Merkel Cell Carcinoma: Critical Review With Guidelines for Multidisciplinary Management

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Received February 2, 2007; revision received March 16, 2007; accepted March 20, 2007.

Merkel cell carcinoma (MCC) is a relatively rare cutaneous malignancy that occurs predominantly in the older white population. The incidence of MCC appears to have tripled during the past 20 years; an increase that is likely to continue because of the growing number of older Americans. The pathogenesis of MCC remains largely unknown. However, ultraviolet radiation and immunosuppression are likely to play a significant pathogenetic role. Many questions currently remain unanswered regarding the biologic behavior and optimal treatment of MCC. Large, prospective, randomized studies are not available and are unlikely to be performed because of the rarity of the disease. The objective of this review was to provide a comprehensive reference for MCC based on a critical evaluation of the current data. The authors investigated the importance of sentinel lymph node biopsy as a staging tool for MCC to assess the status of the regional lymph node basin and to determine the need for additional therapy to the lymph node basin. In an attempt to standardize prospective data collection with the intention to define prognostic indicators, the authors also present histopathologic profiles for primary MCC and sentinel lymph nodes. The controversies regarding the appropriate surgical approach to primary MCC, the use of adjuvant radiation therapy, and the effectiveness of adjuvant chemotherapy were examined critically. Finally, the authors have provided treatment guidelines based on the available evidence and their multidisciplinary experience. ***Cancer* 2007;110:1–12.** © *2007 American Cancer Society.*

KEYWORDS: literature review, Merkel cell carcinoma, multidisciplinary management, sentinel lymph node biopsy, histopathologic profile.

An increasing number of patients presenting with Merkel cell carcinoma (MCC) during the past 2 decades has focused attention on this cutaneous malignancy, which is seen primarily in older individuals. Based on the projection that, by 2030, 1 in 5 Americans will be aged $\geq$65 years, the increasing trend in MCC incidence is likely to continue.[1] Currently, information regarding the biologic behavior and optimal treatment of MCC is limited given the paucity of high-level evidence and the absence of prospective, randomized trials. The objective of this review was to create a current reference for those involved in the care of patients with MCC or the investigation of this potentially aggressive malignancy. This review was based on a critical evaluation of the available data using an extensive PubMed search combined with our experience in the University of Michigan Comprehensive Cancer Center Multidisciplinary MCC program.

Epidemiology

The incidence of MCC is low compared with the incidence of other cutaneous malignancies. However, the trend is toward an increasing

DOI 10.1002/cncr.22765
Published online 22 May 2007 in Wiley InterScience (www.interscience.wiley.com).

number of cases. Based on data from the U.S. Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI), the age-adjusted MCC incidence rate has tripled from 0.15 per 100,000 in 1986 to 0.44 per 100,000 in 2001 (≈1400 cases per year). This represents an annual 8% increase for MCC during this period compared with a 3% increase for melanoma.[2] MCC is 24 times more common in individuals aged >65 years than in individuals aged <65 years, and only 5% of cases are diagnosed before age 50. The majority of patients (94%) who are diagnosed with MCC are white. A slight male predominance is reported by most studies.[2–4]

Risk Factors

Several observations support the hypothesis that ultraviolet (UV) radiation may be a pathogenetic factor in MCC. Most MCCs are located on sun-exposed areas of the skin.[3,4] SEER data from various geographic locations have revealed a correlation between solar UV-B indexes and regional differences in MCC incidence.[5] A 100-fold increase in MCC incidence has been reported in patients with psoriasis who were treated with UV-A and methoxsalen.[6] The concomitant occurrence of MCC and squamous cell carcinoma (SCC) lends further support to the association with UV exposure.[7]

Indirect evidence of an association between MCC and immunosuppression is plentiful. In 1 large series, 14.5% of patients with MCC were receiving or had received immunosuppressive therapy.[4] A transplantation tumor registry reported 48 patients with MCC, mostly in renal transplantation recipients (93%).[8] In contrast to MCC in the general population, 49% of transplantation patients with MCC were aged ≤50 years. The ratio of posttransplantation melanoma to MCC is 6:1 compared with 65:1 in the general population.[9] Several other cases of MCC associated with iatrogenic immunosuppression have been reported.[10,11]

In patients with human immunodeficiency virus or acquired immunodeficiency syndrome, the relative risk of MCC is 13.4 compared with the general population.[12] An increased rate of other malignancies in patients with MCC further supports an impaired immune status in the pathogenesis of some cases of MCC. An increased risk of MCC as a second primary malignancy has been identified among patients with multiple myeloma, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and melanoma.[13] Several cases of MCC have been linked to chronic arsenic exposure, implicating this carcinogen in the pathogenesis of MCC in these patients.[14]

Molecular Pathogenesis

Cytogenetic analysis has revealed several chromosomal abnormalities in MCC tumors and cell lines. Structural aberrations involving the short arm of chromosome 1 (1p) have been observed in 40% of the patients studied.[15] Loss of heterozygosity on 1p occurs frequently in MCC, leading to the hypothesis that one or more tumor suppressor genes on 1p may play a pathogenetic role.[16] Although the localization of proto-oncogenes related to other neural crest-derived tumors, such as neuroblastoma and melanoma, has focused further attention to this region, no conclusive candidate genes have been identified in MCC. UV-B-specific mutations in the *p53* and *Ha-ras* genes are observed commonly in MCC and cutaneous SCC. Farnesylthiosalicylic acid, which is an inhibitor of ras signal transduction, has been shown to up-regulate p53 and induce apoptosis and inhibition of tumor growth in human MCC in a severe combined immunodeficiency (SCID) mouse model.[17] High expression of the *bcl*-2 proto-oncogene, which is capable of inhibiting apoptosis, thereby promoting cell survival and contributing to tumor growth, was observed in 5 of 10 patients with MCC, although no relation between gene expression and survival was observed.[18] *Bcl*-2 antisense treatment did result in a dramatic reduction of tumor growth and complete remission in an SCID mouse model.[19] Activation of the mitogen-activated protein kinase signaling pathway through oncogenic mutations in *BRAF*, which are observed commonly in melanoma, was not observed in MCC, indicating that other signal transduction pathways are most likely involved.[20]

