Cutaneous Merkel Cell Carcinoma

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Introduction

Cutaneous Merkel cell carcinoma (MCC) is a rare neuroendocrine malignancy [1–3]. The age-adjusted incidence is approximately 0.24–0.44 per 100,000 person years [3]. Risk factors for MCC are sun exposure and immune suppression, including chronic lymphocytic leukemia (CLL), solid organ transplant, and human immunodeficiency virus (HIV) [4–6]. Human polyoma virus (MCPyV) appears to be etiologic in a significant proportion of patients with MCC; the presence of MCPyV DNA in the MCC cells may be associated with an improved prognosis [5]. MCC exhibits a slight male preponderance [2, 7]. The vast majority (over 90–95 %) are Caucasian and approximately 90 % are over 50 years of age [3, 7, 8]. The most common sites include the head and neck and extremities. Andea and colleagues reported on 156 patients and observed the following site distribution: extremity, 42 %; head and neck, 37 %; buttocks, 16 %; and trunk 5 % [3].

The majority of MCCs appear relatively innocuous at diagnosis. Most are 2 cm or less in size and the patients are usually asymptomatic [8]. The most common color is red/pink in over 50 % of patients, followed by blue/violaceous [8]. The lesion is often thought to be benign prior to biopsy [8].

The diagnostic evaluation of the patient includes taking a thorough history, physical examination, chest radiograph, and computed tomography (CT) of the primary site and regional lymphatics. Fluourodeoxyglucose-positron emission tomography (FDG-PET)-CT will likely contribute to altered staging and a change in the treatment plan and should be obtained in most patients [9]. The value of sentinel lymph node biopsy (SLNB) is debatable and depends on treatment philosophy [10]. On the one hand, if patients with a pathologically negative SLNB are to be followed and

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adjuvant nodal RT withheld, then SLNB would be valuable to define this subset of patients. Additionally, one could argue that those with pathologically positive SLNBs could be considered for adjuvant chemotherapy because of the increased risk of distant metastases [11]. However, adjuvant chemotherapy has not been shown to improve outcome in high-risk patients and, because of the high likelihood of subclinical disease in clinically negative regional nodes, it is the author's bias to electively irradiate these regions regardless of SLNB status [11, 12]. Thus, in the latter instance, SLNB does not meaningfully contribute to management decisions.

Several staging systems have been described for MCC [13, 14]. The staging system described by Yiengpruksawan et al. is straightforward and has been widely used: stage I, local disease; stage II, regional disease; and stage III, distant metastasis [13]. The staging system described by the American Joint Committee in Cancer (AJCC) is more complex and is ill-suited to an entity that is relatively rare and where the number of patients included in most single institution outcome studies is relatively small [14]. Mojica et al. reported the following stage distribution in 1,665 patients from the Surveillance Epidemiology and End Results (SEER) database: stage I, 55 %; stage II, 31 %; stage III, 6 %; and no data, 8 % [7].

Surgery and radiotherapy (RT) are the mainstays of treatment for patients with stage I and II MCC [10, 12, 15–20]. Although a subset of patients with stage I disease may be managed with surgery alone, the high likelihood of subclinical disease in the clinically negative regional lymphatics and the modest risk of in-transit metastases suggest that the majority of patients benefit from the addition of RT [7, 20]. Patients with stage II disease have approximately a 75 % local-regional control rate after RT alone or combined with surgery [15, 17]. Although debatable, the addition of surgery to RT probably results in improved local-regional control [15–17, 21].

Radiation Therapy Technique

The RT techniques are the same as those employed for squamous cell carcinoma as are the dose fractionation schedules. Treatment techniques vary with primary site and the location of the first echelon lymph nodes. Dose fractionation schedules vary with the suspected or known amount of disease: elective nodal RT, 50 Gy/25 fractions; negative margins postoperatively, 60 Gy/30 fractions; positive margins postoperatively, 66 Gy/33 fractions; and gross disease, 70 Gy/35 fractions.

Treatment Outcomes

The optimal management of patients with cutaneous MCC is not well-defined in large part due to the relative rarity of the disease. Questions include whether surgery and adjuvant RT improves outcomes compared with surgery alone, the relative

Table 1 Five-year outcomes vs. stage

Outcome	Stage I ($N=24$) (%)	Stage II ($N=16$) (%)	All patients (%)	p-Value
Local control	96	87	92	0.3240
Regional control	87	65	78	0.1587
Local-regional control	87	67	79	0.1607
Distant metastasis-free survival	71	37	57	0.0073
Cause-specific survival	58	27	45	0.0090
Overall survival	48	18	36	0.0037

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efficacy of RT alone compared with surgery and RT, and the efficacy of adjuvant chemotherapy. The following is a discussion of some of these issues.

Mendenhall et al. reported on 40 patients treated with curative intent for de novo MCC with surgery and adjuvant RT (37 patients) or RT alone (3 patients) at the University of Florida between 1984 and 2009 [22]. Adjuvant chemotherapy was administered to 11 patients (28 %). Median follow-up for surviving patients was 4.2 years (range, 2.2–14.2 years). No patients were lost to follow-up. Treatment outcomes are depicted in Table 1. No patients experienced a severe late complication.

