High-Risk Merkel Cell Carcinoma of the Skin Treated With Synchronous Carboplatin/Etoposide and Radiation: A Trans-Tasman Radiation Oncology Group Study—TROG 96:07

By Michael Poulsen, Danny Rischin, Euan Walpole, Jennifer Harvey, John Mackintosh, Jill Ainslie, Chris Hamilton, Jacqui Keller, and Lee Tripcony

Purpose: **The effectiveness of synchronous carboplatin, etoposide, and radiation therapy was prospectively assessed in a group of patients with high-risk Merkel cell carcinoma (MCC) of the skin.**

Patients and Methods: **Patients were eligible if they had disease localized to the primary site and nodes, and were required to have at least one of the following high risk features: recurrence after initial therapy, involved nodes, primary tumor size greater than 1 cm, gross residual disease after surgery, or occult primary with nodes. Radiation was delivered to the primary site and nodes to a dose of 50 Gy in 25 fractions over 5 weeks and synchronous carboplatin (area under the curve, 4.5) and intravenous etoposide 80 mg/m² days 1 to 3 was given in weeks 1, 4, 7, and 10. The median age of the group was 67 (range, 43–86) years, and there were 39 males and 14 females. Involved nodes (stage II) were present in 33 cases (62%). The sites involved were head and neck (22 patients), occult primary (13 patients), upper limb (eight patients), lower limb (eight patients), and trunk (two patients).**

Results: **Fifty-three patients were entered between 1996 and 2001. The median potential follow-up was 48 months. There were no treatment related deaths. The 3-year overall survival, locoregional control, and distant control were 76%, 75%, and 76%, respectively. Tumor site and the presence of nodes were factors that were predictive for local control and survival. Multivariate analysis indicated that the major factor influencing survival was the presence of nodes; however, this was not a significant factor in locoregional control.**

Conclusion: **High levels of locoregional control and survival have been achieved with the addition of chemotherapy to radiation treatment for high-risk MCC of the skin. The role of chemoradiotherapy for high-risk MCC warrants further investigation.**

J Clin Oncol 21:4371-4376. © ***2003 by American Society of Clinical Oncology.***

THE TRANS-TASMAN Radiation Oncology Group embarked on a phase II study of synchronous chemoradiotherapy in high-risk Merkel cell carcinoma (MCC) of the skin in 1996. High risk MCC was defined as primary tumors more than 1 cm in diameter, and/or the presence of in-transit or nodal metastases, and/or locally or regionally lymphatic recurrent tumor, but with no evidence of distant disease. The use of radiotherapy in locoregional control of MCC is considered standard treatment, although the optimal combination of surgery and radiotherapy is contentious. The rationale for investigating synchronous chemoradiotherapy was based on the tumor's high metastatic potential, its inherent chemosensitivity and radiosensitivity, and its similarity to small-cell carcinoma of the lung. This approach has become standard practice in the management of small-cell carcinoma of the lung, which has similar histologic morphology and biologic behavior to MCC.

The main aims of the study were to investigate the efficiency and safety of chemotherapy in MCC, and to determine whether this regimen could be delivered in a multi-institutional setting.

This is the first report in the literature, using a standard approach to MCC of the skin, that incorporates chemotherapy and radiation. Most reports have been from individual institutions and suffer from a lack of power because of the small numbers and inconsistent treatment regimens.

A preliminary report on the acute and late toxicity for this protocol was published after the first 40 patients had been treated.[1] We now report the overall survival, locoregional control, and distant metastases control rates achieved with the regimen, as well as updating the toxicity in all 53 patients treated with this protocol.

PATIENTS AND METHODS

Trial Design

Patients were only eligible for this study if they had disease confined to the primary or nodes region, and they were at high-risk of recurrence. This was defined as having at least one of the following criteria: primary size greater than 1 cm, involved nodes, recurrence following initial surgery (providing the recurrence was outside of the previous radiation field), gross residual disease after surgery, or occult primary with nodes.

