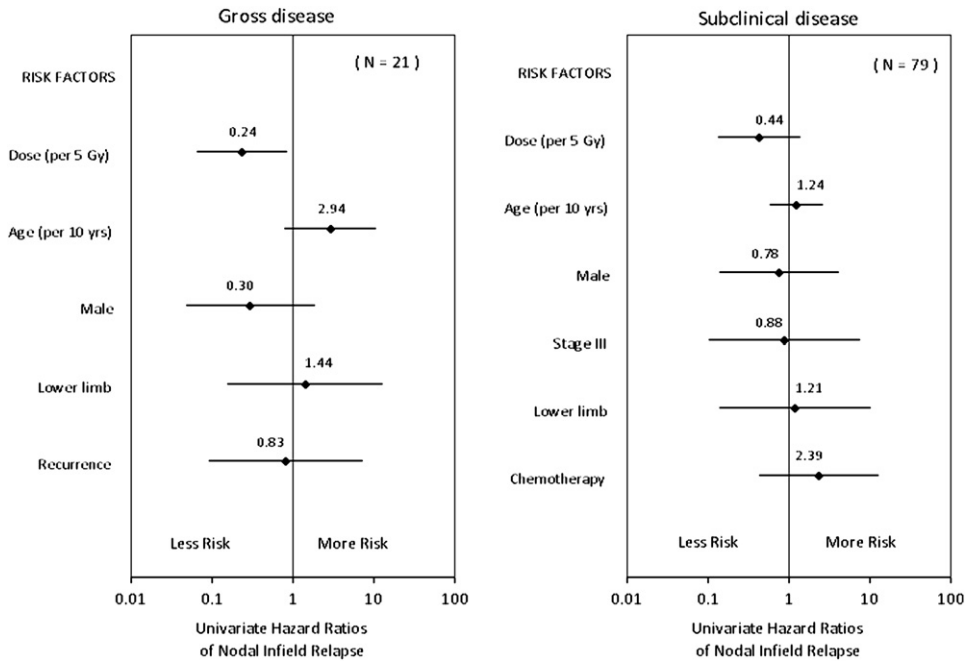

Fig. 3. Univariate Cox proportional hazard ratios with 95% confidence intervals of nodal in-field relapse.

cohort of 112 patients reflects the largest series attempting to define these RT parameters.

The use of retrospective data to estimate dose-response has its limitations. Patients are typically not distributed evenly over the range of doses; approximately one third of all doses in this study were 50 Gy. If the low and high ends of the dose scale are given to specific patients then there is potential for confounding bias. Dose responses in this study were not affected by adjustments for other variables, suggesting that confounding, if any, is minimal.

There are several strengths of this data set. All patients were diagnosed since January 2000 and as such were adequately staged using modern imaging techniques. All patients received RT, and unlike the SEER data (10) we have comprehensive details regarding RT treatment using three-dimensional planning and delivery systems.

Generally, the current literature suggests that the optimum treatment for MCC is with a combination of surgery plus RT in terms of recurrence and survival. Details of trials evaluating the role of adjuvant RT published within the last 10 years (for >30 patients) are outlined in Table 3. It can be seen that the addition of locoregional RT to surgery decreases local and regional recurrence rates.

In the largest series documenting the natural history of this malignancy (13) a wide local excision was attempted on almost all patients with a known primary, with a 94% rate of negative margins. In our series 19% of patients had either positive histologic margins or gross local disease. Despite the less-extensive local surgery in this cohort, the rate of local recurrence was only 12%, with an in-field local recurrence rate of 3%. On univariate analysis gross disease or an excision with positive margins had no influence on the rate of local relapse either in- or out-of-field. This rate of local recurrence is comparable to series in which more extensive surgery was undertaken (4) and suggests that with the addition of RT surgical margin status is not critical.

The meta-analysis by Gupta *et al.* (22) showed that for patients with clinical Stage I and II disease the rate of pathologic node involvement by sentinel lymph node biopsy (SLNB) was 32%. This is similar to our rate of 33% for nodal relapse in patients with Stage I and II disease who did not receive nodal surgery or RT. This nodal relapse rate is significantly higher than the rate of 8% for those who had elective nodal RT for early-stage disease (multivariate HR = 6.03). Because of the high rate of pathologically positive nodes in early-stage (I/II) disease and the effectiveness of elective nodal RT, together with the potential morbidity associated with staging the nodal basin, we recommend elective nodal treatment in all early-stage (I/II) patients in the absence of negative results on SLNB.