The Merkel Cell

In 1875, Friedrich Sigmund Merkel described large, pale cells in the basal layer of the epidermis forming synapse-like contacts with enlarged nerve terminals.[21] These cells, now commonly referred to as Merkel cells, function as mechanoreceptors. Merkel cells resemble cells of the diffuse neuroendocrine system, or amine precursor uptake decarboxylation system. Ultrastructurally, the cells are characterized by a lobulated nucleus, finger-like protoplasmic protrusions, and cytoplasmic dense-core granules facing the nerve terminal. Low-molecular-weight cytokeratins (CKs), CK-20 in particular, are highly specific markers for light microscopic identification of Merkel cells.[22] The neural crest origin of Merkel cells has been confirmed by a transgenic mouse model.[23]

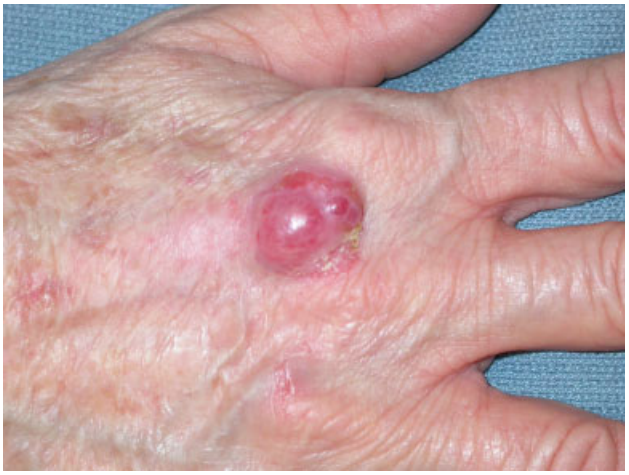


FIGURE 1. Primary Merkel cell carcinoma on the hand.

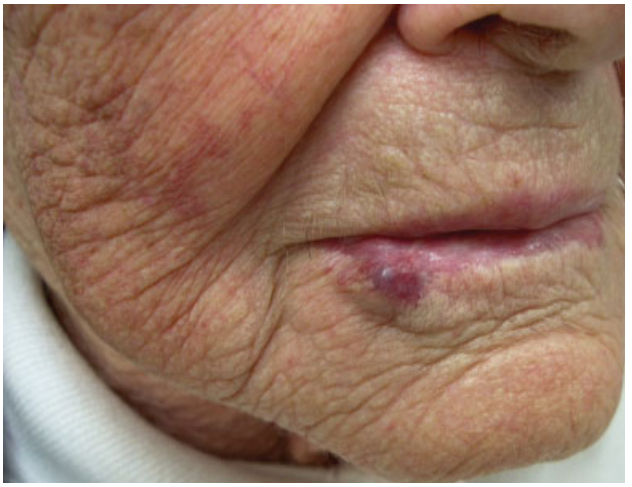


FIGURE 2. Primary Merkel cell carcinoma on the lower lip.

In 1972, Toker described a trabecular carcinoma of the skin that originally was believed to be derived from sweat glands.[24] In 1978, Tang and Toker identified dense-core granules in these trabecular tumors, suggesting an origin from Merkel cells.[25] Whether MCC arises from normal Merkel cells still is debated. Arguments in favor of a normal Merkel cell origin are the mutual presence of dense-core granules and positive staining for neurofilaments and CK-20. Several cases of MCC confined to the epidermis have been reported, suggesting that, at least in some cases, MCC arises from normal epidermal Merkel cells.[26] However, the rarity of such epidermal involvement has lead some to consider a pluripotent dermal stem cell as the cell of origin.[26]

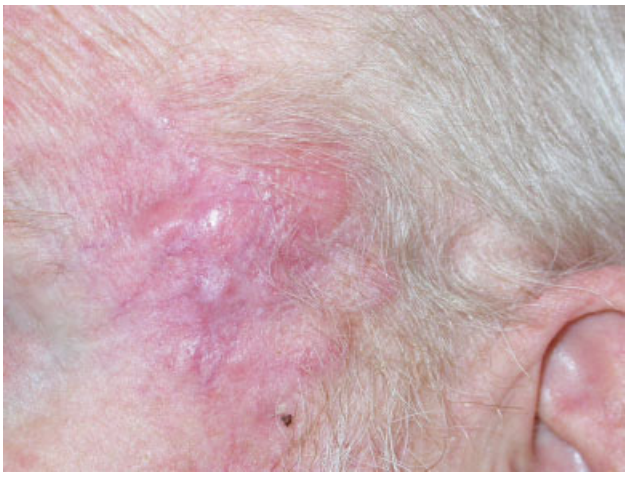


FIGURE 3. Locally recurrent Merkel cell carcinoma on the left temple.