In addition, the following eligibility criteria were required to be met: biopsy proven MCC confined to the primary and regional nodes, Eastern

From the Division of Oncology, Queensland Radium Institute; Royal Brisbane Hospital; Princess Alexandra Hospital; Department of Medical Oncology, Mater Medical Centre, Brisbane; the Department of Medical Oncology and the Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne; Department of Radiation Oncology, Newcastle Mater Misericordia Hospital, Newcastle, Australia.

Submitted March 24, 2003; accepted September 3, 2003.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Michael Poulsen, MD, Mater Queensland Radium Institute, Raymond Tee, South Brisbane, QLD 4101 Australia; e-mail: michael_poulsen@health.qld.gov.au.

0732-183X/03/2123-4371/$20.00

Cooperative Oncology Group performance status of 0 to 2, no previous malignancy in the past 5 years other than nonmelanomatous skin cancer, hemoglobin $>$ 10g/dL, neutrophils $> 2 \times 10^9$/L, platelets $> 100 \times 10^9$/L, and normal renal function (glomerular filtration rate $>$ 50 mL/min). The protocol was approved by each of the hospital ethics committees and written informed consent was obtained on all patients. Activation of the trial occurred in 1996 and closure occurred in 2001. The close out date for the analysis was July 8, 2002.

Pretreatment Evaluation

Paraffin sections were required to be reviewed at the treating hospital to confirm the diagnosis. All patients were evaluated with computed tomography of the chest and abdomen to exclude distant metastatic sites. Full blood count, electrolytes and liver function tests were also performed. Tumor extent was documented on diagrams.

Treatment

Surgery was often performed before referral to the oncology department. Furthermore, the extent of surgery was at the discretion of the local institution as it was thought impracticable to standardize in a heterogeneous disease population, across multiple institutions, and considered a less important factor in achieving locoregional control than the application of the trial's chemoradiotherapy regimen. However, it was recommended that the primary site be resected with clear margins where achievable. Wide surgical clearance of the primary site was not required nor recommended, and it was not a prerequisite to have nodal disease resected or positive margins re-excised.

Radiotherapy

The primary site was encompassed with a generous margin (3 to 5 cm) where possible. Wax build up (appropriate to photon or electron energy) was applied to all scars and primary and in-transit areas to ensure adequate dose to the surrounding dermal lymphatics. The draining lymph nodes were treated in continuity with the primary site, provided the nodes were within 20 cm of the primary.

A dose of 50 Gy (Internation Commission on Radiation Units and Measurements 50) in 25 fractions over 5 weeks was prescribed to macroscopically involved areas or to the operative bed. Electron doses were specified at the 90% isodose line. A shrinking field technique was used after 46 Gy if field volumes were large. Clinically uninvolved areas were treated to a dose of 45 Gy in 25 fractions over 5 weeks (eg, clinically uninvolved nodal areas that are outside the surgical volume). A dose reduction to 45 Gy was recommended for lesions located below the knee or areas where 50 Gy was thought to be poorly tolerated (eg, around the inguinal nodes or adjacent to the orbit).

Chemotherapy

Chemotherapy was administered during weeks 1 and 4 of radiotherapy, and then 2 weeks and 5 weeks after radiotherapy (weeks 7 and 10). Carboplatin dose was calculated according to the Calvert formula,[2] and was given intravenously on day 1 of each course of chemotherapy. Initially an area under the curve of 5 was recommended, but this was dropped to 4.5 in April 1998 when an interim review suggested that there were high levels of neutropenia.

