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Merkel Cell Carcinoma

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Abstract

Merkel cell carcinoma (MCC) is a rare, clinically aggressive cutaneous neuroendocrine neoplasm with a high mortality rate. Though the etiology is not precisely known, Merkel cell polyomavirus (MCV) DNA has been found recently in a large percentage of MCC tumors. Other suggested risk factors include sun-exposure, immunosuppression and a history of prior malignancy. Work-up of patients with MCC most notably includes nodal staging via clinical exam or sentinel lymph node biopsy (SLNB). The prognosis for most patients with MCC is poor, and the rarity of MCC precludes the prospective, randomized clinical trials necessary to elucidate optimum treatment protocols. Most published data support the use of a multimodality approach centered around surgical excision with negative margins, SNLB to establish the presence or absence of nodal metastases, adjuvant radiotherapy (RT) to decrease the risk of recurrence, and systemic chemotherapy in the case of widespread disease.

Keywords

Merkel Cell Carcinoma; Biology; Etiology; Epidemiology; Presentation; Prognostic factors; Imaging; Management; Surgery; Radiation Therapy; Chemotherapy

INTRODUCTION

Merkel cell carcinoma (MCC) was initially described by Toker[1] in 1972 as a trabecular cancer of the dermis with high lymphatic metastatic risk and found mainly in white elderly patients. The past two decades have given rise to a growing interest in characterization of the disease, as well as the best approach to its management. Numerous submitted case reports demonstrate that MCC is a rare, clinically aggressive neuroendocrine tumor of the skin with a high propensity for local, regional, and distant spread. MCC is lethal in 33% of cases and therefore carries a worse prognosis than malignant melanoma.[2] The number of cases of MCC reported annually in the U.S. is quickly rising, likely secondary to advances in diagnostic techniques, a growing elderly population, and a larger number of immunosuppressed patients. Treatment options vary from surgery alone to multimodality

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therapy including surgery, radiation therapy (RT), and chemotherapy (CT). This article will highlight recent developments in the biology and management of patients with MCC.

DISCUSSION

BIOLOGY

The Merkel cell (MC) was first described by Friedrich Sigmund Merkel in 1875 as a nondendritic, nonkeratinocyte epidermal “tastzellen” or “touch cell” that functions as a tactile skin receptor.[3, 4] Although the true function remains enigmatic, it is presumed that the normal MC may play a role in signal transduction and function as slowly adapting mechanoreceptors to sense touch and hair movement.[5, 6] Continued advances in identifying unique immunocytochemical staining patterns in MC has allowed the diagnostician to more readily identify cases of MCC, increasing both recognition of true disease prevalence and rapid delivery of appropriate treatment.[7–10] In addition, the presence of cytoplasmic neurosecretory granules, cytoplasmic processes, and intermediate filaments surrounding the nucleus, demonstrated on EM, can be used to confirm the identity of MC as the progenitor line in MCC.[11–13]

ETIOLOGY

Although the specific etiology of MCC is not clearly known, probable risk factors have been indicated by published case reports, case series, and population-based studies. A history of sun exposure or concurrence of other sun-associated skin conditions, particularly squamous cell carcinoma, is common in patients with MCC.[14–16] Studies have also shown an increased incidence of MCC in patients on immunosuppressive agents for solid organ transplant,[17–19] in patients with HIV infection and low CD4 counts,[20, 21] in patients undergoing radiation or chemotherapy,[22, 23] and in patients chronically exposed to arsenic.[24] More recently, autoimmune disease has been suggested as a risk factor for developing MCC.[25]

The most notable recent discovery concerning the pathogenesis of MCC is the characterization of a new polyomavirus named Merkel cell polyomavirus (MCV) by Moore and Chang.[26] Polyomaviruses have a double-stranded, circular, supercoiled DNA genome and have been shown to have oncogenic potential.[27] Feng *et al.*[26] discovered and sequenced the genome of MCV and identified MCV DNA in 8 of 10 MCC tumors. Since the original report, a multitude of other groups have found MCV DNA in MCC tissue samples.[28–41] Although MCV DNA can be helpful in distinguishing MCC from other cutaneous neoplasms and in identifying the primary tumor in metastatic disease, Tolstov *et al.*[42] report 50% and 80% prevalence of MCV antibodies among people under 15 years and older than 50 years, respectively. Some authors suggest vaccination with MCV virus-like particles could potentially prevent initial MCV infection, although only small pilot animal studies have been performed thus far[43].

EPIDEMIOLOGY

Conflicting nomenclature, ill-defined diagnostic methods and criteria, and a paucity of reported cases are issues that have been addressed as more aggressive and widespread study of the disease has been undertaken. Since a more standardized approach to staging (Table 1) and ICD-9 coding (Table 2) have been implemented, a more reliable population-based registry of MCC over large geographic areas has become available. Using the SEER cancer registry database of the National Cancer Institute, the estimated overall incidence of first primary MCC in the USA for the decade 1992–2001 is 0.32 per 100,000 person-years. Since the majority of MCC cases have been diagnosed since the establishment of a specific immunologic profile for MCC in 1992, calculation of the increasing incidence of first

primary MCC in the general population should use 1992 as the year of reference.[44] Demographically, MCC is found most frequently in the elderly, with only sporadic cases reported before the age of 50. The incidence of MCC in whites is more than 8 times that in blacks and almost double the incidence of other ethnic groups. The incidence of first primary MCC is higher in males than females in all ethnic groups, with a ratio of 2:1 in white and in black, and a ratio of 1.5:1 in all other ethnic groups.[44, 45]

CLINICAL PRESENTATION

MCC has been described in the literature as a classically painless subcutaneous mass with a cystic or nodular appearance, but sometimes presenting with a plaque-like appearance that may be surrounded by small satellite lesions. The tumor size ranges from 2–200mm, but is most often <20mm.[3, 46] Lesions can vastly range in color, most often presenting as red/pink, blue/violaceous, or skin-colored.[46] They can exhibit overlying telangiectasia or a shiny surface, making lesions easily confused with basal cell carcinoma.[47] **Figures 1A–C illustrate various MCC at presentation.** Tumors may exhibit rapid growth in the preceding weeks or months[3] with a mean length of time of 6.2 months (2 weeks to 2 years) between the patient noticing the lesion and presenting for histologic diagnosis.[44] While the majority of cases present in sun-exposed areas, it is important to note that the neoplasm can also present in areas of minimal sun exposure. Various sources cite the incidence of disease of the head and neck to account for approximately 50% of cases, followed in decreasing order by the extremities, trunk, and buttock[3].