Clinical Presentation

MCC is rarely suspected clinically at the time of presentation. The differential diagnosis may include basal cell carcinoma, cyst, SCC, pyogenic granuloma, melanoma, lymphoma cutis, or lipoma. If a typical clinical presentation can be described, then MCC most commonly presents as a blue or red, firm, nontender, solitary, dome-shaped nodule (Figs. 1 and 2). Tumors may have a plaque-like appearance or may present as a subcutaneous mass without epidermal changes (Fig. 3). Although the overlying skin may be ulcerated, it is frequently intact. In our experience, the growth rate appears quite rapid in many patients. Tumor size is frequently <2 cm but may reach 20 cm.[27] Lesions on the head and neck typically are smaller than lesions in other locations.[3] The 2 most common locations for MCC include the head and neck region and the extremities, which, together, account for 70% to 90% of cases. The remaining MCCs are located on the trunk and buttocks.[3,4] Primary MCC also has been reported on the oral and genital mucosa.[28,29]

The reported frequency of in-transit, lymph node, and distant metastasis in MCC ranges widely (20–75%) and may be biased toward tertiary center reports.[3,4,30–32] The most common location of metastasis is the draining lymph node basin (27–60%), followed by distant skin (9–30%), lung (10–23%), central nervous system (18%), bone (10–15%), and liver (13%).[3,4,32] The high reported rate of cutaneous metastasis is likely explained by the inclusion of satellite and in-transit metastases (Fig. 4). Other reported areas of distant metastasis include testis, pancreas, heart, bone marrow, pleura, parotid, gastrointestinal tract, prostate, and bladder.[33–40] The rate of MCC

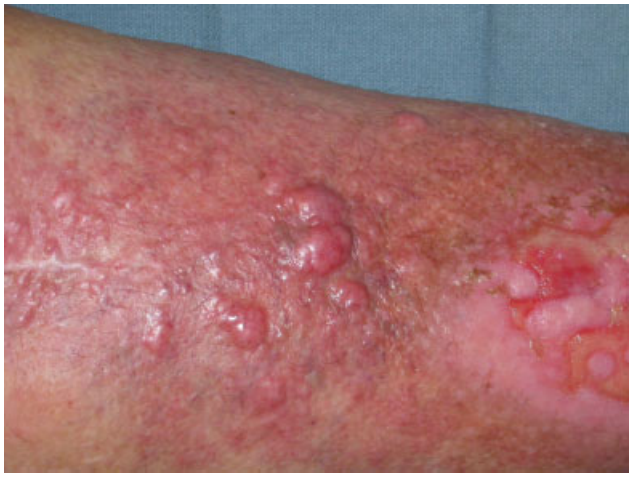


FIGURE 4. Multiple in-transit Merkel cell carcinoma metastases are observed adjacent to primary radiation field.

presenting as metastatic disease with unknown primary ranges from 3% to 19%.[4,41]

Greater than 10 cases of complete spontaneous regression (CSR) of MCC have been reported.[42] Because the estimated prevalence of CSR in all neoplasms is <1 in 60,000 to 100,000 cases, the number of reported cases of CSR in MCC is intriguing.[43] Although the mechanism of CSR in MCC is unknown, an immunologic response triggered by trauma, such as a previous biopsy, has been postulated.[43,44]

Histopathology

MCC typically has the microscopic appearance of a dermal tumor nodule, which frequently extends into the subcutaneous fat (Fig. 5). The tumor is composed of small blue cells with round-to-oval, hyperchromatic nuclei and scant cytoplasm. The nuclei have evenly dispersed, peppered chromatin and inconspicuous nucleoli (Fig. 6). Commonly seen histopathologic features include vascular invasion (31–60%), tumor necrosis (48–60%), perineural invasion (48%), and high mitotic rate (117 in 132 tumors had >5 mitoses per high-power field in 1 large series).[45,46] Ulceration may be present but is observed only a minority of cases.[45,46] Epidermal involvement has been reported in 5% to 30% of tumors either in the form of epidermotropism or carcinoma in situ. Most cases of intraepidermal MCC have been observed in association with squamous cell atypia.[26]

Although they are insignificant clinically, 3 histologic subtypes have been recognized and frequently are admixed. The intermediate variant, which is the most common subtype, is observed in ≥50% of tumors. It is characterized by large, solid nodules