Glomerular filtration rate was calculated according to the Cockcroft and Gault Formula or by measurement of Tc-99m DTPA clearance. The latter method, which was being used at one site, was abandoned as it resulted in higher doses of carboplatin and therefore, lack of uniformity in dose calculations between sites. Etoposide was given in a dose of 80 mg/m^2/d intravenously days 1 to 3. Once the radiation was completed, a further two cycles of chemotherapy were given in weeks 7 and 10, resulting in a total of four cycles. It was specified that the pretreatment neutrophil count should be $> 1.5\times 10^9$/L and platelet count should be $> 100 \times 10^9$/L. Blood counts were required weekly during the chemoradiotherapy. If the neutrophil or platelet count had not recovered by week 4, then the remainder of the chemotherapy was to be given once every 4 weeks (weeks 1, 5, 9, 13). Providing the counts had recovered, the option of once every 3 weeks chemotherapy remained. A dose reduction of carboplatin to AUC 4 and etoposide dose reduction of 20% was recommended if there was any grade 3 or 4 nonhematologic toxicity (excluding skin, hair loss, nausea, vomiting), grade 4 neutropenia, or fever with grade 3 or 4 neutropenia. Weight change of greater than 5% or a change in creatinine greater than 10 μmol/L required recalculation of the chemotherapy doses.

Quality Assurance

A detailed audit was performed on the first 20 patients to examine protocol compliance. This included a review of the clinical, chemotherapy, and radiation details, and an independent review panel outside of the treatment institution reviewed the pretreatment investigations, GFR calculations, and protocol violations for chemotherapy and radiotherapy.

Follow-Up

Acute toxicity was assessed weekly during the radiation therapy and during the third and fourth courses of chemotherapy. Thereafter, reviews monitoring disease status and long-term toxicity were conducted at minimum frequency of every 6 months until death.

Outcome Variables

The close out date for this analysis was July 8, 2002. Survival, locoregional control, and distant control were measured from the date of registration, and toxicity was measured from the start of the radiation treatment. WHO toxicity grading was applied to report acute toxicity. Late toxicity was scored using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system. Toxicity was plotted as actuarial cumulative probability over time. Patients were censored at death or date of last follow-up. Time to toxicity was defined as time from treatment start to the occurrence of the specified grade of toxicity. Late toxicity was graded provided a period of 168 days had elapsed from the start of treatment.

Statistical Methods

A generalized linear interactive modeling package was used to examine the data. χ^2 tests were used to compare proportions. All time-to-event curves were calculated using the actuarial method of Kaplan and Meier and were compared using the log-rank test. Overall survival considered any death as an event (including those from intercurrent illnesses). Locoregional control was defined as the proportion of patients who did not develop failure in the primary site, regional nodes or in-transit areas, with censoring of events occurring at death without locoregional failure. Distant control was defined as the proportion of patients not developing hematogenous spread, with censoring occurring at death in the absence of distant failure. Cox's proportional hazards model was used to derive hazards ratios for prognostic variables using the end points of overall survival, locoregional control, and distant control.

RESULTS

Patient Characteristics

A total of 53 patients were registered from six institutions in Australia. No patients were excluded from the analysis. The median potential follow-up time was 48 (range, 11–70) months and no patients were lost to follow-up. Twelve patients registered in the study presented with recurrence and had received prior therapy. The remaining 41 all received chemoradiotherapy as their initial treatment. No patients had received prior radiation treatment. In total, the chemoradiotherapy was given as an adjuvant treatment in 38 patients (72%) and as definitive therapeutic treatment in 15 patients (28%). The distribution of baseline characteristics is summarized in Table 1.

Table 1. Distribution of Baseline Characteristics (N = 53)

Parameter		No. of Patients
Median age, years	67	
Range	43-86	
Sex		
Male		39
Female		14
Site		
Head and neck		22
Upper limb		8
Lower limb		8
Trunk		2
Occult		13
T Stage		
Tx or unknown		14
T1		28
T2		11
N Stage		
N0		20
N1		21
N2		12
ECOG		
0		41
1		10
2		1
u/k		1
Surgery to primary site		
Nil		13
Excision/clear margins		28
Excision/close margins		5
Excision/involved margins		6
Gross residual		1
Surgery to nodes		
Nil		28
Biopsy		6
Nodectomy		4
Radical removal		15
Radiation dose, Gy		
Median	50	
Range	44-60	
Surgery to RT, days		
Median	47	
Range	14-872	
Chemotherapy courses completed		
1		2
2		3
3		2
4		46

Abbreviations: ECOG, Eastern Cooperative Oncology Group; u/k, unknown; RT, radiotherapy.

