Otolaryngology: Open Access
ISSN: 2161-119X

Duffy et al., Otolaryngology 2014, 4:4
DOI: 10.4172/2161-119X.1000177

Research Article Open Access

Surgical Management of Head and Neck Merkel Cell Carcinoma, are we doing Enough?

Fergal O'Duffy*, Tadhg O'Dwyer and Samir Gendy

Department of Otolaryngology Head and Neck Surgery, the Mater Misericordiae University Hospital, Dublin, Ireland

Abstract

A case series and critical review of the current understanding and guidelines in management of Merkel cell carcinoma are presented. Merkel Cell Carcinoma of the head and neck is highly aggressive and has less predictable lymphatic drainage that that of the trunk and limbs. Variable surgical management strategies exist for the node negative neck including observation, radiation and prophylactic neck dissection.

Current National Comprehensive Cancer Network Guidelines [NCCN] advocate radiation treatment and Sentinel Node Biopsy [SLNB] for the node negative neck. A potential pitfall of this management is the reduced accuracy of SLNB in the neck due to variable lymphatic drainage. Also the short to long term morbidity of irradiating the neck should not be underestimated.

Merkel cell carcinoma is highly aggressive with micro metastasis reported at rates of 23% to 100%. In experienced surgical hands neck dissection in clinically node negative neck can provide excellent disease control with low morbidity and should be considered in the management of head and neck Merkel cell carcinoma.

Keywords: Carcinoma; Merkel cells; Metastatis; Prognosis

Introduction

Four cases of Merkel cell carcinoma treated at our institution over seven year period are presented. A review of the literature regarding optimum treatment is discussed. These tumours are generally pathologically aggressive and unpredictable [1]. We outline our management strategy and the disease factors which are important in dictating such a strategy.

Skin lesions are typically red or purple in appearance and present as a solitary dome-shaped nodule or indurated plaque in a sun-exposed area of the skin. They arise from the neural and epithelial tissues and are more commonly found in the elderly population and most frequently occur in the head and neck region [2,3]. There is a poor prognosis associated with Merkel cell carcinoma. Five year survival rates reported between 30-64% making Merkel cell the most aggressive of all cutaneous malignancies [2,4]. If untreated greater than 50% will develop nodal metastases [5,6]

The level of cell differentiation has been shown to correlate to survival with poorly differentiated tumours carrying a worse prognosis. Similarly advanced disease stage is associated with poorer survival rate. Meacham et al showed that stages I, II and III had a comparative survival of 77.8% at 12 months compared to 57.1 % for patients with stage IV disease [7]

Merkel cell carcinomas high rates of local and regional spread and recurrence even at early stage necessitate equally aggressive treatment of this tumour surgically and oncologically.

Case 1

79 year old male was referred by the dermatology service with a painless right- sided parotid mass, which had been present for 3 months. Six months earlier a one by two centimetre Merkel cell skin carcinoma was excised from the right side of his forehead.

A 2×2 cm parotid mass was palpable in the right parotid on clinical examination. There was no evidence of facial nerve involvement or deep parotid lobe extension. Furthermore a 3×2 cm ipsilateral level II lymph node was palpable. FNA cytology demonstrated multiple small cells infiltrates in both the parotid and lymph node suggestive of metastatic Merkel cell carcinoma. Computed Tomography and Magnetic resonance imaging were carried out (PET/CT not Available) confirming the mass in the superficial lobe of the parotid but also demonstrating metastatic lymph nodes in levels II, III, IV and V of the right neck.

The patient was treated with a right superficial parotidectomy and right radical neck dissection without complication. Intra-operatively the nodal lymphadenopathy was adherent to the internal jugular vein and accessory nerve, both of which were sacrificed along with the sternocleidomastoid muscle. The patient had subsequent adjuvant radiotherapy. The patient remains disease free at 3 years post treatment.

Case 2

78 yr old female presented to another service with a lesion on her left lower eye lid. Histology following excision identified Merkel cell carcinoma. Unfortunately 10 months later she developed a recurrence. A staging CT which demonstrated a 1.6×1cm lesion in the left buccal region with no radiologic evidence of local or regional lymphadenopathy.