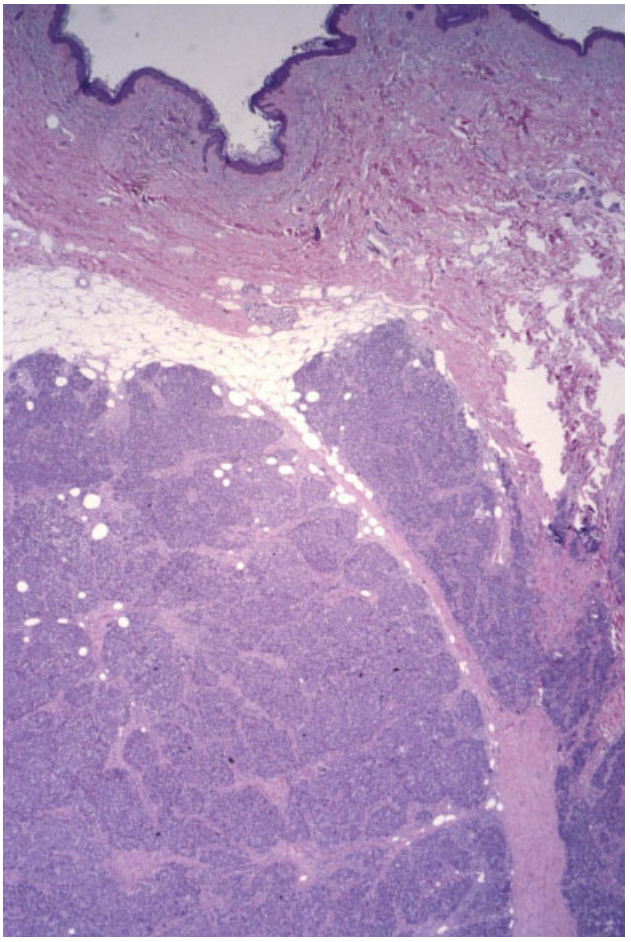


FIGURE 5. Scanning magnification of Merkel cell carcinoma demonstrates a large, multinodular dermal tumor (H & E, original magnification ×20).

and diffuse sheets of basophilic cells. The small cell variant consists of diffusely infiltrating sheets of irregular, hyperchromatic cells that frequently display crush artifact and nuclear molding. This subtype has considerable histologic overlap with bronchial small cell carcinoma. The trabecular variant consists of delicate ribbons of small basophilic cells separated by strands of connective tissue and normally is observed only in association with other histologic subtypes.[27,47]

Immunohistochemistry

MCC, as a small round blue cell tumor, must be differentiated from metastatic visceral neuroendocrine carcinomas, particularly from small cell lung carcinoma (SCLC). This distinction can be accomplished with near certainty by using immunohistochemical analysis. CK-20, a low-molecular-weight intermediate filament, is a highly sensitive marker for MCC, staining positively in a paranuclear, dot-like pattern in

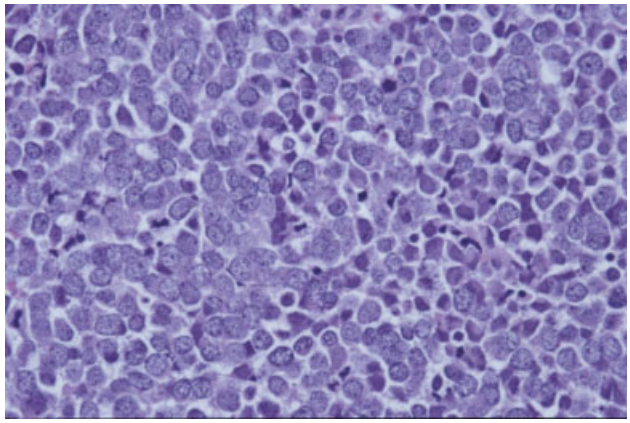


FIGURE 6. Cytologic features of Merkel cell carcinoma demonstrate round, hyperchromatic nuclei; scant cytoplasm; and distinctive, finely stippled chromatin. Mitotic figures and apoptotic tumor cells are identified readily (H & E, original magnification ×400).

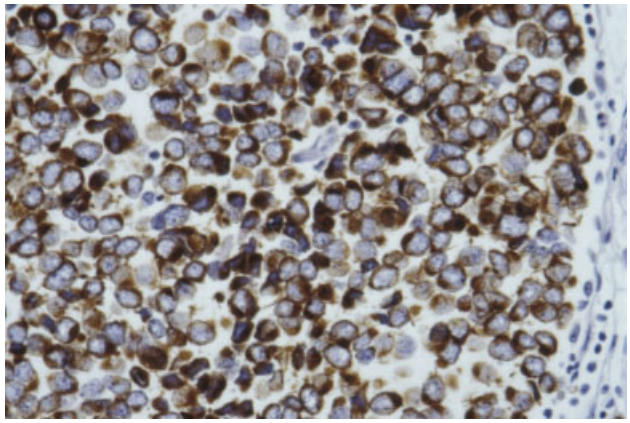


FIGURE 7. Cytokeratin-20 immunostaining of a Merkel cell carcinoma shows characteristic paranuclear, dot-like accentuation (cytokeratin-20 stain, original magnification ×400).

89% to 100% of tumors (Fig. 7). However, up to 33% of SCLC and 3% to 4% of extrapulmonary small cell carcinomas also stain positively for CK-20. The identification of thyroid transcription factor-1 (TTF-1) in SCLC has provided a valuable addition to the immunohistochemical armamentarium. TTF-1 is expressed in 83% to 100% of SCLC yet consistently is absent in MCC.[48,49] However, more variable TTF-1 staining in extrapulmonary small cell carcinomas (3–42% positivity) indicates that, although a negative TTF-1 stain supports a diagnosis of MCC, it does not confirm the diagnosis conclusively.[50] Similarly, CK-7 is expressed in SCLC but characteristically is negative in MCC. Other markers with a high sensitivity for MCC and, to a lesser degree, for SCLC include neuron-specific enolase, chromogranin A, synaptophysin, BER-EP4, and CAM 5.2.[48,51] Neurofilament protein (NFP) is not expressed as frequently (63–100%) in MCC as CK-20; however, because it is consistently negative in SCLC, it is a useful marker to help differentiate MCC from SCLC.[48] MCC invariably is negative for S-100 and leukocyte-common antigen, distinguishing it from small cell melanoma and cutaneous lymphoma, respectively. The majority of primary and metastatic MCCs express KIT receptor tyrosine kinase (CD117), which also is expressed in a variety of other malignancies, including acute myeloid leukemia and SCLC.[52]

Staging, Workup, and Sentinel Lymph Node Biopsy

An established and well-recognized staging system is not yet available for MCC. Most clinicians use a 3-tiered system based on the presence or absence of lymph node or distant disease. Investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) identified tumor diameter as an independent predictor of survival and developed a 4-tiered staging system in 1999.[53] The same group recently proposed a modified 4-tiered system that separates patients with localized disease into stage I (primary tumor dimension <2 cm) and stage II (primary tumor dimension ≥ 2 cm). Patients with regional or distant metastatic disease are classified as stage III and IV, respectively.[3] This classification is consistent with the American Joint Committee on Cancer 4-tiered paradigm for staging systems and is used throughout the remainder of this review.