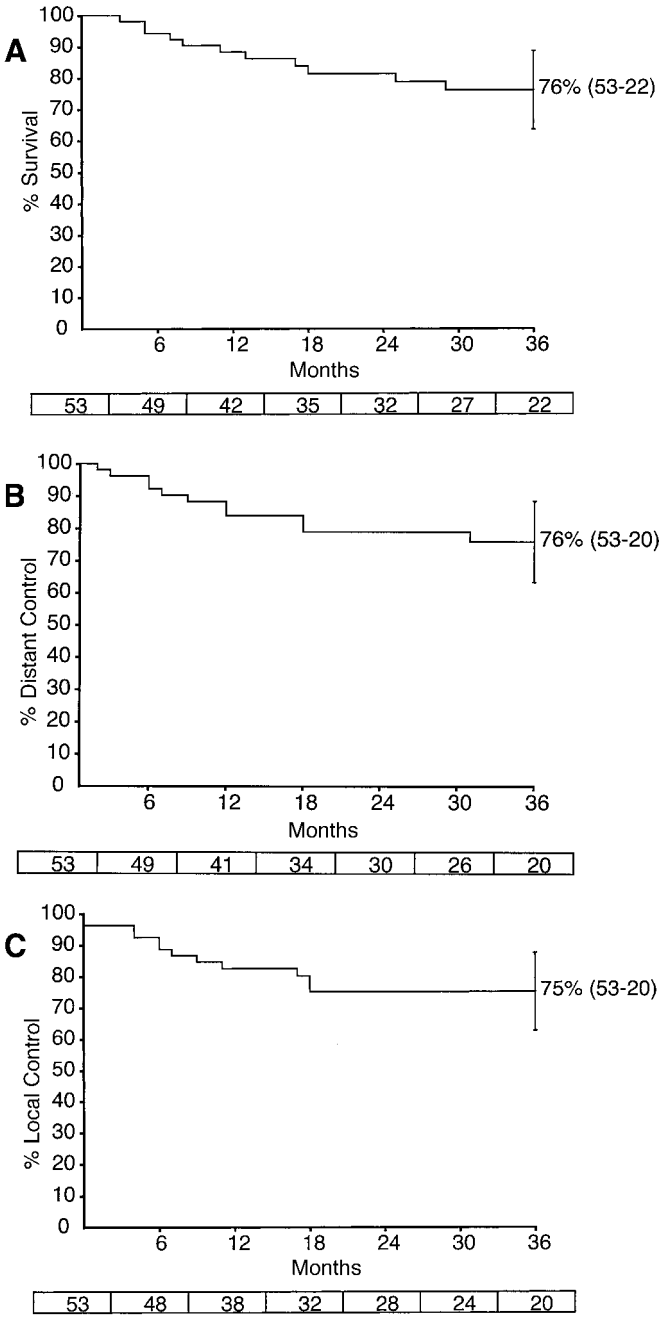

Fig 1. 3-year actuarial curves. The numbers of patients at risk for an event are tabulated below the plot. (A) Overall survival; (B) distant control; (C) locoregional survival.

Survival Analyses

The 3 year overall survival was 76% (95% CI, 63.5 to 88.7; Fig 1A). Relapse free survival was 65% (95% CI, 50.8 to 78.5) and distant control was achieved in 76% (95% CI, 63.4 to 88.7) of patients (Fig 1B). The 3-year survival for those with occult and known primary sites were 83% (95%CI, 61.5 to 100) and 74% (95% CI, 58.7 to 88.8), and distant control rates were 91% (95% CI, 73.9 to 100) and 56% (95% CI, 55.9 to 86.9), respectively.