The lesion was re-excision with neck dissection and defect closure with a cervicofacial flap. Unfortunately after a 2 year period she developed a pre-auricular swelling and left neck level 3

***Corresponding author:** Fergal O'Duffy, ENT Department Mater Misericordiae Hospital, Eccles street, Dublin 7, Ireland, Tel: 00 353 1 8034347; Fax: 00 353 1 8034779; E-mail: fergaloduffy@hotmail.com

Received September 29, 2014; **Accepted** October 14, 2014; **Published** October 23, 2014

Citation: Duffy FO, Dwyer TO, Gendy S (2014) Surgical Management of Head and Neck Merkel Cell Carcinoma, are we doing Enough? Otolaryngology 4: 177. doi:10.4172/2161-119X.1000177

lymphadenopathy. Histology confirmed recurrence of Merkel cell carcinoma. A multidisciplinary decision was made to treat further with chemotherapy and radiotherapy. She responded poorly to chemoradiation. Review five months later identified significant disease progression. Palliative management commenced 2.5 years after her initial presentation.

Case 3

92 year old lady presented with about 9 month history of small, painless enlarging lesion on her right cheek. Clinical examination showed a nodular keratotic lesion on the right cheek which was clinically suspicious for malignancy. An initial impression of squamous cell carcinoma of right cheek was made and she was scheduled to have an excision. The lesion was excised under local anaesthetic in 2008 with primary closure of wound.

Histology of excised tissue showed Merkel cell carcinoma with all margins clear except the deep margin. The deep margin was re-excised and complete excision confirmed histologically. No radiological evidence of lymph node invasion or frank metastasis was found on CT scanning. Given her age and disease co-morbidities no further surgical intervention such as prophylactic neck dissection was advocated. The patient is disease free at four years post diagnosis.

Case 4

72 year old male presented with a seven week history of a lump left side of neck which had increased in size since first noticed. He had evidence of extensive sun damage to the skin including multiple actinic keratosis. Examination found a 2cm skin lesion on the left side of the neck. Clinical inspection was consistent with a basal cell carcinoma. Initial management involved excision of the lesion with primary closure under local anaesthetic. Histology showed a poorly differentiated Merkel cell carcinoma with all margins clear of tumour. Following multidisciplinary discussion the patient was listed for neck dissection. In the short period prior to surgery he developed a second fixed palpable lump 2×2 cm in the inferior aspect of the left parotid gland. Subsequent CT scan identified a discrete lesion in the inferior tail of the left parotid with no evidence of metastasis. This meant extending his planned left neck dissection to include a total parotidectomy with sacrifice of his left facial nerve and pectoralis major flap reconstruction. Surgery was followed by chemoradiotherapy. The patient is disease free at 6 years post treatment.

Pathophysiology

First described in 1972, Merkel Cell Carcinoma [MCC] is presumed to arise from a mechanoreceptor in the basal layer of the epidermis. This layer provides information about touch and hair movement. Recent animal studies have suggested Merkel cell tumours are epithelial in origin as opposed to their previously suggested neural origin [8]. It is the most aggressive of all cutaneous malignancies. More than 2,000 cases are reported in the literature to date and their annual incidence is estimated to be 0.23 per 100,000 for whites and 0.01 per 100,000 for blacks [9].

The pathophysiology is thought to be secondary to actinic damage associated with sun exposure hence their frequency in the head and neck region. Recently viruses have been implicated in the pathogenesis of MCC. A link between infection with Merkel cell polyomavirus and the development of Merkel cell carcinoma and this virus is found in 80% of patients with MCC [10]. It has also been found that Merkel cell polymavirus may have a leukaemogenic role, thus linking development of MCC with increased risk of chronic lymphocytic leukaemia [11].

MCC is one of small blue-cell tumours sometimes confused with small-cell lung cancer, Lymphoma, Neuroblastoma or Ewing sarcoma. Immunohistochemical staining is a useful tool to aid definitive diagnosis. Typical pathological findings in MCC are expression of both neuroendocrine [neurone-specific endolase, synaptophsin] and cytokeratin markers (CK20 CAM5.2). To further aid diagnosis MCC is histologically negative for S100 and leucocyte common antigen. Three histological subgroups have been described; intermediate, small cell and trabecular [12].

Prognostic factors

MCC is a highly aggressive tumour with local recurrence in 25-30% of cases, regional disease in 52-59 % and distant metastatic disease in 34- 36% of cases [5,6]. Several studies have found that the male sex was the only predictor of a worse prognosis [13].

In a large retrospective analysis Smith et al showed anatomical sites including the scalp, neck and lip to be associated with poorer prognostic outcomes. More over lip tumours have the highest rate of invasion into bone, cartilage and muscle with a worse survival on multivariable analysis [3]. Tumours on the trunk and limbs have a high incidence of local recurrence following excision and trunk lesions may carry a worse prognosis [14].