Studies show 71–79% of patients present with clinically negative nodal involvement (stage I and II disease), 19–24% present with regional nodal metastasis (stage III disease), and 5% have evidence of distant metastatic disease (stage IV disease).[48],[49] Secondary sites of involvement include skin (28%), lymph nodes (27%), liver (13%), lung (10%), bone (10%), and brain (6%).[3, 47]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The physical characteristics of MCC can resemble those of an epidermoid cyst, lipoma, dermatofibroma, amelanotic melanoma, basal cell carcinoma, squamous cell carcinoma, lymphoma, sarcoma, or metastatic carcinoma.[50] A recent study of 195 patients by Heath *et al.* outlines the most common clinical features of MCC to aid in its diagnosis. The authors suggest the employment of the mnemonic AEIOU to list significant characteristics: Asymptomatic, Expanding rapidly (doubling in less than 3 months), Immune suppressed, Older than 50 years, and UV exposed skin site, with a subcategory of fair skin. In the 62 patients for which all 5 criteria were available, at least 3 criteria were fulfilled by 89% of patients, at least 4 by 32%, and all 5 were seen in 6% of patients.[46] However, the key to establishing an accurate and timely diagnosis of MCC is a low clinical index of suspicion and prompt biopsy.[50]

Under light microscopy, MCC presents as an intradermal mass, separated from the epidermis by a narrow ‘Grenz zone’ often with necrosis (apoptotic bodies) and patchy lymphocytic infiltrates.[51] Figures 2A, B demonstrate some pathologic features of MCC, characterized by neurosecretory granules, cytoplasmic processes, and intermediate filaments surrounding the nucleus. In addition to the specific clinical and histologic features, MCC is confirmed by immunohistochemistry for proteins such as CK-20, which is detected in a characteristic paranuclear dot-like pattern in 89–100% of Merkel cell tumors but is rarely positive in SCLC (Figures 2C–D).[8]

WORK-UP

Initial staging of MCC should include evaluation of primary site for satellite lesions and dermal seeding. Draining nodes should be palpated. Full blood count, serum electrolytes, and alkaline phosphatase are useful in providing a baseline.[47]

Initial imaging workup based on severity of disease based on clinical presentation. Patients with localized disease without physical or symptomatic evidence of regional or distant metastases should be evaluated for spread to regional nodal basins with sentinel lymph node biopsy (SLNB) or ultrasound.[52] Patients with lesions suspicious for regional lymph node involvement can undergo fine needle aspiration cytology, often with ultrasound guidance for more accurate sampling. When lymph nodes are positive, full-body imaging is generally indicated to detect distant metastases.[52] This can be accomplished with a variety of imaging modalities (Figures 3A–D), with mounting evidence demonstrating the utility of fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in the staging and management of MCC.[53–62] In a recent study of 18 patients, staging was adjusted in 33% of patients, and the treatment approach was altered in 43% of patients after results of FDG-PET were obtained.[54] Figure 3C shows a patient with MCC of the mandible who was found to have metastatic disease to the mediastinum and liver on post-treatment follow-up FDG-PET scan, and figure 3D illustrates the detection of an involved iliac node from a small foot primary MCC by PET-CT scan.

High-resolution CT and MRI can be used for clinical problem solving in special circumstances.[52] CT is useful for imaging of the thorax and abdomen to exclude metastatic lesions (Figure 3A) and primary SCLC, and can also be used to image deeper lymph nodes and nodular metastases in subcutaneous fat.[47, 53] MRI has been recommended for local imaging and regional lymph node staging for patients with MCC (Figure 3B), and in particular for evaluation of local tumor spread in regions not easily accessible by sonography and the deeper fascia of the head and neck region such as the sinonasal region and orbit.

PROGNOSTIC FACTORS

Based on an analysis of prognostic factors in 5823 patient cases for the development of a consensus system by the AJCC, extent of disease at presentation is highly predictive of survival. This is in concordance with prior studies and staging systems.[49, 63, 64] In this study, it was shown that survival at 5 years (relative to age- and sex-matched control/population data) was 64% for local (Stage I or II), 39% for regional nodal (Stage III), and 18% for distant metastatic (Stage IV) disease.[50, 65, 66] In particular, extent of nodal involvement has been shown to have an impact on survival, with a 42% survival at 5 years in patients with only microscopic nodal involvement and 26% survival for those with clinically apparent nodal disease.[50, 65, 66] The impact of this distinction is reflected in the new staging system (Table 1).

The prognostic value of tumor thickness is an area of continued study and controversy. While some researchers have suggested that tumor thickness is positively associated with likelihood of nodal metastasis and poor survival, others have denied this association.[67–69] Other patient and tumor characteristics often considered to portend poor outcome include male sex, age greater than 60 years, presence of co-morbid conditions, immunocompromised state, positive resection margin, high mitotic rate, small cell size, absence of an inflammatory infiltrate, primary site of disease (head/neck, trunk, perineum, lower extremities), and no adjuvant radiotherapy.[7, 10, 44, 63] Prognostic factor analyses of the impact on survival in larger-scale studies are required to determine the true prognostic value of these characteristics.

TREATMENT OPTIONS

The treatment of choice for MCC depends on many factors including the stage of the tumor, particularly with respect to nodal involvement, the location of the tumor, and the medical comorbidities of the patient. Though far from a consensus, most current recommendations include the addition of adjuvant RT to reduce local or nodal relapse and to improve disease-specific and overall survival. A summary of results and recommendations from recent retrospective reviews and meta-analyses is provided in Table 3.

SURGICAL INTERVENTION

The standard of surgical care for MCC has traditionally been wide local excision. Some experts have suggested surgery alone is adequate for early stage disease,[70–72] but a recent study of 95 patients from a database at the National Cancer Institute in Milan further evaluated the use of surgery alone in early stage MCC.[73] The authors report an 80% 5-year disease specific survival rate when lymph nodes were pathologically negative, which dropped to 58% when regional nodal metastases were present. While it was initially thought that margins 3 cm were necessary for the best reduction of local recurrence,[74, 75] margins 2–3 cm wide and 2cm deep are now generally accepted.[51, 76–78] Allen et al reviewed records of 102 patients with MCC treated at Memorial Sloan-Kettering Cancer center over a 27 year period and found no association between width of margins and either recurrence rate or survival.[79] Two additional studies showed no difference in locoregional control or overall survival regardless of margin status.[80, 81]

As with more common skin cancers, Mohs microsurgery is an attractive treatment option for tumors on the head and neck, where the recommended margin width and depth are either cosmetically undesirable or technically impossible. Boyer *et al.* studied recurrence rates and survival in patients with stage I MCC treated with Mohs surgery with or without adjuvant RT and concluded that the addition of adjuvant RT after Mohs surgery was not necessary as it did not provide additional benefit in terms of recurrence or survival.[71] O'Connor *et al.* evaluated patients treated with wide local excision or Mohs surgery and found that, while standard surgical excision resulted in local persistence and regional metastasis in 31.7% and 48.8% of patients respectively, Mohs surgery resulted in only 6.8% and 33.3% local persistence and regional metastasis respectively.[82] O'Connor *et al.* suggested that there may be some benefit in adding adjuvant RT after Mohs surgery to further reduce the risk of nodal metastasis.

