Treatment Options for Merkel Cell Carcinoma

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Key Words
Merkel cell carcinoma, neuroendocrine carcinoma of the skin, sentinel lymph node biopsy, adjuvant radiation therapy, adjuvant chemotherapy

Abstract
Merkel cell carcinoma (MCC) or neuroendocrine carcinoma of the skin is commonly seen in men (male:female ratio, 1.4:1). It is predominantly a cancer of the older population, with a mean age at diagnosis of 69 years (range, 18 to 98 years). MCC occurs almost exclusively in the Caucasian population (98%) and has been causally associated with excessive sun exposure. Solar keratoses and squamous or basal cell carcinoma of the skin are frequently associated with MCC. Limitation of sun exposure and use of sun-blocking lotions may reduce its incidence. Immunosuppressive therapy is associated with the onset of MCC in nearly 15% of cases.

Merkel cell carcinoma (MCC) or neuroendocrine carcinoma of the skin is an uncommon cancer, which is often aggressive and associated with a poor prognosis. In 1972, Toker described it as trabecular cell carcinoma. Because MCC is uncommon, no consensus has been reached regarding optimal therapy. The relative roles of surgery, radiation therapy, and chemotherapy have remained controversial. We recently reported on our experience with MCC at the University of Alabama at Birmingham and presented an extensive review of the English language literature.

The three-year overall survival for patients with MCC is only 31%, and the extent of disease at presentation is predictive of outcome. Before an improvement in long-term survival can be realized, early detection, appropriate use of surgery and radiation therapy, and the development of effective systemic chemotherapy are required.

Merkel cells are located in the basal layer of the epidermis and are closely associated with terminal axons. MCC is seen more frequently in men (male:female ratio, 1.4:1). It is predominantly a cancer of the older population, with a mean age at diagnosis of 69 years (range, 18 to 98 years). MCC occurs almost exclusively in the Caucasian population (98%) and has been causally associated with excessive sun exposure. Solar keratoses and squamous or basal cell carcinoma of the skin are frequently associated with MCC. Limitation of sun exposure and use of sun-blocking lotions may reduce its incidence. Immunosuppressive therapy is associated with the onset of MCC in nearly 15% of cases.

MCC usually presents as a solitary, painless, dermal nodule with a slightly erythematous to deeply violaceous color. It occurs most frequently in the sun-exposed skin of the head, neck, and extremities (Table 1), with a predilection for the periocular region. It involves regional lymph nodes at presentation in up to 45% of cases, and regional lymph node metastases develop in up to 75% of cases at some time during the course of the cancer. Distant metastases develop in up to 50% of cases, with the most common sites of involvement being distant lymph nodes (60%), distant skin (30%), lung (23%), central nervous system (18%), and bone (15%). After excision of the primary cancer, local recurrence has been reported to develop in up to 53% of patients, recurrence often being associated with inadequate surgical margins.
MCC is found within the dermis but may extend into the subcutaneous tissues. Histologically, it has been classified into three distinct subtypes: trabecular, intermediate, and small cell.

**Trabecular**
Trabecular is the least frequent histologic pattern of MCC identified. The cells are arranged in distinct clusters and trabeculae. They are round to polygonal in shape and are compactly arranged with abundant cytoplasm. Mitoses are few in number. This type of MCC is found adjacent to adnexal structures, particularly hair follicles.

**Intermediate**
Intermediate is the most frequent histologic subtype of MCC identified, and it behaves in a more aggressive manner than the trabecular type. It exhibits both solid and diffuse growth patterns. The cells are less compactly arranged, and the cytoplasm is less abundant. Mitoses and focal areas of necrosis are frequently seen. This type of MCC also arises adjacent to adnexal structures, but may invade the epidermis.

**Small Cell**
This histologic pattern of MCC mimics small cell carcinoma of other sites and exhibits aggressive behavior. It arises in the dermis and appears as solid sheets and clusters of cells. Areas of necrosis are frequently seen.

Pretherapy assessment of the MCC patient includes a complete history and physical examination, chest radiograph, and liver function studies. Brain, chest, abdominal, and pelvic computed tomography (CT) scans are employed when necessary. Positron-emission tomography (PET) and octreotide scans are currently being investigated for detection and follow-up of distant or recurrent disease. No standardized staging classification has been created for MCC, but based on clinical presentation, MCC has been categorized as follows:

**Stage I:** Primary cancer with no regional lymph node involvement or distant metastases. Most MCC presents in this fashion (Table 2).

**Stage II:** Primary cancer with regional lymph node involvement but no distant metastases.

**Stage III:** Primary cancer with or without regional lymph node involvement and with distant metastases.

### Treatment Options

#### Primary Cancer

Because of a historically high recurrence rate after treatment using local excision alone, complete surgical excision with histologic documentation of clear resection margins is now recommended for primary MCC. Moh’s surgery, Moh’s surgery followed by an additional margin for permanent section assessment, local excision with permanent section assessment of all peripheral and deep margins, and 1- to 2-cm wide local excision with extension of the resection to the underlying muscle fascia or periosteum are recommended. We use wide local excision with a 1- or 2-cm margin of grossly uninvolved skin and subcutaneous tissue for the primary MCC. We extend our resection down to the fascia of underlying muscle or to periosteum and always employ permanent section control of the surgical margins. Adjuvant radiation therapy to the primary site has been advocated by some, whereas others have found no benefit from adjuvant radiation therapy after adequate surgical therapy. In general, radiation therapy has been recommended for larger or unresectable cancers and for cancers that approach the surgical margins of resection or show lymphovascular