The variability often found in the literature further illustrates the unpredictable nature of this tumour which is yet to be fully elucidated. A pathologic study performed by Skelton et al. at the Armed Forces Institute of Pathology [15], examined 132 cases of MCC to determine whether there were clinical or histological characteristics that predict its behaviour. They found that cell size, mitosis, and tumour size were all predictive of survival. Sandel et al found that there was no correlation between tumour size and depth to patient survival and metastasis. However they found a trend towards recurrence when comparing size/depth in tumours which had positive margins at resection [16]. A single institution study of 252 patients over 32 years in Memorial Sloan-Kettering found disease stage to be the only independent predictor of 5 year disease specific survival [stage I, 81%; stage II, 67%; stage III, 52%; stage IV, 11%; P=.001] [17]. Further negative prognostic indicators include AIDS and with other cell-mediated immune deficiencies, B-cell neoplasms, and ultraviolet radiation exposure which are associated with an 11-fold increased risk of MCC [2].

Staging

The primary MCC site should be assessed for satellite lesions and dermal seeding. Assessment of local disease extent, nodal spread or distance spread is achieved with CT or MRI scanning to include the chest and liver. Sentinel node scintigraphy, somatostatin receptor scintigraphy and PET scans are also useful tools in staging MCC [18].

The division of stages I – III into subgroups A and B is used to denote the method of assessment of nodal involvement. Sub stage A: have pathologically proven node negative disease with improved survival. Sub stage B: only clinically evaluated node negative disease. Stage II has a further prognostic subgroup 'C' which denotes extracutaneous invasion (Table 1).

Treatment

At present treatment involves a multidisciplinary approach with primary surgical excision where feasible and assessment of nodal

Stage	TNM	Description
IA	T1 pN0 M0	≤ 2cm diameter
IB	T1 cN0 M0	≤ 2 cm diameter
IIA	T2/3 pN0 M0	> 2 cm node negative
IIB	T2/3 cN0 M0	> 2 cm node negative
IIC	T4 N0 M0	> 2 cm, extracutaneous invasion, node negative
IIIA	Any T N1a M0	Any size, microscopic node positive
IIIB	Any T N1b/N2 M0	Any size, macroscopic node positive
IV	Any T Any N M1	Node positive with metastasis

Table 1: Combined anatomical and prognostic staging system.

involvement radiologically +/- lymph node biopsy. Adjuvant therapy to surgery includes radiation therapy with limited use of chemotherapy for patients with extensive disease burden. Our standard practice involves dissection of associated lymph node beds in clinically node positive and negative necks.

Surgery

As with all cutaneous malignancies clear surgical margins are essential when clinically feasible. Varied approaches to achieving this principle of excision are available to surgeons; wide local excision with 1-2cm margins, Mohs technique or CCPDMA [Complete Circumferential and Peripheral Deep-Margin Assessment]. Studies suggest improved survival and decreased regional recurrence with the use of sentinel lymph node biopsy [SLNB] [19,20]. In the presence of a positive SLNB the patient should have a completion lymph node dissection and/or radiation therapy [NCCN].

The management of the nodal bed in the head and neck remains contentious. The incidence of micro metastasis has been reported at rates unto 100% [21] with prophylactic neck dissections potentially reducing local recurrence by up to 76% [1]. The benefit of SLNB is clearly recognised in the trunk and limbs which have a more reliable drainage pattern. The sensitivity of SLNB in the head and neck is less reliable given more variable lymph node drainage patterns [22]. This reduced reliability of SLNB in such a pathologically aggressive tumour is one of the key reasons we undertake neck dissections in our patients. The second reason being the relatively low morbidity associated with surgical neck dissection in the presence of high rates of regional metastasis thus favouring surgical intervention.

Allen et al, Memorial Sloan – Kettering, found that Pathologic nodal staging in the clinically node negative neck occurred in 23% of patients and was associated with improved stage-specific survival probabilities and decreased nodal recurrence [17].

Radiation therapy

There is increasing evidence supporting the use of radiation therapy for primary and as an adjunct to surgery. Primary treatment with radiation therapy should be reserved for cases where complete surgical excision is not possible or surgery is refused by the patient. In a retrospective analysis of 45 patients Mohs microsurgery and adjuvant radiation was only recommended for patients unable to have complete excision or those without complete histological margin control [23]. Radiation therapy can be used to palliate bone and brain metastases [24].