Fang et al. reported on 50 patients treated at the University of Washington between 1985 and 2007 for microscopically positive (26 patients) or macroscopically positive (24 patients) nodes [15]. The 2-year regional control rates for 26 patients with microscopically positive SLNBs were 100 % whether the patients were treated with RT alone (19 patients) or neck dissection with or without RT (7 patients). The median follow-up for this subset of patients was 18 months (range, 5–62 months). The 2-year regional control rates for those with macroscopically positive nodes were 78 % after RT alone (9 patients) compared with 73 % after surgery alone or combined with RT (15 patients) ($p=0.8$). The median follow-up was 16 months (range, 5–109 months). The authors concluded that RT alone results in equivalent regional control compared with surgery alone or combined with RT for patients with positive regional nodes. Caveats pertaining to this study are that selection bias could have impacted outcomes, the number of patients is relatively small, and the follow-up is short.

Veness and co-workers reported on an unfavorable series of 43 patients treated at Westmead Hospital (21 patients) and Royal Brisbane/Mater Hospital (22 patients) between 1993 and 2007 with RT alone for medically or technically inoperable MCC [17]. RT was delivered at initial diagnosis in 24 patients (56 %) and for recurrence in the remainder (usually nodal recurrence in a previously untreated nodal basin). The median maximum tumor diameter was 3 cm (range, 0.5–13 cm). The median follow-up was 39 months (range, 4–78 months). The median RT dose to the primary lesion was 51 Gy; the median RT dose to the nodes was 50 Gy. The median dose per

fraction was 2 Gy. Recurrence developed in 60 % of patients; 15 (35 %) of 45 patients recurred outside of the RT fields. The in-field control rate was 75 % and the 5-year overall survival rate was 37 %. Interesting points regarding this study are that the in-field control and 5-year survival rates are surprisingly favorable after relatively modest dose RT in an unfavorable series of patients.

Foote et al. reported on 112 patients treated with curative intent RT between 2000 and 2005 at three public radiotherapy treatment centers in Queensland, Australia [18]. Nine patients were treated for recurrent MCC and 103 patients were previously untreated. RT was delivered to the primary site in 88 % of patients for gross (11 %) or subclinical (78 %) disease and to the regional nodes in 89 % of patients, mostly for subclinical disease (71 %). Gross nodal disease was treated with RT in 19 % of patients. The likelihood of failure in the clinically negative regional nodes was 33 % for those who did not receive elective nodal irradiation (ENI), which was significantly higher than for those who did receive ENI. The likelihood of in-field disease control was higher for those who received ≥50 Gy for subclinical disease and ≥55 Gy for gross disease.

Clark and colleagues reported on 110 patients with head and neck MCC treated at Princess Margaret Hospital (Toronto), Westmead Hospital (Sydney), and the Royal Prince Alfred Hospital (Sydney) with either surgery or RT (44 patients) or combined surgery and adjuvant RT (66 patients); survivors had a mean follow-up of 2.3 years [19]. The 5-year local control rate was 84 %; the 5-year regional control rate was 69 %. Surgery and adjuvant RT resulted in improved local control ($p=0.009$) and regional control ($p=0.006$) compared with single modality therapy. The 5-year cause-specific and overall survival rates were 62 % and 49 %, respectively. Combined modality treatment resulted in improved disease-free survival ($p=0.013$) compared with single modality therapy.

Mojica et al. reported on 1,665 patients included in the SEER database from 1973 to 2002; 1,487 patients (89 %) received surgery as a component of their therapy [7]. Adjuvant RT was administered to approximately 40 % of the surgically treated patients and was associated with a significant improvement in median survival compared with surgery alone (63 months vs. 45 months, $p=0.0002$).

Poulsen and co-workers reported on 40 patients with high-risk MCC who received adjuvant chemotherapy according to the Trans-Tasman Radiation Oncology Group TROG 96:07 study from 1997 to 2001 [11]. Patients had ≥1 of the following high-risk factors: recurrent disease, positive nodes, primary tumor size >1 cm, and gross residual disease after surgery. The primary site and regional nodes received 50 Gy/25 fractions/5 weeks and patients received concomitant carboplatin (AUC 4.5) and etoposide 80 mg/m^2 on days 1–3 of weeks 1, 4, 7, and 10. Patients were compared with a historic group of 62 patients treated between 1988 and 1996 with surgery and RT. Multivariate analyses revealed that the following factors significantly impacted treatment outcomes: (1) overall survival-recurrent disease, age, and presence of residual disease; (2) cause-specific survival-recurrent disease; (3) local-regional control-lower extremity primary site; and (4) distant metastasis-free survival-residual disease. The data suggest that adjuvant chemotherapy had no significant impact in any of the treatment outcomes, including survival.

Conclusion

The likelihood of local-regional control is relatively high after RT alone or combined with surgery. Our treatment philosophy, which does not vary with primary site, is to proceed with surgery if a gross total resection (R0 or R1) can be achieved followed by postoperative RT. An elective node dissection is not indicated because elective nodal RT is likely to be as effective and is employed in all clinically N0 patients. Similarly, SLNB is not required because it does not alter the treatment plan. Our dose fractionation guidelines are similar to those employed for squamous cell carcinoma. Patients with medically or technically unresectable gross disease are treated with RT alone. Although relatively high in-field control rates have been reported with moderate dose RT, our bias is to treat aggressively to 70 Gy in 35 fractions over 7 weeks or to employ altered fractionation, such as 74.4 in 62 twice-daily fractions over 6.5 weeks. Although the dominant failure pattern is distant, there is no convincing evidence that adjuvant chemotherapy improves the likelihood of cure. On the other hand, given the rarity of cutaneous MCC and the existing data, it is not possible to definitively state that adjuvant chemotherapy is ineffective. Patients at particularly high risk for distant relapse, such as those with recurrent disease and/or multiple positive nodes, may be considered for a chemotherapy regimen similar to those used for small cell neuroendocrine carcinoma (i.e., cisplatin and etoposide) given concomitantly with RT.

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