Merkel cell carcinoma: a review of management

Michael J. Veness, Carsten E. Palme and Gary J. Morgan

Head and Neck Cancer Service, Westmead Hospital, University of Sydney, Sydney, Australia

Correspondence to Associate Professor Michael J. Veness, MBBS, MD (UNSW) MMed, FRANZCR, Radiation Oncologist, Senior Staff Specialist, Department of Radiation Oncology, University of Sydney, Westmead Hospital, Westmead, Sydney, NSW, 2145, Australia
Tel: +61 2 984 56499; fax: +61 2 9891 5814; e-mail: michael.veness@swahs.health.nsw.gov.au

Current Opinion in Otolaryngology & Head and Neck Surgery 2008, 16:170–174

Purpose of review

Merkel cell carcinoma is an uncommon but aggressive primary cutaneous neuroendocrine (small cell) carcinoma. The head and neck is a frequent site (50–60%) for presentation. The optimal treatment of patients with Merkel cell carcinoma remains debated with recent evidence adding support for a multimodality approach. Despite this the outcome for patients with unfavourable disease remains poor and in many series 25–50% of patients die as a direct result of Merkel cell carcinoma.

Recent findings

Wide excision (2–3 cm) of the primary lesion has been recommended, although achieving this is often impossible within the functional and cosmetic constraints of the head and neck. The well-documented responsiveness of this disease to radiotherapy and chemotherapy has strengthened the case for less radical surgery. Current best practice, as presented in recent publications, would support adjuvant wide-field radiotherapy, delivered after wide excision with negative microscopic margins, as best practice. The role of platinum-based chemotherapy remains under investigation.

Summary

Most patients with a Merkel cell carcinoma should be recommended wide-field adjuvant radiotherapy to encompass the primary site, in-transit tissue and first echelon lymph nodes following surgery. The benefit of adding chemotherapy is currently unproven and should be considered on an individual basis.

Keywords

chemotherapy, Merkel cell carcinoma, radiotherapy

Curr Opin Otolaryngol Head Neck Surg 16:170–174

1040-872X

Introduction

Merkel cell carcinoma (MCC) is an uncommon aggressive primary cutaneous neuroendocrine (small cell) cancer. While most patients with a nonmelanoma skin cancer (NMSC) are cured many patients diagnosed with MCC have a poor outcome characterized by locoregional and distant relapse [1–3]. Cancer specific death occurs in 25–50% of patients and those presenting with clinically localized disease have the best chance of cure. The low incidence of MCC in the population means there is a lack of high-level evidence from controlled trials to guide clinicians, but there are published institutional series that often include multivariate analysis [4–11]. There is emerging evidence that multimodality treatment, incorporating adjuvant radiotherapy, improves outcome (locoregional control and survival) compared with surgery alone [4,6,8,12–14]. Despite this, some clinicians still consider surgery alone as adequate treatment, at least in early stage disease [15–17]. The routine use of adjuvant chemotherapy remains unresolved although there is evidence to suggest a potential role in improving outcome in select patients [18].

Background and epidemiology

Based on the United States Surveillance, Epidemiology, and End-Results (SEER) database the annual incidence in males and females is 0.34/100 000 and 0.17/100 000, respectively [19] with most patients older than 65 years and white (94%). In this study just under half (46%) of all lesions occurred in the head and neck and at diagnosis half of all patients had localized disease with nodal metastases present in just over a quarter of all patients. Chronic sun exposure, similar to other NMSCs, is probably the major contributor to the development of MCC as typified by the classic presentation of a lesion located on the head and neck in an older white patient. As with other NMSCs, especially squamous cell carcinoma, immunosuppressed patients (organ transplant recipients) [20,21] or those diagnosed with chronic lymphocytic leukaemia (CLL) [22] are at higher risk of developing MCC than the

general population and having a poor outcome. In a study of 41 organ transplant recipients with MCC many were younger, most (68%) had nodal disease at diagnosis and almost 60% died of their disease [21].