Earlier studies by Gillenwater et al. demonstrated that postoperative radiotherapy reduced local recurrence from 44% to 12% [20]. Lawenda et al. also found local control for all stages was significantly improved in patients who had undergone radiation therapy, 95% control achieved for those who had undergone radiation therapy to the primary site versus 69% for those who had not [25]. The same analysis did not find a statistical improvement in regional control with radiation therapy. More recent Meta-analysis by Lewis et al. comparing surgery alone with surgery and radiation combined found a reduced risk of local and regional recurrence provided surgical excision was complete. Radiation volume should include the primary site and an area of 3-5 cm to ensure that the dermal lymphatics surrounding the primary are treated [6].

Chemotherapy

Chemotherapy is generally reserved only for stage IV disease with or without surgery and/or radiation therapy. Current data does not show prolonged survival for adjuvant chemotherapy [26]. There are insufficient studies to support the use of chemotherapy to improve survival in metastatic MCC [27]. One of the most commonly used chemotherapy regimens are cyclophosphamide/doxorubicin with an overall complete response rate of 30-40% [28]. Patients with distant disease have a median survival of nine months. The organs most frequently involved include liver, lung, bone and skin. Platinum based regimens yield a complete response in 44% of patients; however this response is short lived. Stage II patients treated surgically with synchronous chemoradiotherapy and adjuvant chemotherapy achieved a 73% three year survival for stage II disease [29].

National Comprehensive Cancer Network [NCCN]

Guidelines 2012 version 1.2014

These guidelines, as undated in 2014, provide an excellent evidence based approach for the management of Merkel cell cancer. As with all guidelines they provide a framework on which to assess and manage patients with individual treatments tailored to best suit patients. Management is divided into lymph node status and presence of metastatic disease, a short summary is provided below:

Clinically node negative disease

If the patient has had prior wide local excision consider observation or radiation therapy. In surgically naïve patient management depends on the location of the MCC. Head and neck lesions should have local excision followed by radiation therapy to the primary site and nodal bed. Radiotherapy is considered as a primary therapy in selected cases when complete excision is not feasible or refused by the patient.

SLN is offered to patients with clinical N0 disease for accurate nodal staging.

Merkel cell lesion on the trunk and limbs should have Sentinel Lymph [SLN] node biopsy followed by local excision. SLN positive should have node dissection and/or radiation therapy with consideration to adjuvant chemotherapy, following MDT discussion. SLN negative MCC of trunk and limbs consider observation or radiation.

Clinically node positive disease

Confirm clinical findings with Fine Needle Aspirate [FNA]. If negative proceed to open biopsy. If this is negative manage as for clinically node negative above. If FNA or open biopsy are positive imaging may be appropriate to assess lymph node or organ involvement and proceed to management for node positive disease; MDT discussion, node dissection and/or radiation treatment. Node positive should be considered for chemotherapy though current retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.

Clinically metastatic disease

Primarily consider best palliation with consideration for any of

the following treatments alone or in combination; surgery, radiation, chemotherapy. Surgery may be beneficial for selected patients with oligometastasis

Follow-up

Physical examination should be undertaken every 3-6 months for 2 years and every 6-12 months thereafter for life. Imaging studies are advised as clinically indicated.

Recurrence

Disease recurrence is restaged by clinically exam and radiological findings and should be managed according to stage. Eng et al. recommend specific management strategies for recurrent disease. Salvage surgery was recommended for locally or nodal recurrent MCC due to its aggressive nature. Adjuvant chemoradiotherapy should be used if the patient has sufficient physiological reserve and did not receive the maximum radiotherapy dose of 60 Gy. The overall survival rate for the 46 patients in this study was 37% with median survival of 12 months for patients with distant recurrence and 32 months survival for patients with local recurrence [31-39].

Discussion

These cases highlight several key points in the management of Merkel cell carcinoma. Initial aggressive surgical management with either close radiological follow up +/- adjuvant radiotherapy in even this early stage is necessary to improve survival. Cases two and four had recurrence at 10 and 4 months respectively highlighting the rapid and aggressive nature of local and distance recurrence. Indeed the final case developed local metastasis in a rapid time frame following local excision, necessitating not just a prophylactic neck dissection but also a radical parotidectomy. This illustrates the necessity to closely follow up Merkel cell carcinomas. To date only one of the four cases managed has not had a recurrence. This rapid regional metastasis occurred in the other three cases, presenting up to a maximum of ten months later.