To analyze different dose and fractionation schedules in this cohort all doses were converted to 2-Gy equivalents

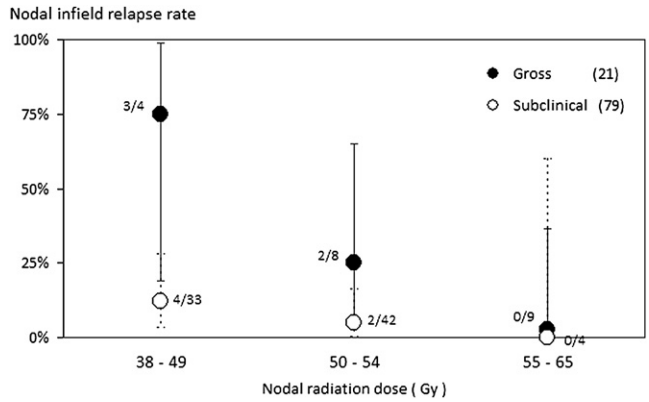

Fig. 4. Proportion of nodal in-field relapse relating to radiotherapy dose.

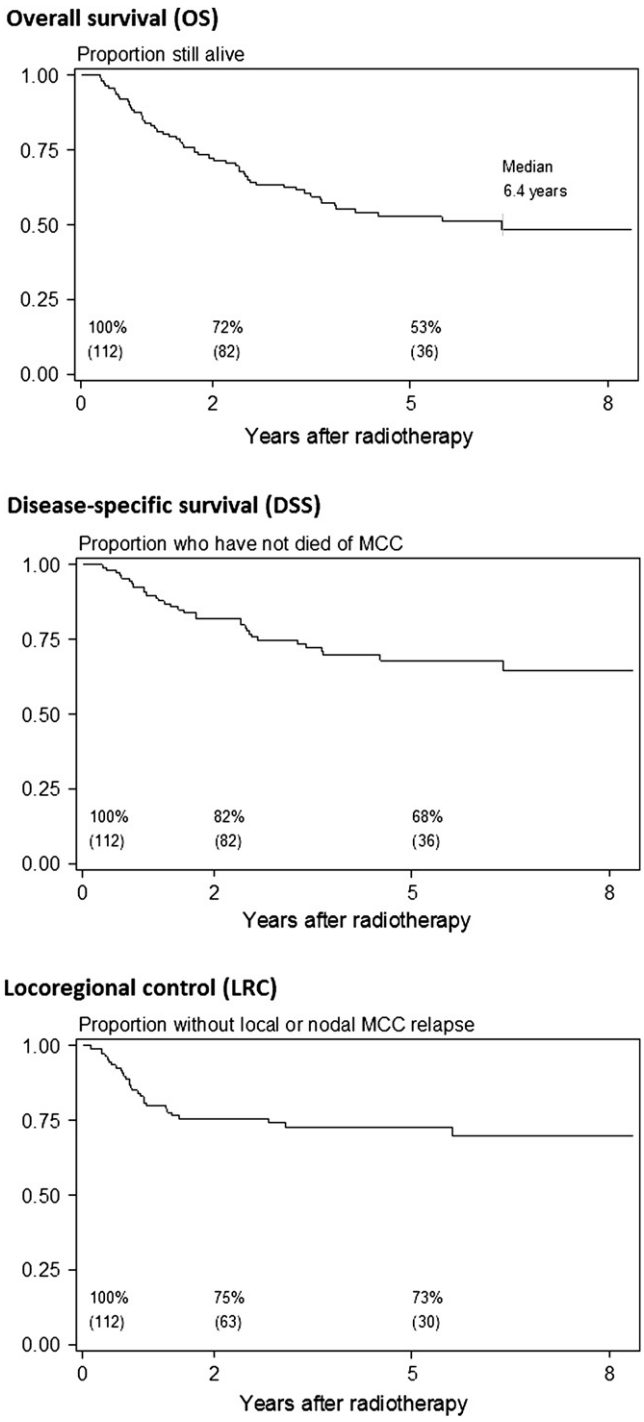

Fig. 5. Kaplan-Meier curves of Merkel cell carcinoma (MCC) survival and locoregional control.

according to the Withers formula (23), with an α/β of 10. It is noteworthy that patients who received hypofractionated treatment had doses that were somewhat lower using this adjustment, and the reduction in overall treatment time may be significant in a rapidly proliferating tumor. To establish a dose-response, we classified both local and nodal failures as in-field or out-of-field. We believe that this is justified given that out-of-field failures are a reflection of inadequate RT volumes as opposed to dose. Figure 1 suggests that there were no in-field failures in the primary or nodal sites for subclinical disease for doses of >50 Gy.