Presentation, diagnosis and staging

Patients often present with a painless nonulcerative dermal-based purplish lesion that may progress rapidly. The rarity of MCC means many clinicians (especially general practitioners) have not previously diagnosed a patient with MCC and therefore may not suspect a diagnosis of MCC. Diagnosis is usually established following excision of a lesion with pathology confirming MCC. Specific histochemical markers are needed to establish a diagnosis of MCC and exclude lymphoma or melanoma. The presence of cytokeratin 20 and neuroendocrine markers such as neuron-specific enolase, synaptophysin and chromogranin in association with negative markers for melanoma and lymphoma support a diagnosis of MCC [23]. Once pathology confirms the presence of cutaneous small cell carcinoma clinicians need to consider the possibility of metastatic small cell lung cancer, especially in smokers. All patients should have chest imaging to exclude lung cancer or the possibility of pulmonary metastases. Patients presenting with clinical nodal metastases should also have computed tomography scans of the abdomen and of the head and neck if the primary is located there. The role of PET scanning in staging MCC is unclear but potentially useful in select patients especially in restaging patients with recurrent disease and in investigating patients with suspected distant metastases at initial presentation [24].

A staging system developed by the Memorial Sloan Kettering Cancer Center separates patients into those with primary lesions less than 2 cm (stage I) and those greater than or equal to 2 cm (stage II) [17]. Patients with nodal disease are stage III and those with distant disease are stage IV. Of note patients may also present with metastatic nodal disease without an obvious index lesion. In one large study 19% of patients had metastatic MCC to nodes from an unknown primary [11] similar to another study of 80 patients that documented a 16% rate of nodal metastases from an unknown primary [8].

Prognostic factors

Prognostic factors based on clinical (site, size, stage) and treatment (addition of adjuvant treatment) factors as the most relevant predictors in MCC. In one study [17] stage at presentation was the only independent predictor of survival. Similarly others report a marked difference in 5-year survival in patients with localized disease only compared with those with locoregional disease (44 versus 23%; $P = 0.07$) [25]. The presence of clinical nodal metastases is a predictor of poor outcome [26]. In patients without clinical nodal metastases lesion size has been shown to predict outcome by some [9,27,28] but not by others [4,11,16,29]. Adjuvant radiotherapy has consistently been proven to confer a benefit in improving locoregional control [3,4,6,8,10–13,30]. Studies even suggest a survival benefit to the addition of adjuvant radiotherapy [6,10–13,30,31]. An Australian series [11] reported a significant benefit in median disease free survival with the addition of adjuvant locoregional radiotherapy (10.5 versus 4 months; $P < 0.01$). There are also emerging data that molecular markers may aid in predicting prognosis with a recent study [32] suggesting patients expressing p63 have a significantly worse outcome.

Treatment

Most patients with MCC should be treated with curative intent. A minority (<10%) will have distant metastases (skeletal or visceral) at presentation, and although treatable, are not curable. Patients with poor performance status may be offered a short course of radiotherapy to improve their quality of life.

Surgery

Surgery remains the initial treatment in patients with operable disease that are fit for an operation and do not have distant metastases. Patients with distant disease often still warrant local treatment, usually palliative radiotherapy, although in selected cases palliative surgery may be considered. There are proponents of local excision as appropriate treatment for selected patients without nodal involvement [3,5,15–17] although most studies support a multimodality approach in most patients.

Excision margins

Achieving the often recommended wide excision margins of 2–3 cm is difficult in the head and neck. In one study [17] of patients undergoing wide excision 94% achieved a negative margin but with only a mean excision margin of 11 mm despite only 29% of patients having a lesion located in the head and neck. With the addition of wide-field adjuvant radiotherapy the need to obtain wide excision margins at the expense of function or form is not necessary assuming a negative microscopic margin is obtained [33]. Although proponents of excision alone suggest surgery as appropriate treatment in many patients in a review of 1024 cases of MCC the authors identified 11 series ($n = 441$) that documented local relapse rates with, and without, adjuvant radiotherapy. The mean relapse rate reported with the addition of adjuvant radiotherapy was 10 versus 53% without ($P = 0.00001$) [31].