### Table 1 Anatomic Location of Primary MCC

<table>
<thead>
<tr>
<th>Location</th>
<th>UAB Experience (n = 16)</th>
<th>Literature Review (n = 1024)</th>
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</thead>
<tbody>
<tr>
<td>Head and Neck</td>
<td>63%</td>
<td>41%</td>
</tr>
<tr>
<td>Trunk</td>
<td>0</td>
<td>23%</td>
</tr>
<tr>
<td>Extremities</td>
<td>37%</td>
<td>33%</td>
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<tr>
<td>Unknown</td>
<td>0</td>
<td>3%</td>
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### Table 2 Stage at Presentation

<table>
<thead>
<tr>
<th>Stage</th>
<th>UAB Experience (n = 16)</th>
<th>Literature Review (n = 1024)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>63%</td>
<td>73%</td>
</tr>
<tr>
<td>II</td>
<td>37%</td>
<td>23%</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>4%</td>
</tr>
</tbody>
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invasion. Total radiation doses of 40 to 60 Gy have been used.\textsuperscript{11,13,15,17} For unresectable cancers or when gross cancer is found at the margins of resection, doses of 56 to 65 Gy have been recommended.\textsuperscript{11}

Like other neuroendocrine carcinomas, MCC is considered radiosensitive, although variation in radiosensitivity has been reported in small cell carcinoma cell lines.\textsuperscript{20} Although no evidence has been found in the English language literature that adjuvant radiotherapy prolongs survival in MCC, retrospective analysis of clinical data strongly suggests that local control of cancer is improved.\textsuperscript{2,7,8} Total radiation doses of 45 to 50 Gy, at 2 Gy per fraction to the resection bed, have been recommended for the adjuvant setting.\textsuperscript{21} Although adjuvant radiation therapy improves local control, marginal recurrences have been described. Of 31 patients treated at the M. D. Anderson Cancer Center, only one patient developed an in-field recurrence, but three patients developed marginal recurrences.\textsuperscript{21} We recommend that the radiation ports encompass a treatment field that extends 3 to 5 cm beyond the area of surgical resection.

**Regional Metastases**

Lymphatic dissemination occurs often and early in MCC. Although general agreement exists that the presence of regional lymph node metastases portends a worse prognosis, the role of elective lymph node dissection (ELND) for stage I MCC is controversial.\textsuperscript{2,5–9} It has been recommended for larger cancers, for cancers with more than 10 mitoses per high-power field, for the small cell histologic subtype, and for cancers that show lymphovascular invasion.\textsuperscript{11,12,14}

Currently, the role of sentinel lymph node biopsy is being investigated. We have employed this technique in eight stage-I MCC patients treated at the University of Alabama at Birmingham between August 1998 and May 2003 (Table 3). All patients were Caucasian men and had a primary MCC of an extremity. The median age was 60 years (range, 44 to 80 years). All patients underwent preoperative lymphoscintigraphy, and, intraoperatively, the sentinel lymph node was identified by gamma counter and isotopically blue dye localization. In three cases, the sentinel lymph node contained metastases found using hematoxylin and eosin (H&E) staining, and subsequent regional lymph node dissection was performed. In two of these cases, no other metastases were found, and in the third case, 21 of 30 regional lymph nodes removed contained metastases. In five cases in which the sentinel lymph node was free of metastases according to H&E staining, neither ELND nor elective regional radiotherapy was employed. After a median follow-up of 16 months (range, 3 to 27 months), one of these patients (20%) had developed a regional recurrence and subsequently underwent regional lymph node dissection. When no palpable lymphadenopathy is present, our current practice is to perform sentinel lymph node biopsy with regional lymph node dissection only when metastases are identified.

**Distant Metastases**

Chemotherapy frequently is used for patients with stage III MCC.\textsuperscript{11,12,22,23} Chemotherapy regimens similar to those employed for small cell carcinoma of the lung have been recommended. Paclitaxel or etoposide in combination with platinum compounds have been shown to have definite activity in patients with advanced MCC. Doxorubicin-containing regimens have been used also. Although patients initially respond well to chemotherapy, the responses are usually short-lived.

**Recurrent Cancer**

Patients with recurrent cancer are treated based on their initial therapy. Recurrent primary cancers are resected if possible. We have selectively employed hyperthermic isolated limb perfusion (Fig. 1) for local recurrence of extremity MCC.\textsuperscript{24} Regional lymph node dissection is appropriate for regional lymph node metastases. Chemotherapy may be an option for patients with unresectable recurrent cancers or for patients who have already received adjuvant radiation therapy.

In summary, MCC is an aggressive cancer with high rates of regional and distant metastases. Complete surgical excision of the primary cancer with histologic documentation of clear resection margins is an essential component of successful treatment. Adjuvant external beam radiotherapy provides for improved local

<table>
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<th>Table 3 Sentinel Lymph Node Biopsy for Extremity MCC</th>
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<tbody>
<tr>
<td>Sentinel Node</td>
</tr>
<tr>
<td>With Metastases</td>
</tr>
<tr>
<td># of Cases</td>
</tr>
<tr>
<td>Regional Lymph Node Dissection Performed</td>
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<tr>
<td>Regional Recurrence</td>
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control. Sentinel lymph node biopsy is a useful method of determining the need for regional lymph node dissection in stage 1 patients. Chemotherapy regimens similar to those employed for small cell carcinoma of the lung are recommended for advanced cancers, but responses to therapy usually are short-lived.

References