Another point of disagreement among surgeons is whether or not SLNB or LND is necessary for patients undergoing surgical excision of MCC. Even in patients with no clinical evidence of lymph node involvement, 25%-100% of primary draining lymph nodes may contain microscopic metastases[79, 83–85] that can lead to nodal relapse in up to 76% of patients.[51, 86–88] Since MCC is thought to spread in an orderly fashion similar to melanoma, SLNB can detect subclinical nodal metastatic disease before progression to stage IV disease[89–91]. Allen *et al.* showed data suggesting incidence of positive lymph nodes was independent of tumor size[72], so routine SLNB should be offered to all patients undergoing surgical excision for MCC. Fang *et al.* also describe the morbidity due to LND and offer data to suggest lymph node irradiation can provide comparable control rates to LND whether lymph node disease is detected clinically or by SLNB.[92]

RADIATION THERAPY

RT has been advocated by a few authors as definitive treatment, particularly for patients who are poor surgical candidates.[93, 94] While RT is typically added when patients present at a higher stage or with nodal metastases, Mortier *et al.*[93] reported data on 26 patients with stage I MCC. There was no difference in disease-specific or overall survival between

patients with stage I MCC treated with RT alone or surgery + RT. The 9 patients treated with definitive RT received a median dose of 60 Gy, and the majority received prophylactic nodal irradiation. More recently, Veness *et al*[94] presented an analysis of 46 patients treated with definitive RT. Included patients were inoperable either due to advanced disease or because of medical comorbidities. In fact, 77% of the patients examined had nodal metastases at the time of treatment. A slightly lower mean radiation dose was used for the nodal basins (51–55 Gy), but the authors reported a 75% in-field control rate. Even though the numbers are small, these two studies show that RT may be a viable alternative to surgery for patients unable to withstand an operation, but adjuvant or concurrent RT to the nodal basins is recommended even in patients presenting with stage I disease.

There have been few studies examining the optimum RT dose for the treatment of MCC. The similarities between MCC and SCLC have led to the common use of doses of 45–60 Gy, depending on the presence or absence of gross disease. Morrison *et al*[95] recommend 56–60 Gy for gross unresected disease and 46–50 Gy for adjuvant treatment of the primary tumor site and draining lymphatics after resection. A more recent study confirmed the role of RT in reducing local and nodal relapses and demonstrated a dose-response relationship of up to 50 Gy for subclinical disease and >55 Gy for gross disease.[96]

The majority of retrospective studies conducted over the past 15 years have consistently demonstrated better local control after surgery when adjuvant RT is added.[80, 96–104] In one of the largest single institution studies, Gillenwater *et al.* analyzed 66 cases of MCC of the head and neck treated at M.D. Anderson Cancer Center.[80] Although width of surgical margins did not significantly affect survival, the authors did report significantly lower local and regional recurrence rates in the 26 patients receiving post-operative RT, even in the 77% of patients with clinically negative lymph nodes. In contrast, Allen *et al.*[72] published the largest single institution study to date and found no difference in local or regional recurrence upon the addition of adjuvant RT. The 5-year disease specific survival for the patients included in this study was 64%, with 97% in patients found to be node-negative on pathological staging and 52% in patients with positive nodes. The authors concluded that adjuvant RT to the nodal basin was not necessary if operative nodal staging had been performed. Although most major academic institutions have not treated a sufficient number of MCC patients over the past few decades to definitively assess the efficacy of adjuvant RT, more statistical power is gained through review of multiple single-institution case series. Lewis *et al*[100] published a meta-analysis pooling the data from 132 studies yielding the inclusion of 1254 patients who carried a pathologic diagnosis of MCC, received surgical excision with negative margins and had at least one month of follow up. Regardless of stage at presentation, local recurrence was reported in 24.5% when treated with surgery only and 6.9% also treated with adjuvant RT. Out of the 566 patients presenting with stage I disease, local recurrence was reported in 44.8% of patients treated with surgery only and 13.2% of patients who received adjuvant RT. This calls into question the common clinical practice of offering adjuvant RT only when lymph nodes metastases are present. Finally, there was no survival benefit shown upon adding adjuvant RT after excision of stage I MCC, but the authors noted that 3 times as many patients would be necessary to obtain 80% power. More recently, Mojica *et al.*[103] offered further evidence for the addition of adjuvant RT with data from 1665 patients in the SEER cancer registry database. The authors found adjuvant RT was associated with a significant improvement in overall survival with a median survival 45 months with surgery alone and 63 months with surgery + RT. Though these studies are no substitute for a randomized, prospective clinical trial, the majority of experts seem to agree that adjuvant RT benefits patients in terms of decreased recurrence and overall survival. The practice guidelines recently updated by the National Comprehensive Cancer Network currently recommend the routine use of adjuvant RT to the lymph nodes in all cases unless the patient has had a negative SLNB.[105]

CHEMOTHERAPY

As is the case with RT doses and schedules, the majority of the chemotherapeutic regimens used to treat MCC are similar to those found to be effective in the treatment of SCLC. Carboplatin, cisplatin, etoposide, cyclophosphamide, 5-fluorouracil, vincristine and doxorubicin are some of the more common agents used. Traditionally, primary chemotherapy has been reserved for those patients with unresectable disease, whether due to poor surgical candidacy because of metastatic disease or due to medical comorbidities. Adjuvant chemotherapy has been suggested to be of benefit when added to surgery and adjuvant RT for the treatment of stage II disease.[47] In a study of 40 patients with stage I and II MCC, Poulsen *et al.* showed no beneficial effect of chemotherapy, but reported wide confidence intervals and an underpowered study.[106] In addition to the small number of MCC patients treated with chemotherapy, the advanced stage at which chemotherapy is added makes drawing definitive conclusions problematic. In a study of 35 patients, Kokoska *et al.*[107] reported no benefit when chemotherapy was added to adjuvant therapy regimens. Likewise, Allen *et al.*[72] reported no benefit in survival upon the addition of adjuvant chemotherapy. Conversely, several authors have reported chemotherapy to be beneficial in terms of recurrence and survival especially for patients with high risk MCC. [80, 95, 98, 108]

Two retrospective analyses sought to further characterize the utility of chemotherapy for MCC with larger groups of patients.[109, 110] Voog *et al.*[109] reported an impressive 61% response rate (57% for metastatic disease and 69% for advanced disease). However, the authors found that while MCC is chemosensitive, it is rarely curable, and the 7.7% risk of toxic death due to neutropenia further complicates the treatment decision. Tai *et al.*[110] analyzed a larger group of patients treated with chemotherapy and found an even more impressive response rate of 75.7%.