Nodal treatment (clinically node negative)

Local excision alone does not address the high risk of subclinical nodal disease. In one series [3] there was a

44% rate of nodal relapse in patients with lesions less than 10 mm. In an Australian study of patients treated with local excision 33 and 50% of patients, respectively, developed regional relapse with lesions 5–10 and greater than 10 mm in size [11]. In a review of the literature of 181 patients undergoing local surgery a total of 83 (46%) experienced nodal relapse [34]. Similarly the authors of one study [31] reported a 50% nodal relapse rate in patients treated with surgery alone compared to 19% in patients receiving adjuvant radiotherapy. With some exceptions (small midline facial lesions or lesions located below the knee) consideration should be given to electively treating first-echelon nodes. Both radiotherapy and surgery have been proposed as options and the modality chosen often depends on whether a patient is to be recommended adjuvant radiotherapy. In many cases of head and neck MCC nearby nodal basins can often be encompassed in en-bloc radiotherapy fields that also treat the primary site and intransit dermal lymphatics (e.g. parotid and upper cervical nodes treated in conjunction with a temple or cheek lesion). An alternative approach proposed by some clinicians is to perform sentinel node biopsy (SNB) as opposed to electively treating lymph nodes (see below).

Sentinel node biopsy

SNB may improve the ability to detect subclinical nodal metastases. In a small meta-analysis [35] 60 patients were identified from the literature. The authors reported 67% having a negative SNB with almost all patients (97%) remaining relapse-free, although median follow-up was only 7.3 months. In keeping with the high rate of subclinical metastases 33% of patients had a positive SNB. A third of this node-positive group subsequently developed locoregional or distant relapse highlighting the unfavorable outcome of patients with node-positive MCC. Of interest 15 SNB-positive patients that proceeded to node dissection (with or without radiotherapy or chemotherapy) all remained free of regional recurrence compared with a 75% regional relapse in those that were SNB-positive but did not receive nodal treatment. The qualified conclusions from this meta-analysis were that SNB-negative patients probably should not be recommended adjuvant treatment based on the low rate of relapse. In another review of 122 patients without clinical nodal disease 32% had pathological nodal metastases identified following SNB [36]. In this study the addition of adjuvant nodal radiotherapy to SNB-negative patients did not significantly impact on relapse-free survival (90 versus 70%; $P = 0.26$). At least one study [37] has highlighted discordant lymphatic drainage patterns in patients with cutaneous head and neck malignancies (including MCC). While there may be some evidence to support the routine use of SNB in many MCC patients further larger and prospective studies are needed to validate the results from these mainly small case series.

Nodal treatment (clinically node positive)

In patients with nodal disease surgery and adjuvant locoregional radiotherapy are recommended. One study [11] demonstrated improved regional control with this multimodality approach compared with nodal dissection alone (14 versus 43%). In a study of patients with both clinical and pathological nodal disease [17] nodal recurrence was 13% after surgery and radiotherapy versus 26% following surgery alone ($P = 0.13$). Despite not reaching statistical significance the crude difference in recurrence is of clinical relevance. Patients usually have multiple nodes, extranodal spread or close margins following nodal surgery putting them at risk of regional relapse. Patients with regional relapse are usually incurable either because of untreatable regional disease or the development of distant metastases. In patients with previously untreated unresectable nodal disease high-dose radiotherapy (approximately 60 Gy) may 'downstage' the patient so that nodal dissection could follow if disease regression improves operability.