The majority of patients with MCC (70%) present with stage I or II disease, 25% have palpable regional lymphadenopathy at presentation (stage III), and 5% present with distant metastases (stage IV).[3,4,54] The overall 5-year survival rates reportedly range from 30% to 64%.[41,55–59] Disease stage was identified as the strongest predictor of survival in 1 large series (stage I, 81% 5-year survival rate; stage II, 67% 5-year survival rate; stage III, 52% 5-year survival rate; stage IV, 11% 2-year survival rate).[3] Although disease-specific survival rates based on stage are reported infrequently in other studies, 5-year survival rates have been reported as 44% to 68% for localized disease (stages I and II) and 23% to 42% for regional or distant metastatic disease (stages III and IV).[30,60] The reported overall recurrence rate ranged from 40% to 45% in several large series but reportedly was as high as 77% on the head and neck.[3,4,61] Higher recurrence rates in smaller series may be influenced by unintentional retrospective and tertiary center bias. The median time to recurrence consistently is reported as ≈8 months,

TABLE 1
Merkel Cell Carcinoma: Histologic Primary Tumor Profile

Body site
Growth pattern (circumscribed or diffusely infiltrative)
Clark level (I-V)
Depth of invasion (mm)
Greatest horizontal dimension (mm)
Ulceration (present or absent)
Mitoses/mm^2
Tumor-infiltrating lymphocytes (present or absent)
Angiolymphatic invasion (identified or not identified)
Immunohistochemical staining (cytokeratin-20, other)
Margin status
Unusual features (squamous and/or eccrine differentiation, epidermotropism, etc)

TABLE 2
Merkel Cell Carcinoma: Histologic Sentinel Lymph Node Profile

Body site
Lymphoscintigraphy count
Lymphazurin blue (yes or no)
Diagnosis (positive, negative, or equivocal)
Hematoxylin and eosin (positive, negative, or equivocal)
Immunohistochemical staining (positive, negative, equivocal, or not applicable)
Tumor burden (% surface area involved, dimension of largest aggregate)
Location of metastasis (subcapsular sinus, parenchyma, germinal center)
Extracapsular extension (present, absent, equivocal)

with the majority of recurrences (90%) occurring within 2 years of diagnosis.[3,4,61,62]

Although a chest x-ray is warranted in the initial workup of a patient with MCC to exclude SCLC, the value of additional imaging studies is uncertain. Computed tomography (CT), magnetic resonance imaging, and positron emission tomography reportedly have been used to detect occult metastatic disease.[63,64] However, no curative treatment is available for stage IV disease, and there is no evidence that early detection and treatment of asymptomatic, distant metastatic disease has any impact on overall survival. Moreover, the use of routine imaging studies in asymptomatic patients with clinically localized MCC is likely to generate a high false-positive rate, leading to additional tests and increased patient anxiety.[65] A recent study reported that CT imaging lead to a false-positive rate of 49% for distant MCC metastases yet failed to detect true lymph node disease in 80% of patients.[66]

Several clinical, histologic and immunohistochemical parameters have been considered as prognostic indicators for patients with MCC.[67–69] Although a recent study indicated that tumor depth was the only parameter that was correlated with survival in a multivariate analysis, that finding could not be confirmed by others.[70,71] To investigate prognostic indicators, we have instituted a primary tumor histologic profile and a sentinel lymph node (SLN) histologic profile (Tables 1 and 2). Although smaller, mostly retrospective series may have dismissed several parameters as prognostic indicators, a systematic, prospective evaluation, which our histologic profiles will provide, may or may not validate these observations. In addition, new prognosticators may be identified.

The most consistent predictor of survival in MCC to date is the presence or absence of lymph node disease. In that regard, SLN biopsy (SLNB) is an invaluable tool. Because of the absence of other reliable prognostic indicators, SLNB is standard care for all clinically lymph node-negative patients with MCC at our institution, unless it is contraindicated medically. Already endorsed by the American Society for Clinical Oncology as the preferred staging procedure for breast cancer, level I evidence for the value of SLNB as a staging test for intermediate depth melanoma recently was provided.[72] Although studies are based on much smaller patient numbers, the value of SLNB as a staging procedure appears equally important in MCC. Numerous studies have reported the use of SLNB for patients with clinically lymph node-negative MCC and found a fairly consistent SLNB positivity rate of approximately 20% to 30%.[66,73,74] Immunohistochemical analysis of SLNs, in particular with anti-CK-20, is essential to provide acceptable sensitivity and specificity in identifying micrometastatic MCC (Fig. 8).[52,75] In the largest reported series from a single institution that involved 251 patients, investigators from MSKCC reported a 5-year survival rate of 97% versus 52% for pathologically staged lymph node-negative patients versus lymph node-positive patients, respectively. The only independent predictor of survival was the pathologic lymph node status.[3] The prognostic value of lymph node staging by SLNB in patients with MCC has been confirmed in smaller series at other institutions.[66,74,76]

Treatment

Patients with MCC, a tumor that is amenable to surgery and is considered both radiosensitive and chemosensitive, benefit from management in a multidisciplinary fashion. In melanoma, it has been demonstrated that a multidisciplinary approach is beneficial with respect to patient care, efficiency, outcome, education, research, and cost.[77] To emphasize the value of multidisciplinary care for patients with MCC, treatment is discussed below based on the stage of disease rather than by medical specialty.