Univariate analyses were performed by splitting the groups according to age, nodal status, site, and presence of gross residual disease at the time of chemoradiotherapy. The 3-year survival for patients with involved nodes compared with no nodal involvement was 66% and 93% ($P = .27$). Patients who had gross residual disease at the time of chemoradiotherapy had a poorer outcome of 45%, compared to 90% ($P = .07$).

Locoregional Control

Two patients had persistent disease at the end of chemoradiotherapy, both with primary site in the lower limb. The actuarial locoregional control at 3 years was 75% (95% CI, 62.7 to 87.5;

Table 2. Grades of Acute Reactions

	Grade				
	0	1	2	3	4
Skin	0	5	14	30	4
Nausea	13	29	6	5	0
Neutrophils	2	8	13	12	18
Hemoglobin	34	13	4	2	0
Platelets	39	6	3	4	1

Fig 1C). Locoregional control rates for occult and known primaries were 91% (95% CI, 73.9 to 100) and 70% (95% CI, 55.2 to 85.3), respectively. The locoregional control rate for the 38 patients who received adjuvant chemoradiotherapy was 77% (95% CI, 46 to 95.3), and for the 15 patients who received therapeutic chemoradiotherapy, the locoregional control rate was 71% (95% CI, 62.8 to 91.2). Locoregional failure at the primary site, in-transit areas, or the draining nodes occurred in nine of the 53 patients; seven of these occurred in the absence of distant disease and two in the presence of distant disease. The median time to locoregional recurrence was 187 (range, 0–544) days.

Acute Toxicity

Grade 3 and 4 reactions occurred in the skin in 34 patients (64%). Four of these reactions were grade 4. Neutropenia of grade 3 or higher occurred in 30 patients (57%) and febrile neutropenia occurred in 19 patients (35%). These results are tabulated in Table 2. Febrile neutropenia was most likely to occur at the nadir of the second cycle of chemotherapy when the radiation reactions in the skin or mucosa were most severe, providing a possible portal of entry for infection.

Late Toxicity

Grade 3 or higher late skin and subcutaneous toxicity was 15% and 13%, respectively, at 3 years. One patient developed acute arterial obstruction in the femoral vessels at the site of an inguinal radiotherapy field 4 years after registration in the study. The inguinal node had been resected before radiotherapy and radiotherapy/chemotherapy was delivered to the involved inguinal and iliac nodes as per protocol. This patient had experienced a grade 4 skin reaction in the groin and had severe late and subcutaneous changes present in the radiation field. She was also noted to have risk factors for peripheral vascular disease.

The obstruction was successfully treated with a bypass procedure but she went on to have an amputation 18 months later when the graft occluded.

Multivariate Analysis

The most powerful prognostic factor for overall survival was the presence of nodes. The hazard ratio for N1 and N2 disease was 4.34 and 76.71 respectively, the latter being statistically significant ($P = .001$). The presence of gross disease at the time of chemoradiotherapy had a hazard ratio of 0.82 indicating no increased risk of death as a result of incomplete disease resection before chemoradiotherapy.

Table 3. Cox's Proportional Hazards Modeling for Overall Survival

Covariate	Hazard Ratio	95% CI	*P*
Age			
< 67 years	1		
≥ 67 years	3.09	0.87 to 10.99	.08
Head and neck	1		
Upper limb	0.24	0.04 to 1.53	.13
Lower limb	4.18	0.83 to 21.16	.08
Trunk	4.41	0.45 to 43.57	.20
Occult	0.02	0.00 to 0.22	.002
N stage			
N0	1		
N1	4.34	0.8 to 23.46	.09
N2	76.71	5.76 to 1021	.001
No gross residual disease	1		
Gross residual disease	0.82	0.21 to 3.23	.78

The presence of nodes was not significant when locoregional control was used as an end point. Primary sites in the lower limb had a significant risk of locoregional failure with a hazard ratio of 12.67 ($P = .002$). The results of the Cox's proportional hazards modeling have been summarized in Table 3 and 4.