CONCLUSION

Recent developments have improved accuracy in diagnosing MCC, and the discovery of MCV DNA in MCC tumors has shed considerable light on the pathogenesis. Although the incidence has been shown to be increasing, there are still far too few cases of MCC presenting to any one institution for definitive conclusions to be drawn. Collaboration will be the key to future breakthroughs in terms of diagnosis, prognosis and treatment of this rare neoplasm. The consensus staging system and revised ICD-9 codes are two steps taken recently in standardizing the way MCC cases are reported. A definitive staging system may be a first important step in making possible a world-wide, multi-institutional prospective, randomized case-control study to definitively determine whether a multimodality regimen is superior to surgical resection alone in the treatment MCC. Such large scale trials will also be necessary to answer existing questions concerning the use of chemotherapy. Until such data becomes available, there is ample data to advocate for the use of adjuvant RT after surgical resection due to the high incidence of local, nodal and distant metastatic relapse. Although MCC is chemosensitive, there is less data on the efficacy of chemotherapy, and its role in adjuvant therapy continues to be debated.

References

1. Toker C. Trabecular carcinoma of the skin. Arch Dermatol. 1972; 105:107–110. [PubMed: 5009611]
2. Hodgson NC. Merkel cell carcinoma: changing incidence trends. J Surg Oncol. 2005; 89:1–4. [PubMed: 15611998]
3. Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. J Clin Oncol. 2002; 20:588–598. [PubMed: 11786590]

4. Merkel F. Tastzellen and Tastkoerperchen bei Den Hausthieren und beim men- schen. Arch Mikrosco Anat. 1875; 11:636–652.
5. Frigerio B, Capella C, Eusebi V, et al. Merkel cell carcinoma of the skin: the structure and origin of normal Merkel cells. Histopathology. 1983; 7:229–249. [PubMed: 6852784]
6. Kivela T, Tarkkanen A. The Merkel cell and associated neoplasms in the eyelids and periocular region. Surv Ophthalmol. 1990; 35:171–187. [PubMed: 2274847]
7. Bichakjian CK, Lowe L, Lao CD, et al. Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. Cancer. 2007; 110:1–12. [PubMed: 17520670]
8. Bobos M, Hytiroglou P, Kostopoulos I, et al. Immunohistochemical distinction between merkel cell carcinoma and small cell carcinoma of the lung. Am J Dermatopathol. 2006; 28:99–104. [PubMed: 16625069]
9. Becker JC, Kauczok CS, Ugurel S, et al. Merkel cell carcinoma: molecular pathogenesis, clinical features and therapy. J Dtsch Dermatol Ges. 2008; 6:709–719. [PubMed: 19000060]
10. Merkel cell carcinoma: recent progress and current priorities on etiology, pathogenesis, and clinical management. J Clin Oncol. 2009; 27:4021–4026. [PubMed: 19597021]
11. Tang CK, Toker C. Trabecular carcinoma of the skin: an ultrastructural study. Cancer. 1978; 42:2311–2321. [PubMed: 719609]
12. Tang CK, Toker C. Trabecular carcinoma of the skin: further clinicopathologic and ultrastructural study. Mt Sinai J Med. 1979; 46:516–523. [PubMed: 317141]
13. Eng TY, Boersma MG, Fuller CD, et al. A comprehensive review of the treatment of Merkel cell carcinoma. Am J Clin Oncol. 2007; 30:624–636. [PubMed: 18091058]
14. Cerroni L, Kerl H. Primary cutaneous neuroendocrine (Merkel cell) carcinoma in association with squamous- and basal-cell carcinoma. Am J Dermatopathol. 1997; 19:610–613. [PubMed: 9415620]
15. Gomez LG, DiMaio S, Silva EG, Mackay B. Association between neuroendocrine (Merkel cell) carcinoma and squamous carcinoma of the skin. Am J Surg Pathol. 1983; 7:171–177. [PubMed: 6859392]
16. Popp S, Waltering S, Herbst C, et al. UV-B-type mutations and chromosomal imbalances indicate common pathways for the development of Merkel and skin squamous cell carcinomas. Int J Cancer. 2002; 99:352–360. [PubMed: 11992403]
17. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation. 1999; 68:1717–1721. [PubMed: 10609948]
18. Koljonen V, Kukko H, Tukiainen E, et al. Incidence of Merkel cell carcinoma in renal transplant recipients. Nephrol Dial Transplant. 2009; 24:3231–3235. [PubMed: 19586970]
19. Bensaleh H, Perney P, Dereure O, et al. Merkel cell carcinoma in a liver transplant patient. Am J Clin Dermatol. 2007; 8:239–241. [PubMed: 17645379]
20. An KP, Ratner D. Merkel cell carcinoma in the setting of HIV infection. J Am Acad Dermatol. 2001; 45:309–312. [PubMed: 11464198]
21. Engels EA, Frisch M, Goedert JJ, et al. Merkel cell carcinoma and HIV infection. Lancet. 2002; 359:497–498. [PubMed: 11853800]
22. Tuneu A, Pujol RM, Moreno A, et al. Postirradiation Merkel cell carcinoma. J Am Acad Dermatol. 1989; 20:505–507. [PubMed: 2918118]
23. Lunder EJ, Stern RS. Merkel-cell carcinomas in patients treated with methoxsalen and ultraviolet A radiation. N Engl J Med. 1998; 339:1247–1248. [PubMed: 9786759]
24. Ho SY, Tsai YC, Lee MC, Guo HR. Merkel cell carcinoma in patients with long-term ingestion of arsenic. J Occup Health. 2005; 47:188–192. [PubMed: 15824485]
25. Lanoy E, Engels EA. Skin cancers associated with autoimmune conditions among elderly adults. Br J Cancer. 2010; 103:112–114. [PubMed: 20551958]
26. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008; 319:1096–1100. [PubMed: 18202256]
27. zur Hausen H. Novel human polyomaviruses--re-emergence of a well known virus family as possible human carcinogens. Int J Cancer. 2008; 123:247–250. [PubMed: 18449881]