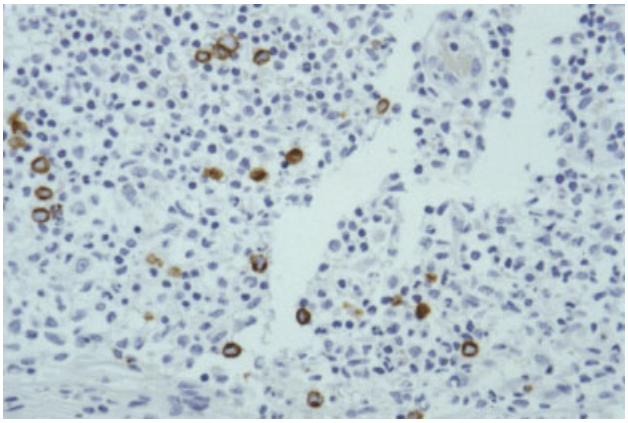


FIGURE 8. Cytokeratin-20 immunostaining of a sentinel lymph node identifies rare positive cells in lymph node parenchyma consistent with micrometastatic Merkel cell carcinoma (cytokeratin-20 stain, original magnification ×400).

Localized disease

There is little disagreement that the initial treatment of primary MCC is usually surgical. Some controversy exists regarding the appropriate surgical margin. Although wide local excision (WLE) with margins from 2 cm to 3 cm historically has been recommended, low local recurrence rates (8%) have been achieved after margin-negative excision with margins that averaged 1.1 cm.[3,78–80] Obtaining margins <1 cm did not lead to higher recurrence rates compared with obtaining margins ≥1 cm (9% vs 10% respectively, $P = .83$).[3] Another study that examined Mohs micrographic surgery for primary MCC, primarily on the head, neck, and extremities, reported that a mean margin of only 1.67 cm, with a median margin of 1 cm, was required to achieve negative margins with a mean primary tumor size of 1.58 cm.[81] Although the limited data, potentially biased toward smaller lesions, have indicated low local recurrence rates after Mohs surgery (4–8%), the rates are comparable to those reported with WLE by several groups (4–14%).[3,4,41] To our knowledge, no controlled trials comparing different margins of excision have been performed.

Disagreement exists regarding the use of adjuvant radiation therapy (RT) to the primary site after WLE. Adjuvant RT doses for MCC vary from 45 Gray (Gy) to 50 Gy.[56] When reviewing the available literature, a distinction must be made between adjuvant RT to the primary site, the regional lymph node basin, or both. Similarly, when assessing the benefit of adjuvant RT to the primary site, local recurrence rates must be distinguished from regional or *locoregional* recurrences. Several groups have reported relatively low local recurrence rates after WLE only (4–14%) that did not decrease significantly when adjuvant RT to the primary site was added.[3,4,41,81]

Other studies, however, have reported or shown in much higher recurrence rates after surgery alone.[30,55,82] Careful review of these studies raises several concerns. Most report locoregional recurrence rates that greatly overestimate the number of true local recurrences.[3] In the largest single-institution series that showed a benefit from adjuvant RT, a recurrence rate of 100% was reported after surgery alone, which reflected both local and regional recurrences.[82] The true local recurrence rate after surgery without adjuvant RT was 21% (8 of 38 patients). Those investigators reported surgical margins as narrow as 5 mm. Another concern is the heterogeneous nature of the treatment within the *surgery only* group, ranging from excision of the primary tumor with positive margins to amputation and complete lymph node dissection (CLND).[30,41] Conversely, in a study reporting low local recurrence rates after surgery only, adjuvant RT to the primary basin rarely was delivered (14%), making a comparison less reliable.[3]

The question whether excision of primary MCC should be followed by adjuvant RT to the surgical bed will remain unanswered until higher level evidence is available. Based on existing evidence, every effort should be made to excise a primary MCC with clear surgical margins. Margins of 1 cm frequently will be negative for small lesions that measure <2 cm in greatest dimension. A 2-cm margin should be reserved for larger lesions that measure >2 cm in greatest dimension when feasible.[3,4,81] These margins usually are achievable without high morbidity. Although cosmetic concerns should not be neglected, tumor clearance of this potentially aggressive malignancy should be the highest priority. When considering Mohs surgery, the following issues must be considered: If a patient with MCC is taken to the operating room to undergo SLNB, then it may be in the patient's best interest to undergo concurrent wide excision of the primary tumor rather than performing Mohs surgery on a separate occasion. However, if tissue-sparing is a high priority in locations, such as the eyelid or nasal ala, then this approach may be preferable *after* the patient has undergone SLNB. Mohs surgery also may be considered if surgical margins are close or positive.