It is of interest that dose ≥50 Gy was a significant factor for local relapse for local gross and subclinical disease (HR = 0.28). In addition, for subclinical disease, there were no in-field relapses for doses >50 Gy, and out-of-field relapse was also low for doses >50 Gy. The reason for the lower rate of out-of-field relapse in relation to radiation dose is difficult to understand. Patients who had hypofractionated treatment had relatively lower doses than standard fractionation and are overrepresented in the group that had out-of-field relapse.

For nodal RT there is a dose-response for gross disease, and as outlined in Fig. 3 there seems to be a dose-response for subclinical disease. As displayed in Fig. 4, there seems to be little benefit for doses >50 Gy for subclinical nodal disease and >55 Gy for gross nodal disease. We have shown that a dose of 50 Gy seems adequate for elective and adjuvant treatments. Higher doses are required for gross disease and should be tailored to the burden of disease.

There is increasing interest regarding the role of chemotherapy in MCC of the skin, particularly for those patients with high-risk disease (14). In this series, which includes a large proportion of patients with Stage I disease, chemotherapy was used in 15% of patients. As such there are insufficient numbers to make any comment regarding the addition of this in terms of locoregional and distant metastatic control.

On the basis of the data presented here, we can make recommendations of 50 Gy for subclinical disease and >55 Gy for gross disease. In most patients with local relapse this was out-of-field, generally in close proximity to the field edge. Almost half of the patients with regional relapse had out-of-field relapse. To reduce the rate of out-of-field relapse, we recommend increasing the field size for local RT to encompass the primary disease with a minimum 4-cm radial margin where practical. Although hypofractionation may be reasonable in some patients, this should not be at the expense of a reduction in field size. For elective, adjuvant, and radical nodal RT we recommend treating the entire draining lymph node basin where possible.

CONCLUSIONS

The important role of RT in reducing local and nodal relapses has been confirmed. There seems to be a dose-response up to 50 Gy for subclinical disease and for gross disease at >55 Gy. These doses achieve very high in-field local control rates. The problem of out-of-field failures can only be lowered by more generous field sizes. Obtaining wide surgical margins does not seem to offer improved control rates, providing RT is to be incorporated into the treatment regimen. For early-stage (I/II) disease we recommend elective nodal RT in the absence of negative results on SLNB.

Table 3. Recent trials evaluating adjuvant RT

Study (ref)	Stage (% of patients)	Treatment (*n*)	Radiotherapy outcomes
Allen *et al.* (13) (n = 251)	I (44)	Surgery ± RT and/or chemotherapy	RT not associated with improvement in local (p = 0.76) or regional (p = 0.13) control.
	II (26)	Adjuvant RT to primary (17)	Local recurrence with RT 10%
	III (24)	Adjuvant RT to nodes (9)	Regional recurrence with RT 13%
	IV (6)	Adjuvant RT to both (15)	
Allen *et al.* (15) (n = 102)	I and II (76)	Surgery ± RT and/or chemotherapy	RT not associated with improvement in local (p = 0.84) control.
	III (22)	Adjuvant RT to primary (15)	Local recurrence with RT 13%
	IV (2)	Adjuvant RT to nodes (6)	
Boyer *et al.* (16) (n = 45)	I (80)	Mohs surgery ± RT	RT not associated with improvement in local control.
	II (20)	Adjuvant RT to primary (20)	Local recurrence with RT 0%
Eich *et al.* (17) (n = 46)	I and II (84)	Surgery ± RT	RT associated with improved locoregional control (p = 0.02).
	III (13)	Adjuvant RT to primary and/or nodes (16)	Local recurrence with RT 6%
	IV (3)	Surgery ± RT	Regional recurrence with RT 19%
Muller *et al.* (18) (n = 36)	I and II (92)	Adjuvant RT to primary and/or nodes (7)	RT associated with improved locoregional control.
	III (6)		Locoregional recurrence with RT 43%
	IV (2)		
Senchenkov *et al.* (19) (n = 38)	I and II (71)	Surgery (WLE or Mohs) ± RT	RT associated with improved recurrence rates (p = .02).
	III (29)	Adjuvant RT to primary (13) Adjuvant RT to nodes (8)	Recurrence with RT 53% (includes distant)
Veness *et al.* (20) (n = 86)	I and II (59)	Surgery ± RT and/or chemotherapy	RT associated with improved locoregional control (p = 0.002).
	III (41)	Adjuvant RT to primary and/or nodes (43)	Local recurrence with RT 12% Regional recurrence with RT 13%
Veness *et al.* (21) (n = 37)	I or II (78)	Surgery ± RT and/or chemotherapy	RT associated with improved disease-free survival (p = 0.09).
	III (22)	Adjuvant RT to primary and/or nodes (20)	Local recurrence with RT 11% Regional recurrence with RT 26%

Abbreviations: RT = radiotherapy; WLE = wide local excision.

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