28. Kassem A, Schopflin A, Diaz C, et al. Frequent detection of Merkel cell polyomavirus in human Merkel cell carcinomas and identification of a unique deletion in the VP1 gene. *Cancer Res.* 2008; 68:5009–5013. [PubMed: 18593898]
29. Foulongne V, Kluger N, Dereure O, et al. Merkel cell polyomavirus and Merkel cell carcinoma, France. *Emerg Infect Dis.* 2008; 14:1491–1493. [PubMed: 18760031]
30. Bhatia K, Modali R, Goedert JJ. Merkel cell polyomavirus is not detected in mesotheliomas. *J Clin Virol.* 2010; 47:196–198. [PubMed: 20006539]
31. Garneski KM, Warcola AH, Feng Q, et al. Merkel cell polyomavirus is more frequently present in North American than Australian Merkel cell carcinoma tumors. *J Invest Dermatol.* 2009; 129:246–248. [PubMed: 18650846]
32. Becker JC, Houben R, Ugurel S, et al. MC polyomavirus is frequently present in Merkel cell carcinoma of European patients. *J Invest Dermatol.* 2009; 129:248–250. [PubMed: 18633441]
33. Varga E, Kiss M, Szabo K, Kemeny L. Detection of Merkel cell polyomavirus DNA in Merkel cell carcinomas. *Br J Dermatol.* 2009; 161:930–932. [PubMed: 19438857]
34. Touze A, Gaitan J, Maruani A, et al. Merkel cell polyomavirus strains in patients with merkel cell carcinoma. *Emerg Infect Dis.* 2009; 15:960–962. [PubMed: 19523303]
35. Sastre-Garau X, Peter M, Avril MF, et al. Merkel cell carcinoma of the skin: pathological and molecular evidence for a causative role of MCV in oncogenesis. *J Pathol.* 2009; 218:48–56. [PubMed: 19291712]
36. Duncavage EJ, Zehnauer BA, Pfeifer JD. Prevalence of Merkel cell polyomavirus in Merkel cell carcinoma. *Mod Pathol.* 2009; 22:516–521. [PubMed: 19252474]
37. Wetzels CT, Hoefnagel JG, Bakkers JM, et al. Ultrastructural proof of polyomavirus in Merkel cell carcinoma tumour cells and its absence in small cell carcinoma of the lung. *PLoS One.* 2009; 4:e4958. [PubMed: 19305499]
38. Helmbold P, Lahtz C, Enk A, et al. Frequent occurrence of RASSF1A promoter hypermethylation and Merkel cell polyomavirus in Merkel cell carcinoma. *Mol Carcinog.* 2009; 48:903–909. [PubMed: 19326371]
39. Andres C, Belloni B, Puchta U, et al. Prevalence of MCPyV in Merkel cell carcinoma and non-MCC tumors. *J Cutan Pathol.* 2009
40. Nakajima H, Takaishi M, Yamamoto M, et al. Screening of the specific polyoma virus as diagnostic and prognostic tools for Merkel cell carcinoma. *J Dermatol Sci.* 2009; 56:211–213. [PubMed: 19709861]
41. Busam KJ, Jungbluth AA, Rekthman N, et al. Merkel cell polyomavirus expression in merkel cell carcinomas and its absence in combined tumors and pulmonary neuroendocrine carcinomas. *Am J Surg Pathol.* 2009; 33:1378–1385. [PubMed: 19609205]
42. Tolstov YL, Pastrana DV, Feng H, et al. Human Merkel cell polyomavirus infection II. MCV is a common human infection that can be detected by conformational capsid epitope immunoassays. *Int J Cancer.* 2009; 125:1250–1256. [PubMed: 19499548]
43. Pastrana DV, Tolstov YL, Becker JC, et al. Quantitation of human seroresponsiveness to Merkel cell polyomavirus. *PLoS Pathog.* 2009; 5:e1000578. [PubMed: 19750217]
44. Agelli M, Clegg LX, Becker JC, Rollison DE. The etiology and epidemiology of merkel cell carcinoma. *Curr Probl Cancer.* 2010; 34:14–37. [PubMed: 20371072]
45. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol.* 2003; 49:832–841. [PubMed: 14576661]
46. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol.* 2008; 58:375–381. [PubMed: 18280333]
47. Poulsen M. Merkel cell carcinoma of skin: diagnosis and management strategies. *Drugs Aging.* 2005; 22:219–229. [PubMed: 15813655]
48. Stokes JB, Graw KS, Dengel LT, et al. Patients with Merkel cell carcinoma tumors ≤ 1.0 cm in diameter are unlikely to harbor regional lymph node metastasis. *J Clin Oncol.* 2009; 27:3772–3777. [PubMed: 19581538]
49. Guler-Nizam E, Leiter U, Metzler G, et al. Clinical course and prognostic factors of Merkel cell carcinoma of the skin. *Br J Dermatol.* 2009; 161:90–94. [PubMed: 19438439]