Based on existing data, after WLE with clear surgical margins of smaller primary lesions that measure <2 cm in greatest dimension, adjuvant RT to the primary site most likely may be omitted.[3,4,41,81] When clear surgical margins cannot be obtained or for larger primary tumors that measure ≥2 cm,

strong consideration should be given to adjuvant RT to the surgical bed until there is further evidence to the contrary. Both therapeutic options, however, should be viewed in conjunction with SLNB. The use of RT as primary treatment has been reported for very poor surgical candidates. Successful treatment with RT alone was reported in 9 patients with primary MCC, which had been considered inoperable, without recurrence after a mean follow-up of 3 years.[83]

Regional disease

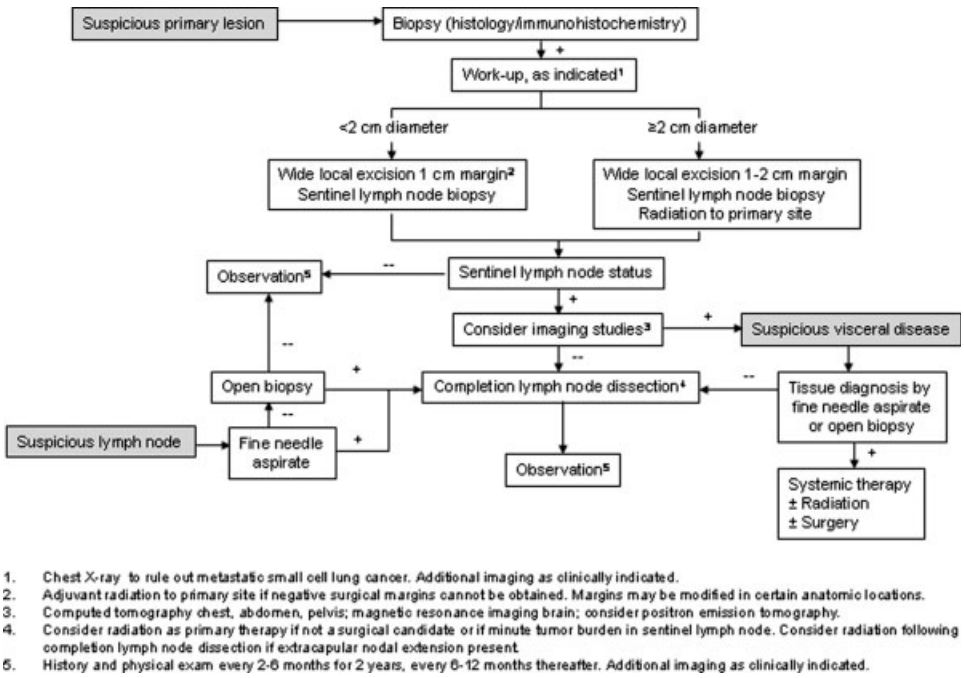
Lymph node recurrences frequently are lumped into *locoregional* recurrence rates and are reported as a measure of local treatment failure. However, in the absence of local recurrence, lymph node recurrence most often represents the delayed manifestation of micrometastatic disease present at the time of treatment of the primary tumor rather than the result of inadequate local therapy.[84] The rate of lymph node recurrence is used repeatedly to compare the effectiveness of surgery versus RT. However, most studies compare excision of the primary site without regional lymph node therapy versus excision of the primary tumor, frequently in combination with CLND, followed by adjuvant RT to the primary site and the regional lymph node basin.[30,61,82] For example, Veness et al reported a 37% lymph node recurrence rate and a 4-month median disease-free survival after surgery versus an 18% lymph node recurrence rate and a 10.5-month median disease-free survival after surgery and adjuvant RT.[41] Twenty-seven of 36 patients (75%) in the surgery arm underwent WLE without addressing the lymph node basin. All patients in the adjuvant RT group underwent RT to the lymph node basin after treatment of the primary tumor, and nearly 50% of patients (17 of 36 patients) underwent CLND.[41] These studies do not adequately compare therapeutic modalities for the regional lymph node basin but, instead, suggest that patients had a better outcome when the regional lymph node basin was addressed. This point is highlighted in a study by Kokoska et al, who reported a recurrence rate of 0% (0 of 11 patients) when CLND was performed compared with 91% (20 of 22 patients) without CLND and a recurrence rate of 15% (2 of 13 patients) with RT (presumably regional) and 90% (18 of 20 patients) without RT.[78]

The compelling question is how best to address the regional lymph node basin. Adjuvant RT and elective lymph node dissection are options. However, both approaches are associated with problems historically encountered in melanoma. First, the majority of patients without lymph node disease are exposed to unnecessary treatment. Second, electively treating the regional lymph node basin, particularly in areas of ambiguous lymphatic drainage (such as the trunk or head and neck), whether with surgery or RT, may not target the correct basin and/or interval lymph node.[85]

Thus, SLNB should be performed to stage the lymph node basin. This is the most sensitive and specific test to select appropriate patients and identify the correct basin(s) to direct regional therapy. With this approach, patients who have negative SLNB results carry a favorable prognosis and are spared the morbidity of additional surgery or RT. A recent study indicated that there was no significant difference in 3-year recurrence-free survival among patients with a negative SLNB between those who did or did not receive adjuvant lymph node therapy.[66] The best treatment for patients with micrometastatic MCC currently is unknown. CLND is the most commonly reported treatment after a positive SLNB with low rates of regional lymph node recurrence in several small published series.[73,74,76] Successful treatment of the lymph node basin with RT alone after a positive SLNB also has been reported.[86] Failure to treat the lymph node basin after a positive SLNB resulted in high recurrence rates in 2 small series.[66,76]

Based on the limited data available, low-level evidence, and multidisciplinary consensus, CLND is considered first-line treatment for most patients with micrometastatic disease. When the morbidity of CLND is deemed unacceptable by the patient or the multidisciplinary tumor board, then RT to the lymph node basin is considered as alternative therapy. For patients who have extensive lymph node disease or extracapsular lymph node extension in the SLN, adjuvant RT after CLND should be considered. SLNB is not attempted if a patient is not able to undergo additional therapy. The approach to patients with palpable lymphadenopathy is identical to that described for patients with micrometastatic disease.