Quality Assurance

An audit of the first 20 patients indicated that the percentage of patients treated strictly according to protocol (with no variation in timing or dose) was 50% for chemotherapy and 55% for radiotherapy. Compliance with the recommended radiation dose was checked in all 53 patients. Patients were treated as per protocol (defined as ± 5%) in 83% of cases. Minor deviations in dose occurred in 9.5% of cases. Major dose deviations of an acceptable nature occurred in 7.5% of cases. There were no major deviations in dose of an unacceptable nature.

All four chemotherapy doses were given in 46 patients. There were two patients who received only one cycle, three that received two cycles, and two patients that received three cycles. In total there were 145 gaps or time intervals between the chemotherapy cycles. One hundred and thirty one (90.3%) of these time intervals were as per protocol (< 27 days). Prolon-

Table 4. Cox's Proportional Hazards Modeling for Locoregional Control

Covariate	Hazard Ratio	95% CI	*P*
Age			
< 67 years	1		
≥ 67 years	0.37	0.11 to 1.25	.11
Head and neck	1		
Upper limb	0.3	0.03 to 3.01	.31
Lower limb	12.67	2.59 to 61.86	.002
Trunk	0.01	0.00 to 13555243	.67
Occult	0.09	0.01 to 1.19	.07
N stage			
N0	1		
N1	1.33	0.20 to 8.92	.77
N2	6.46	0.51 to 82.36	.15
No gross residual disease	1		
Gross residual disease	1.26	0.20 to 7.71	.80

gations of 8 to 14 days beyond the recommended interval occurred in 12 (8.3%) occasions and on two occasions there were prolongations of greater than 28 days.

DISCUSSION

Unlike previous reports in the literature, this group of patients has been prospectively assessed and treated with a uniform protocol of chemoradiotherapy with curative intent. There has been a high level of compliance in the delivery of the radiation dose and 87% of the patients were able to complete all four courses of chemotherapy. Only 9.7% of patients had protracted intervals greater than the recommendations in the protocol.

The extent of the surgical treatment of primary and nodal disease could not be rigorously standardized in this trial because of the heterogeneity of disease status and the variety of anatomic locations in this rare skin malignancy. Furthermore, surgery was frequently performed before referral to the oncologist, and there is no evidence that further radical surgery would confer any benefit to locoregional control over and above this radical chemoradiotherapy trial regimen. Conversely, delaying the chemoradiotherapy treatment to undertake further radical surgery (that was likely to reduce tolerance of the trial regimen) was considered potentially detrimental to tumor control by reducing treatment efficacy.

Although the treatment protocol was standardized for the chemotherapy and radiation therapy, the patient population was relatively heterogeneous in terms of patient and tumor parameters. The study only included patients who were perceived to be at high risk of recurrence, but they had to be fit enough to tolerate chemoradiation. All reported Merkel cell carcinoma studies suffer from some degree of heterogeneity in the patient population, and this limits the ability to compare since any differences detected may be as a result of patient selection rather than the treatment itself. The heterogeneity in this study should be less than others as we have confined our study group to patients that have high-risk locoregional disease, but good performance status; that is, patients with low-risk disease, distant metastatic disease, or poor performance status are excluded. Nevertheless, it is acknowledged that there are real limitations in comparing these results with others in the literature.

Prognostic factors have been well described in previous reports[3-12] and a recent review by Goessling et al[13] summarizes these. In comparing these results with those reported in the literature, it is important to match the proportion of patients with adverse prognostic variables, the most important being the presence of nodal metastases.[3-7] Thirty-three patients (62%) registered on this study had involved nodes (stage II) at presentation. This contrasts with the literature where the reported incidence of nodes at presentation varied from 9% to 33%,[3-5,8-11] and confirms the particularly poor prognostic profile of patients in this trial (being at high risk of disseminated disease).