50. Sarnaik AA, Lien MH, Nghiem P, Bichakjian CK. Clinical recognition, diagnosis, and staging of merkel cell carcinoma, and the role of the multidisciplinary management team. *Curr Probl Cancer*. 2010; 34:38–46. [PubMed: 20371073]
51. Haag ML, Glass LF, Fenske NA. Merkel cell carcinoma. Diagnosis and treatment. *Dermatol Surg*. 1995; 21:669–683. [PubMed: 7633811]
52. Zager JS, Brodsky S, Berman CG. Imaging of Merkel cell carcinoma. *Curr Probl Cancer*. 2010; 34:65–76. [PubMed: 20371075]
53. Peloschek P, Novotny C, Mueller-Mang C, et al. Diagnostic imaging in Merkel cell carcinoma: lessons to learn from 16 cases with correlation of sonography, CT, MRI and PET. *Eur J Radiol*. 2010; 73:317–323. [PubMed: 19108971]
54. Concannon R, Larcos GS, Veness M. The impact of (18)F-FDG PET-CT scanning for staging and management of Merkel cell carcinoma: results from Westmead Hospital, Sydney, Australia. *J Am Acad Dermatol*. 2010; 62:76–84. [PubMed: 20082888]
55. Lampreave JL, Benard F, Alavi A, et al. PET evaluation of therapeutic limb perfusion in Merkel's cell carcinoma. *J Nucl Med*. 1998; 39:2087–2090. [PubMed: 9867147]
56. Golan H, Volkov O, Linchinsky O, Melloul M. FDG-PET imaging in Merkel cell carcinoma - value of head-to-toe scan. *Nucl Med Rev Cent East Eur*. 2005; 8:135–136. [PubMed: 16437401]
57. Yao M, Smith RB, Hoffman HT, et al. Merkel cell carcinoma: two case reports focusing on the role of fluorodeoxyglucose positron emission tomography imaging in staging and surveillance. *Am J Clin Oncol*. 2005; 28:205–210. [PubMed: 15803018]
58. Wong CO, Pham AN, Dworkin HJ. F-18 FDG Accumulation in an Octreotide Negative Merkel Cell Tumor. *Clin Positron Imaging*. 2000; 3:71–73. [PubMed: 10838403]
59. Nguyen BD. Positron emission tomographic imaging of Merkel cell carcinoma. *Clin Nucl Med*. 2002; 27:922–923. [PubMed: 12607889]
60. Talbot JN, Kerrou K, Missoum F, et al. 6-[F-18]fluoro-L-DOPA positron emission tomography in the imaging of Merkel cell carcinoma: preliminary report of three cases with 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography or pentetreotide-(111In) SPECT data. *Mol Imaging Biol*. 2005; 7:257–261. [PubMed: 16082495]
61. Iagaru A, Quon A, McDougall IR, Gambhir SS. Merkel cell carcinoma: Is there a role for 2-deoxy-2-[f-18]fluoro-D-glucose-positron emission tomography/computed tomography? *Mol Imaging Biol*. 2006; 8:212–217. [PubMed: 16724293]
62. Belhocine T, Pierard GE, Fruhling J, et al. Clinical added-value of 18FDG PET in neuroendocrine-merkel cell carcinoma. *Oncol Rep*. 2006; 16:347–352. [PubMed: 16820914]
63. Tai P. Merkel cell cancer: update on biology and treatment. *Curr Opin Oncol*. 2008; 20:196–200. [PubMed: 18300770]
64. Pectasides D, Pectasides M, Economopoulos T. Merkel cell cancer of the skin. *Ann Oncol*. 2006; 17:1489–1495. [PubMed: 16565213]
65. Merkel cell carcinoma. American Joint Committee on Cancer.: *AJCC Cancer Staging Manual*. 7. New York, NY: Springer; 2010. p. 315-319.
66. Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, et al. Development of the first American joint committee on cancer staging system for Merkel cell carcinoma based upon prognostic factors analysis of 5.823 national cancer database cases. *J Clin Oncol*. 2009
67. Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: histologic features and prognosis. *Cancer*. 2008; 113:2549–2558. [PubMed: 18798233]
68. Goldberg SR, Neifeld JP, Frable WJ. Prognostic value of tumor thickness in patients with Merkel cell carcinoma. *J Surg Oncol*. 2007; 95:618–622. [PubMed: 17345617]
69. Sandel, HDT; Day, T.; Richardson, MS., et al. Merkel cell carcinoma: does tumor size or depth of invasion correlate with recurrence, metastasis, or patient survival? *Laryngoscope*. 2006; 116:791–795. [PubMed: 16652089]
70. Mann GB, Allen PJ, Coit DG. Merkel cell carcinoma. *Aust N Z J Surg*. 1999; 69:87. [PubMed: 10030807]
71. Boyer JD, Zitelli JA, Brodland DG, D'Angelo G. Local control of primary Merkel cell carcinoma: review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. *J Am Acad Dermatol*. 2002; 47:885–892. [PubMed: 12451374]

72. Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol*. 2005; 23:2300–2309. [PubMed: 15800320]
73. Bajetta E, Celio L, Platania M, et al. Single-institution series of early-stage Merkel cell carcinoma: long-term outcomes in 95 patients managed with surgery alone. *Ann Surg Oncol*. 2009; 16:2985–2993. [PubMed: 19609619]
74. O'Connor WJ, Brodland DG. Merkel cell carcinoma. *Dermatol Surg*. 1996; 22:262–267. [PubMed: 8599738]
75. Fenig E, Brenner B, Katz A, et al. The role of radiation therapy and chemotherapy in the treatment of Merkel cell carcinoma. *Cancer*. 1997; 80:881–885. [PubMed: 9307187]
76. Lawenda BD, Thiringer JK, Foss RD, Johnstone PA. Merkel cell carcinoma arising in the head and neck: optimizing therapy. *Am J Clin Oncol*. 2001; 24:35–42. [PubMed: 11232947]
77. Brady MS. Current management of patients with merkel cell carcinoma. *Dermatol Surg*. 2004; 30:321–325. [PubMed: 14871227]
78. Veness MJ. Merkel cell carcinoma (primary cutaneous neuroendocrine carcinoma): an overview on management. *Australas J Dermatol*. 2006; 47:160–165. [PubMed: 16866994]
79. Allen PJ, Zhang ZF, Coit DG. Surgical management of Merkel cell carcinoma. *Ann Surg*. 1999; 229:97–105. [PubMed: 9923806]
80. Gillenwater AM, Hessel AC, Morrison WH, et al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. *Arch Otolaryngol Head Neck Surg*. 2001; 127:149–154. [PubMed: 11177031]
81. Ott MJ, Tanabe KK, Gadd MA, et al. Multimodality management of Merkel cell carcinoma. *Arch Surg*. 1999; 134:388–392. discussion 392–383. [PubMed: 10199311]
82. O'Connor WJ, Roenigk RK, Brodland DG. Merkel cell carcinoma. Comparison of Mohs micrographic surgery and wide excision in eighty-six patients. *Dermatol Surg*. 1997; 23:929–933. [PubMed: 9357504]
83. Messina JL, Reintgen DS, Cruse CW, et al. Selective lymphadenectomy in patients with Merkel cell (cutaneous neuroendocrine) carcinoma. *Ann Surg Oncol*. 1997; 4:389–395. [PubMed: 9259965]
84. Victor NS, Morton B, Smith JW. Merkel cell cancer: is prophylactic lymph node dissection indicated? *Am Surg*. 1996; 62:879–882. [PubMed: 8895705]
85. Gupta SG, Wang LC, Penas PF, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. *Arch Dermatol*. 2006; 142:685–690. [PubMed: 16785370]
86. Ratner D, Nelson BR, Brown MD, Johnson TM. Merkel cell carcinoma. *J Am Acad Dermatol*. 1993; 29:143–156. [PubMed: 8335732]
87. Boyle F, Pendlebury S, Bell D. Further insights into the natural history and management of primary cutaneous neuroendocrine (Merkel cell) carcinoma. *Int J Radiat Oncol Biol Phys*. 1995; 31:315–323. [PubMed: 7836085]
88. Yiengpruksawan A, Coit DG, Thaler HT, et al. Merkel cell carcinoma. Prognosis and management. *Arch Surg*. 1991; 126:1514–1519. [PubMed: 1842182]
89. Maza S, Trefzer U, Hofmann M, et al. Impact of sentinel lymph node biopsy in patients with Merkel cell carcinoma: results of a prospective study and review of the literature. *Eur J Nucl Med Mol Imaging*. 2006; 33:433–440. [PubMed: 16432719]
90. Leong SP. Selective sentinel lymphadenectomy for malignant melanoma, Merkel cell carcinoma, and squamous cell carcinoma. *Cancer Treat Res*. 2005; 127:39–76. [PubMed: 16209077]
91. Kurul S, Mudun A, Aksakal N, Aygen M. Lymphatic mapping for Merkel cell carcinoma. *Plast Reconstr Surg*. 2000; 105:680–683. [PubMed: 10697177]
92. Fang LC, Lemos B, Douglas J, et al. Radiation monotherapy as regional treatment for lymph node-positive Merkel cell carcinoma. *Cancer*. 2010; 116:1783–1790. [PubMed: 20162707]
93. Mortier L, Mirabel X, Fournier C, et al. Radiotherapy alone for primary Merkel cell carcinoma. *Arch Dermatol*. 2003; 139:1587–1590. [PubMed: 14676075]