Adjuvant radiotherapy

With few exceptions most studies report a marked benefit to locoregional control and survival to the addition of adjuvant radiotherapy. In the largest study ($n = 1665$) of its type the addition of adjuvant radiotherapy significantly improved median overall survival in patients with lesions larger than 2 cm from 21 to 50 months ($P = 0.0003$) [38••]. Lewis *et al.* [30] in a meta-analysis of 1254 patients reported a significant reduction in local (HR, 0.27; $P < 0.001$) and regional recurrence (HR, 0.34; $P < 0.001$) and a benefit in overall survival (HR, 0.63; $P = 0.04$) in patients treated with surgery and adjuvant radiotherapy compared with surgery alone. A University of Florida series of 34 patients treated mainly with surgery and adjuvant radiotherapy documented a low 6% local recurrence rate, although 38% of patients ultimately developed distant metastases [25]. Clark *et al.* [39•] analysed data from two Australian Hospitals (Westmead and Royal Prince Alfred Hospitals, Sydney) and from Princess Margaret Hospital, Canada and documented significant improvement in local control ($P = 0.009$), regional control ($P = 0.006$) and disease-free survival ($P = 0.013$) from combined treatment versus surgery alone. Jabbour *et al.* [40] in an Australian study confirmed both a survival benefit (HR 0.39; $P = 0.013$) and prolonged time to first recurrence (HR 0.39; $P = 0.004$) for patients receiving radiotherapy. In a study of patients with extremity MCC ($n = 38$) adjuvant radiotherapy significantly reduced the rate of local recurrence (HR 0.29). Of note 44% of patients that had observation of nearby lymph nodes developed relapse further highlighting the propensity for MCC to travel to draining nodal basins [41].

Chemotherapy

The routine use of adjuvant chemotherapy is unclear. Previous studies have utilized typical small cell lung cancer regimes of chemotherapy (carboplatinum and

etoposide). In an Australian phase II single-arm study 53 patients received concurrent (weeks 1 and 4) and adjuvant chemotherapy (weeks 7 and 10) (carboplatinum and etoposide) with radiotherapy with a 3-year overall survival, locoregional control and distant control rate of 76, 75 and 76%, respectively [18]. These impressive results, in patients with poor prognostic features, particularly the presence of nodal metastases in 33 (62%) patients, strongly suggest a potential benefit to the addition of combination chemotherapy in patients with unfavourable features. Another study [42] analysed patients treated with the addition of chemotherapy to radiotherapy ($n = 40$) compared with 62 patients treated without chemotherapy. The authors reported no significant overall survival benefit to those patients receiving chemotherapy ($P = 0.16$) and no improvement in distant control (65 versus 70%; $P = 0.61$). While not excluding a possible benefit to chemotherapy these results further add support for a randomized controlled trial to confirm the hypothesis that chemotherapy will benefit these patients. Such a study should aim to randomize patients to surgery and adjuvant radiotherapy alone versus surgery, adjuvant radiotherapy and chemotherapy (concurrent/adjuvant platinum based combination). Any proposed studies, however, will require a multinational institutional collaboration to achieve an adequate sample size.

Recurrent disease

Patients developing distant recurrence (visceral or skeletal) are incurable with a median survival of 6–12 months. Patients developing distant recurrence without locoregional failure almost certainly had microscopic distant disease present at diagnosis. Symptomatic patients may be candidates for palliative chemotherapy in the form of single-agent carboplatinum or even oral etoposide, a taxane, gemcitabine or irinotecan all of which have reported activity in neuroendocrine malignancies. Such treatment may improve symptoms and quality of life but is unlikely to extend survival beyond a few extra months compared to no chemotherapy. Many, however, are medically unfit for this treatment and should be referred to a palliative care physician. Similarly, patients may also benefit from palliative radiotherapy (20–25 Gy in four to five fractions) to sites of symptomatic local disease (e.g. painful bone metastases, nodal masses). A minority (20–30%) may develop only locoregional recurrence and are still potentially curable although the prognosis remains poor. In a study of 46 patients with recurrent MCC the overall survival was reported as 37%, although almost half (47%) had only local recurrence/persistence followed by distant (40%) and regional failure (13%), respectively [43]. In another study [42], 5-year survival was significantly worse in patients treated (with curative intent) in the setting of locoregional (stage I/II) recurrence compared with those without recurrence (22 versus 52%; $P \leq 0.001$). Clinicians should consider fully restaging patients in the setting of locoregional failure if there is consideration for radical intent retreatment.