On several occasions, we have identified a single CK-20-positive cell or only rare CK-20-positive cells in the SLN. The minimal tumor burden for which additional treatment is indicated is unknown. Reliable predictors of the rate of positivity of remaining lymph nodes removed in a CLND after a positive SLNB have yet to be determined. Patients with minute tumor burden are discussed by our multidisciplinary tumor board on a case-by-case basis. Various therapeutic options, including CLND, RT, and observation, are considered. It is postulated that the SLNB may be therapeutic in patients who have minute tumor burden, although to our knowledge no proof exists to date.



1. Chest X-ray to rule out metastatic small cell lung cancer. Additional imaging as clinically indicated.
2. Adjuvant radiation to primary site if negative surgical margins cannot be obtained. Margins may be modified in certain anatomic locations.
3. Computed tomography chest, abdomen, pelvis; magnetic resonance imaging brain; consider positron emission tomography.
4. Consider radiation as primary therapy if not a surgical candidate or if minute tumor burden in sentinel lymph node. Consider radiation following completion lymph node dissection if extracapular nodal extension present.
5. History and physical exam every 2-6 months for 2 years, every 6-12 months thereafter. Additional imaging as clinically indicated.

FIGURE 9. Algorithm for the management of Merkel cell carcinoma (± indicates with or without).

Chemotherapy is the least studied treatment modality for MCC, and the available data on its role, particularly as adjuvant therapy, are limited. Several studies have suggested a potential role for adjuvant chemotherapy with or without RT in the treatment of patients with high-risk, primary or regional MCC.[87,88] However, a recent prospective study in which patients with high-risk, localized disease received synchronous radiochemotherapy and adjuvant chemotherapy using carboplatin and etoposide, failed to demonstrate a survival benefit with the addition of chemotherapy in a multivariate analysis.[89] A retrospective subgroup analysis of 76 patients at MSKCC also failed to reveal a survival benefit associated with adjuvant chemotherapy.[3] Given the significant morbidity associated with chemotherapeutic regimens, particularly in the elderly MCC population, adjuvant chemotherapy currently has no established role in the treatment of localized or regional MCC. However, several studies have reported complete or partial resolution of in-transit MCC metastases with hyperthermic isolated limb perfusion using tumor necrosis factor α, interferon γ, and/or melphalan.[90,91]

Distant disease

Numerous chemotherapeutic regimens similar to those for patients with SCLC have been used in patients with metastatic MCC or as primary therapy for patients with inoperable disease.[32,92] Most commonly, combination therapy with cisplatin, doxorubicin, and vincristine or with etoposide and platinum have been used. MCC generally is considered a chemosensitive tumor with initial overall response rates of approximately 60% to 70%. Small series have achieved initial response rates of 100% with doxorubicin and cisplatin; 92% with 5-fluorouracil-containing regimens; and 76% with cyclophosphamide, doxorubicin/epirubicin, and vincristine. However, the median duration of response is only 8 months. Moreover, the response rates of second-line and third-line chemotherapy decrease to 45% and 20%, respectively. Given the high but relatively short response rate, no regimen clearly has demonstrated an impact on survival or response longevity in metastatic patients with MCC, who have a median overall survival of 10 months. Because of the rarity of MCC, very few NCI-sponsored trials currently are open for patients with advanced disease.

A concern in the elderly population of patients with MCC is the associated toxicity, primarily related to myelosuppression. Skin toxicity with moist desquamation and tumor lysis syndrome with acute renal failure requiring hemodialysis also have been reported.[93,94] Despite a likely selection bias toward patients who are deemed capable of tolerating chemotherapeutic regimens, a toxic death rate of 7.7% has been reported in MCC.[32] By comparison, among a cohort of 1976 patients who received chemotherapy

for various malignancies, only 12 deaths (0.6%) directly related to chemotherapy were reported.[95] Less toxic chemotherapy regimens are possible, although data suggest that this approach is less effective for elderly patients who have a good performance status.[96] Therefore, initiation of treatment should not be based solely on age. Combination chemotherapy of cisplatin or carboplatin plus etoposide are reasonably effective and tolerable treatments that should be considered for all patients who have inoperable MCC and a good performance status.[97] For second-line therapy or for patients who are less fit, treatment with single-agent topotecan, oral etoposide, irinotecan, taxanes, or gemcitabine can be considered because of the demonstrated activity of these agents in advanced neuroendocrine tumors.[98–100]

The role of surgery in the treatment of patients with distant metastatic MCC is limited and mostly palliative in nature. Metastasectomy rarely has been reported for patients with a solitary distant metastasis.

Our knowledge of the biologic behavior of MCC and the existing data to determine the optimal treatment for this disease are limited. However, as in many other diseases for which we lack high-level evidence, treatment guidelines can and have been generated in an attempt to interpret the available data for use in clinical practice.[101] Based on a multidisciplinary interpretation of the existing evidence, our current guidelines for the management of MCC are summarized in Figure 9. Many questions remain unanswered, and future data certainly will change our understanding and management of this disease.

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