94. Veness M, Foote M, Gebiski V, Poulsen M. The Role of Radiotherapy Alone in Patients With Merkel Cell Carcinoma: Reporting the Australian Experience of 43 Patients. *Int J Radiat Oncol Biol Phys.* 2009
95. Morrison WH, Peters LJ, Silva EG, et al. The essential role of radiation therapy in securing locoregional control of Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys.* 1990; 19:583–591. [PubMed: 2211207]
96. Foote M, Harvey J, Porceddu S, et al. Effect of radiotherapy dose and volume on relapse in Merkel cell cancer of the skin. *Int J Radiat Oncol Biol Phys.* 2010; 77:677–684. [PubMed: 19906498]
97. Wilder RB, Harari PM, Graham AR, et al. Merkel cell carcinoma. Improved locoregional control with postoperative radiation therapy. *Cancer.* 1991; 68:1004–1008. [PubMed: 1913471]
98. Meeuwissen JA, Bourne RG, Kearsley JH. The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys.* 1995; 31:325–331. [PubMed: 7836086]
99. Veness MJ, Perera L, McCourt J, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. *ANZ J Surg.* 2005; 75:275–281. [PubMed: 15932436]
100. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol.* 2006; 142:693–700. [PubMed: 16785371]
101. Poulsen M, Round C, Keller J, et al. Factors influencing relapse-free survival in Merkel cell carcinoma of the lower limb--a review of 60 cases. *Int J Radiat Oncol Biol Phys.* 2010; 76:393–397. [PubMed: 19515508]
102. Tai P, Yu E, Assouline A, et al. Management of Merkel cell carcinoma with emphasis on small primary tumors--a case series and review of the current literature. *J Drugs Dermatol.* 2010; 9:105–110. [PubMed: 20214170]
103. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *J Clin Oncol.* 2007; 25:1043–1047. [PubMed: 17369567]
104. Clark JR, Veness MJ, Gilbert R, et al. Merkel cell carcinoma of the head and neck: is adjuvant radiotherapy necessary? *Head Neck.* 2007; 29:249–257. [PubMed: 17163472]
105. Merkel cell carcinoma. NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2010:1.
106. Poulsen MG, Rischin D, Porter I, et al. Does chemotherapy improve survival in high-risk stage I and II Merkel cell carcinoma of the skin? *Int J Radiat Oncol Biol Phys.* 2006; 64:114–119. [PubMed: 16125873]
107. Kokoska ER, Kokoska MS, Collins BT, et al. Early aggressive treatment for Merkel cell carcinoma improves outcome. *Am J Surg.* 1997; 174:688–693. [PubMed: 9409598]
108. Poulsen M, Rischin D, Walpole E, et al. 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. *J Clin Oncol.* 2003; 21:4371–4376. [PubMed: 14645427]
109. Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Cancer.* 1999; 85:2589–2595. [PubMed: 10375107]
110. Tai PT, Yu E, Winquist E, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. *J Clin Oncol.* 2000; 18:2493–2499. [PubMed: 10856110]

Figure 1.

Figures 1A–E illustrate clinical appearance of MCC.

- A.** Rapidly growing violaceous firm painless nodule in the right ear.
- B.** A large ulcerative lesion in the lower lip with clinical positive neck nodes. (Reprint request is pending)
- C.** Multiple erythematous cutaneous nodules with central ulceration in buttock. (Reprint request is pending)
- D.** Biopsy-proven MCC in the right lateral foot in proximity to previous squamous cell carcinoma.
- E.** Metastatic MCC in the left breast.

Figure 2.

Figures 2A–B. MCC histology demonstrating cords, trabeculae, or sheets of small monomorphic cell proliferation, with hyperchromatic nuclei and scanty cytoplasm, frequent mitoses and apoptotic bodies. Vascular invasion (arrow) is seen on 2B. Figures 2C–D. Immunostains illustrating uptake of CK20 (punctuated paranuclear stain) and NSE (in cytoplasm with a dark rim around the large round nucleus) immunostain.

A. H&E stain, 100X.

B. H&E stain, 400X

C. CK20 stain, 400X (Reprint request is pending)

D. NSE stain, 400X

Figure 3.

Figures 3A–D. MCC Imaging.

A. Abdominal CT illustrates metastatic retroperitoneal MCC.

B. MRI shows recurrent MCC in distal right arm

C. FDG-PET scan demonstrates metastatic MCC in the mediastinum and liver from a mandibular primary. (Reprint request is pending)

D. PET-CT demonstrates metastatic biopsy-proven MCC in the right iliac node from a small foot primary.

Table 1**AJCC Staging for Merkel Cell Carcinoma**

T	N	M
TX: Primary tumor cannot be assessed. T0: No evidence of primary tumor (e.g. nodal/metastatic presentation without associated primary). Tis: <i>In situ</i> primary tumor. T1: 2 cm maximum tumor dimension T2: >2 cm but 5 cm maximum tumor dimension. T3: >5cm maximum tumor dimension. T4: Primary tumor invades bone, muscle, fascia, or cartilage.	NX: Regional lymph nodes cannot be assessed. N0: No regional lymph node metastasis. cN0: Nodes negative by clinical exam (via inspection, palpation, and/or imaging, but no pathologic node exam performed). pN0: Nodes negative by pathologic exam. N1: Metastases in regional lymph node(s). N1a: Micrometastasis (diagnosed after sentinel or elective lymphadenectomy). N1b: Macrometastasis (clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy). N2: In transit metastasis (distinct from 1° lesion and located either between 1° lesion and draining regional LN or distal to the 1° lesion).	M0: No distant metastasis. M1: Metastases beyond regional lymph nodes. M1a: Metastases to skin, subcutaneous tissues, or distant lymph nodes. M1b: Metastasis to lung. M1c: Metastases to all other visceral sites.