Conclusion

There remains debate in the literature regarding the optimal approach to treating patients with MCC [44–48]. The heterogeneity of patients and treatment approaches reported in small institutional studies adds further to this uncertainty. Review articles that present an overview on managing MCC patients are not always in agreement on stage-related treatment recommendations particularly the role of adjuvant treatment [49,50•]. Despite this, and while some clinicians also present favorable outcome data on patients treated with surgery alone, the weight of current evidence adds strong support to a combined approach incorporating locoregional adjuvant radiotherapy as best practice [51•]. The role of platinum-based chemotherapy, or newer agents, requires further evaluation prior to incorporating this treatment into any standard approach.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 177).

1 Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. J Clin Oncol 2002; 20:588–598.

2 Tai PT, Yu E, Winquist E, *et al.* Chemotherapy in neuro-endocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. J Clin Oncol 2000; 18:2493–2499.

3 Gillenwater AM, Hessel AC, Morrison WH, *et al.* Merkel cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 2001; 127:149–154.

4 Ott MJ, Tanabe KK, Gadd MA, *et al.* Multimodality management of Merkel cell carcinoma. Arch Surg 1999; 134:388–393.

5 Allen PJ, Zhang ZF, Coit DG. Surgical management of Merkel cell carcinoma. Ann Surg 1999; 229:97–105.

6 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; 31:323–331.

7 Pacella J, Ashby M, Ainsle J, Minty C. The role of radiotherapy in the management of primary cutaneous neuroendocrine tumors (Merkel cell or trabecular carcinoma): experience at the Peter MacCallum Cancer Institute (Melbourne, Australia). Int J Radiat Oncol Biol Phys 1988; 14:1077–1084.

8 Wong KC, Zuletta F, Clarke SJ, Kennedy PJ. Clinical management and treatment outcomes of Merkel cell carcinoma. ANZ J Surg 1998; 68:354–358.

9 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.

10 Veness MJ, Morgan GJ, Gebski V. Adjuvant locoregional radiotherapy should be considered best practice in Merkel cell carcinoma of the head and neck. Head Neck 2005; 27:208–216.

11 Veness MJ, Perera L, McCourt J, *et al.* Merkel cell carcinoma: Improved regional control and survival with adjuvant radiotherapy. ANZ J Surg 2005; 75:275–281.

12 Kokoska ER, Kokoska MS, Collins BT, *et al.* Early aggressive treatment for merkel cell carcinoma improves outcome. Am J Surg 1997; 174:688–693.

13 Morrison WH, Peters LJ, Silvia 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.

14 Eng TY, Boersma MGK, Fuller CD, *et al.* Treatment of Merkel cell carcinoma. Am J Clin Oncol 2004; 27:510–515.

15 Mann GB, Allen PJ, Corr DG. Merkel cell carcinoma (personal View). ANZ J Surg 1999; 69:87.

16 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 radiotherapy. J Am Acad Dermatol 2002; 47:885–892.

17 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.

18 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.

19 Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol 2003; 49:832–841.

20 Veness MJ. Aggressive skin cancers in a cardiac transplant recipient. Australas Radiol 1997; 41:363–366.

21 Penn I, Roy FM. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation 1999; 68:1717–1721.

22 Vlad R, Woodlock TJ. Merkel cell carcinoma after chronic lymphocytic leukemia. Case report and literature review. Am J Clin Oncol 2003; 26:531–534.

23 Suarez C, Rodrigo JP, Ferlito A, *et al.* Merkel cell carcinoma of the head and neck. Oral Oncol 2004; 40:773–779.

24 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.

25 McAfee WJ, Morris CG, Mendenhall CM, *et al.* Merkel cell carcinoma: Treatment and outcome. Cancer 2005; 104:1761–1764.

26 Poulsen M. Merkel-cell carcinoma of the skin. Lancet Oncol 2005; 5:593–599.

27 Allen PJ, Busam K, Hill AD, *et al.* Immunohistochemical analysis of sentinel lymph nodes from patients with Merkel cell carcinoma. Cancer 2001; 92:1650–1655.

28 Eich HT, Eich D, Staar S, *et al.* Role of postoperative radiotherapy in the management of Merkel cell carcinoma. Am J Clin Oncol 2002; 25:50–56.