The 3-year survival of 76% compares favorably with others in the literature. Meeuwissen et al[3] reported 68% 3-year survival for a group of 80 patients (33% had stage II disease) treated at the Queensland Radium Institute, and Morrison et al[4] achieved 30% 5-year survival for a group of 54 patients (16% had stage II disease). Other reports claim 63% 5-year survival (20% had stage II disease);[14] 58% 3-year survival (26% had stage II disease);[5] 64% 5-year survival (31% had stage II disease);[6] 35% 3-year survival (9% had stage II disease);[10] and 40% 5-year survival (18% had stage II disease).[15]

Eleven (21%) of 53 patients suffered locoregional failure, and the 3-year actuarial locoregional control was 75%. In a review of the literature, Haag et al[16] reported that local recurrence developed in 26% to 44% of patients, and during the course of the disease, 55% to 66% of patients developed regional node metastases. Given that 28% of patients had gross disease at either the primary site or the nodes, and 36% had recurrence before registering on the study, these figures compare favorably with those in the literature.

Distant control at 3 years for the whole group was 76%, or looking at the crude figure, nine (17%) of 53 patients developed distant metastases. Early reported series quote rates of distant metastatic disease to be 30%,[14,16,17] with some as high as 70%.[8] This does suggest that chemotherapy may have had a positive influence in reducing distant metastatic disease. However, great caution must be taken in interpreting this data, given the significant diversity of patients, stages of disease, and various methods of reporting in these series.

Occult primaries have been reported in a number of MCC series. The incidence varies from 0% to 18%,[3,4,8,15] and can be attributed to spontaneous regression of the primary[18] or metastatic neuroendocrine carcinoma from a noncutaneous site. The incidence in this series was proportionally higher (25%) and may be as a result of several factors. Excluding patients with primaries less than 10 mm from entering the study could have caused a relative increase in numbers with an occult primary. The hazard ratio for occult primaries was 0.02, indicating that this was a favorable prognostic variable. This may have biased the results of this series favorably compared with some of the historic series. Although the superior outcome in the occult primary group is counterintuitive, a possible explanation could be that patients with occult primaries have had an immunologic response to their cancer.

A detailed report on toxicity was made after the first 40 patients were treated.[1] This suggested that the most threatening side effect was associated with neutropenia. The incidence of febrile neutropenia was highest after the second cycle of chemotherapy, which coincided with maximal radiation skin reactions. It is postulated that this provided a portal of entry for bacteria at a time when the white cell count was low. We are now embarking on a pilot study aimed at reducing the incidence of febrile neutropenia. Patients will be treated with radiotherapy to a dose of 45 to 50 Gy with synchronous weekly carboplatin in a dose of AUC 2.0 to a maximum of five courses. This will be followed by three cycles of carboplatin and etoposide in the same doses in TROG 96:07. If the toxicity of this schedule is acceptable, it may form the basis of an experimental arm of a phase III randomized trial. International collaboration will be required for such as a study. The acceptability of a radiation-alone arm may cause some difficulties in the future. However,

this will be the only way to overcome the biases that occur when retrospective comparisons are made with historical controls.

This prospective phase II study demonstrates that chemoradiotherapy with curative intent for high risk MCC is tolerable for the vast majority of patients. Results indicate that despite the high proportion of patients with nodal metastases and gross residual disease at the time of chemoradiotherapy, 76% of patients were alive at 3 years. This survival and favorable locoregional and distant control rates appear superior to reported retrospective series in the literature even though it is recognized that we are comparing a diverse range of patients with MCC. However, a phase III study is needed if the true magnitude of the benefit of synchronous chemotherapy is to be defined.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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