Stage	T	N	M
0	Tis	N0	M0
IA	T1	pN0	M0
IB	T1	cN0	M0
IIA	T2/T3	pN0	M0
IIB	T2/T3	cN0	M0
IIC	T4	N0	M0
IIIA	Any T	N1a	M0
IIIB	Any T	N1b/N2	M0
IV	Any T	Any N	M1

Merkel cell carcinoma. In: American Join Committee on Cancer: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 318-9.

Table 2

ICD Codes for Merkel Cell Carcinoma

CODE	NAME
209.31	Merkel cell carcinoma of the face
209.32	Merkel cell carcinoma of the scalp and neck
209.33	Merkel cell carcinoma of the upper limb
209.34	Merkel cell carcinoma of the lower limb
209.35	Merkel cell carcinoma of the trunk
209.36	Merkel cell carcinoma of other sites
209.75	Secondary Merkel cell carcinoma
V10.91	Personal history of malignant neuroendocrine tumor

Table 3

Treatment Results of Selected Studies of Merkel Cell Carcinoma

Author (Year)	n	Treatment	Radiation Dose (Gy)	Chemotherapy	Results	p	Conclusions
Fang <i>et al.</i> 92 (2010)	50	S ± RT ± C	Unspecified	Cis/Carbo/Etop (10), Etop (1), Cyclophos 5FU/MTX (1), Etop/Doxo (1), unknown (1)	2-yr RFRS 78% vs 73% 2-yr DSS 73% vs 59% RT vs CLND 2-yr OS 81% vs 61% Microscopic vs palpable nodes	0.8 0.9 0.05	Radiation monotherapy showed similar efficacy compared to CLND in regional control of lymph-node positive MCC.
Footo <i>et al.</i> 96 (2010)	112	S ± RT ± C	25–62	Platinum based (15)	2-yr OS 72%, 2-yr local-regional control rate 75% Relapse rate lower with elective nodal RT	<0.05	Demonstrates dose-response of elective nodal RT for subclinical (50 Gy) and gross disease (55 Gy).
Poulsen <i>et al.</i> 101 (2010)	60	S ± RT ± C	30–60 50 median	Carbo/Etop (9)	5-yr RFS 0% vs 28% S vs S + RT ± C.	<0.05	Study of MCC in lower limb. Elective RT to inguinal nodes reduces relapse.
Tai <i>et al.</i> 102 (2010)	145	S ± RT ± C	50 (most common)	Etop, Cis, Carbo, Cyclophos, Adriamycin, vincristine, taxotere.	LN mets 17%, 39%, 60% Recurrence 30%, 52%, 77% In tumors <1cm, 1–2cm, and >2cm respectively.	0.002 0.007	Favorable factors include early stage of presentation, wide LE, LND and use of adjuvant RT (p<0.03)
Bajetta <i>et al.</i> 73 (2009)	95	S alone	None	None	5-yr DSS 67% overall; 5-yr regional recurrence 0% vs 39% with 2 vs >2 metastatic LN	0.004	Results vary when surgery alone is used for MCC. >2 metastatic nodes increased regional and distant recurrence.
Veness <i>et al.</i> 94 (2009)	43	RT alone	50 median	None specified	In-field control 75%, Relapse 53%. Nodal status assoc with RFS	0.005	RT can achieve high chance of local control. Recommend 50–55 Gy.
Clark <i>et al.</i> 104 (2007)	110	S + RT vs RT or S alone	9–70 50 median	Platinum-based (8), Etop (5), alkalooids (3).	5-yr LC 84%, 5-yr LRC 69% S + RT had better DSS on univariable analysis	0.013	S + RT improves DSS for tumors >1cm even if node negative head and neck MCC
Mojica <i>et al.</i> 103 (2007)	1665	S ± RT ± C *	Not specified	Not specified *	Median OS 45mo vs 63mo S alone vs S + RT	<0.001	Analysis of SEER registry data supports adjuvant RT to improve survival.

Author (Year)	n	Treatment	Radiation Dose (Gy)	Chemotherapy	Results	p	Conclusions
Lewis <i>et al.</i> ¹⁰⁰ (2006)	1254	S ± RT	Not specified	None specified	Local recur 24.5% vs 9.6% S only vs S + RT Regional recur 44.8% vs 13.2% S only vs S + RT	<0.001 <0.001	Metanalysis study supports local adjuvant RT to reduce local and regional recurrence.
Allen <i>et al.</i> ⁷² (2005)	251	S ± RT ± C	38–61	Carbo/Etop, Vincristine, Cyclophos, Doxo (25)	5-yr DSS 64% Stages I-IV: 81%, 67%, 52%, 11% LR 10% vs 8% Nodal relapse 13% vs 26% Adjuvant RT vs no RT	0.001 0.76 0.13	Pathologic stage predicts long-term survival. Recommend negative margins and nodal staging. RT does not reduce LR.
McAfee <i>et al.</i> ¹¹¹ (2005)	34	S ± RT vs C + RT (2)	30–74.4 (Median 60)	Carbo, Cis (9)	5-yr LC 94%; LRC 80%; free DM 60%; CSS 52%; OS 37%		If treated aggressively with S + RT, about 50% chance of cure. Recommend adjuvant RT
Veness <i>et al.</i> ⁹⁹ (2005)	86	S ± RT ± C	18–70	Platinum-based (6)	Total relapse 55% Nodal relapse 18% vs 37% Adjuvant RT vs no RT 5-yr OS 47%; 5-yr DFS 25%	<0.001	Recommend adjuvant RT for improvement of regional control rates.
Eng <i>et al.</i> ¹¹² (2004)	85	S ± RT ± C	50–60	Mostly Cis/Etop (16)	Recurrence 40% Persistent disease 12% 5-yr actuarial survival 55% Stage 1 survival 68%	<0.01	Adjuvant R ± C decreased recurrence. Predictors of good outcome were female sex, early stage
Poulsen <i>et al.</i> ¹⁰⁸ (2003)	53	S + RT/C	50	Carbo/Etop (53)	RFS 65%; 3-yr OS 76%; LRC 75%; overall distant control 76%.		Phase II study of high risk patients shows good results with combined therapy.

S, surgery; RT, radiation therapy; C, chemotherapy; Cis, cisplatin; Carbo, carboplatin; Etop, etoposide; Cyclophos, cyclophosphamide; 5FU, 5-fluorouracil; MTX, methotrexate; Doxo, doxorubicin; RRFs, regional recurrence free survival; DSS, disease specific survival; CLND, completion lymphadenectomy; OS, overall survival; RFS, relapse free survival; LN, lymph node; LE, local excision; LC, local control; LRC, locoregional control; LR, local recurrence; RR, regional recurrence; DM, distant metastasis; CSS, cause specific survival.

* SEER Database does not provide information about chemotherapy or about SLNB.