29 Sandel HD, 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.

30 Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. Arch Dermatol 2006; 142:693–700.

31 Medina-Franco H, Urist MM, Fiveash J, *et al.* Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol 2001; 8:204–208.

32 Asioli S, Righi A, Volante M, *et al.* P63 expression as a new prognostic marker in Merkel cell carcinoma. Cancer 2007; 110:640–647.

33 Poulsen M, Harvey J. Is there a diminishing role for surgery for Merkel cell carcinoma of the skin? A review of current management. ANZ J Surg 2002; 72:142–146.

34 Shaw JHF, Rumball E. Merkel cell carcinoma: clinical behaviour and treatment. Br J Surg 1991; 78:138–142.

35 Mehrany K, Otley CC, Weenig RH, *et al.* A meta-analysis of the prognostic significance of sentinel lymph node status in merkel cell carcinoma. Dermatol Surg 2002; 28:113–117.

36 Gupta SG, Wang LC, Penas PF, *et al.* Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma. Arch Dermatol 2006; 142:685–690.

37 Willis AI, Ridge JA. Discordant lymphatic drainage patterns revealed by serial lymphoscintigraphy in cutaneous head and neck malignancies. Head Neck 2007; 29:979–985.

38 •• Mojica P, Smith D, Ellenhorn JDI. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. J Clin Oncol 2007; 27:1043–1047.
The results from this large national data set present findings that no single study or series of studies could achieve. The results strongly support the addition of adjuvant radiotherapy in improving survival especially for patients with tumors >2 cm.

39 • 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.
This article presents the combined results of 110 patients with MCC located on the head and neck treated at three different tertiary institutions using various modalities. In keeping with the recent analysis of the SEER database [38••] patients with stage II disease obtained the greatest benefit from combined treatment in this study.

40 Jabbour J, Cumming R, Scolyer RA, *et al.* Merkel cell carcinoma: assessing the effect of wide local excision, lymph node dissection, and radiotherapy on recurrence and survival in early stage disease-results from a review of 82 consecutive cases diagnosed between 1992 and 2004. Ann Surg Oncol 2007; 14:1943–1952.

41 Senchenkov A, Barnes SA, Moran SL. Predictors of survival and recurrence in the surgical treatment of Merkel cell carcinoma of the extremities. J Surg Oncol 2007; 95:229–234.

42 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.

43 Eng TY, Naguib M, Fuller CD, *et al.* Treatment of recurrent Merkel cell carcinoma: an analysis of 46 cases. Am J Clin Oncol 2004; 24:576–583.

44 Wilson LD, Gruber SB. Merkel cell carcinoma and the controversial role of adjuvant radiation therapy: clinical choices in the absence of statistical evidence. J Am Acad Dermatol 2004; 50:435–437.

45 Boyer JD, Zitelli JA, Brodland DG, D'Angelo GM. Merkel cell carcinoma and the controversial role of adjuvant radiation therapy: clinical choices in the absence of statistical evidence [reply]. J Am Acad Dermatol 2004; 50:437–438.

46 Veness MJ. Merkel cell carcinoma: improved outcome with the addition of adjuvant therapy. J Clin Oncol 2005; 23:7235–7236.

47 Wilson LD, Housmann D, Smith BD. Improved outcome with the addition of adjuvant therapy. J Clin Oncol 2005; 23:7236–7237.

48 Allen PJ, Bowne WB, Jaques DP, *et al.* Improved outcome with the addition of adjuvant therapy (reply). J Clin Oncol 2005; 23:7237–7238.

49 Swann MH, Yoon J. Merkel cell carcinoma. Semin Oncol 2007; 34:51–56.

50 • Bichakjian CK, Lowe L, Loa CD, *et al.* Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. Cancer 2007; 110:1–12.
This is a comprehensive evidence-based overview on current management. The authors discuss at length the many controversies and uncertainties that are involved when treating these patients and emphasize the need for high-level evidence.

51 • Garneski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: Current data support radiation but not chemotherapy. J Am Acad Dermatol 2007; 57:166–169.
This is a concise and well-written review on the current role of adjuvant treatment in patients with MCC.