Debate still surrounds surgical management of the node negative bed. Current literature recommends the use of radiation therapy to the nodal bed. Our management involves neck dissection for node negative and positive patients, an exception was the single patient with significant co-morbidities deemed not suitable for further surgery. The rational for this is based on variable lymph node drainage patterns in the head and neck making sentinel lymph node biopsy less reliable. Until large scale studies definitively elucidate the merits of this approach we argue that in the face of such high rates of micro metastasis and locoregional recurrence a neck dissection has a high potential benefit with a relatively low morbidity when performed by an experienced surgeon. Our experience of Merkel cell carcinoma to date has shown it to be a remarkably aggressive and rapidly metastasising malignancy. This unpredictable tumour should be treated aggressively to improve survival. Thus we advocate prophylactic neck dissection for all clinically node negative necks in the management of MCC.

References

1. Lawenda BD, Thiringer JK, Foss RD, Johnstone PA (2001) Merkel cell carcinoma arising in the head and neck: optimizing therapy. Am J Clin Oncol 24: 35-42.
2. Rockville Merkel Cell Carcinoma Group (2009) Merkel cell carcinoma: recent progress and current priorities on etiology, pathogenesis, and clinical management. J Clin Oncol 27: 4021-4026.
3. Rockville Merkel Cell Carcinoma Group (2009) Merkel cell carcinoma: recent progress and current priorities on etiology, pathogenesis, and clinical management. J Clin Oncol 27: 4021-4026.
4. Smith VA, MaDan OP, Lentsch EJ (2012) Tumor location is an independent prognostic factor in head and neck Merkel cell carcinoma. Otolaryngol Head Neck Surg 146: 403-408.
5. Nasseri E (2012) Merkel cell carcinoma. Can Fam Physician 58: 967-969.
6. Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, et al. (2001) Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol 8: 204-208.
7. Gillenwater AM, Hessel AC, Morrison WH, Burgess M, Silva EG, et al. (2001) Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. Arch Otolaryngol Head Neck Surg 127: 149-154.
8. Gillenwater AM, Hessel AC, Morrison WH, Burgess M, Silva EG, et al. (2001) Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. Arch Otolaryngol Head Neck Surg 127: 149-154.
9. Meacham R, Matrka L, Ozer E, Ozer HG, Wakely P, et al. (2012) Neuroendocrine carcinoma of the head and neck: a 20-year case series. Ear Nose Throat J 91: E20-24.
10. Morrison KM, Miesegaes GR, Lumpkin EA, Maricich SM (2009) Mammalian Merkel cells are descended from the epidermal lineage. Dev Biol 336: 76-83.
11. Morrison KM, Miesegaes GR, Lumpkin EA, Maricich SM (2009) Mammalian Merkel cells are descended from the epidermal lineage. Dev Biol 336: 76-83.
12. Chuang TY, Su WP, Muller SA (1990) Incidence of cutaneous T cell lymphoma and other rare skin cancers in a defined population. J Am Acad Dermatol 23: 254-256.
13. Foulongne V, Dereure O, Kluger N, Molès JP, Guillot B, et al. (2010) Merkel cell polyomavirus DNA detection in lesional and nonlesional skin from patients with Merkel cell carcinoma or other skin diseases. Br J Dermatol 162: 59-63.
14. Cimino PJ Jr, Bahler DW, Duncavage EJ (2012) Detection of Merkel cell Polyomavirus in Chronic Lymphocytic Leukemia T-cells. Exp Mol Pathol. Sep 28. pii: S0014-4800(12)00141-4.
15. Munde PB, Khandekar SP, Dive AM, Sharma A (2013) Pathophysiology of merkel cell. J Oral Maxillofac Pathol 17: 408-412.
16. Pectasides D, Pectasides M, Economopoulos T (2006) Merkel cell cancer of the skin. Ann Oncol 17: 1489-1495.
17. Ott MJ, Tanabe KK, Gadd MA, Stark P, Smith BL, et al. (1999) Multimodality management of Merkel cell carcinoma. Arch Surg 134: 388-392.
18. Skelton HG, Smith KJ, Hitchcock CL, McCarthy WF, Lupton GP, et al. (1997) Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. J Am Acad Dermatol 37: 734-739.
19. Sandel HD, Day T, Richardson MS, Gutman KA,Scarlett M 2006, Merkel cell carcinoma: does tumour size or depth of invasion correlate with recurrence, metastasis or patient survival? Laryngoscope. 116 :791-795.
20. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, et al. (2005) Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol 23: 2300-2309.
21. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, et al. (2005) Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol 23: 2300-2309.
22. Maury G, Dereure O, Du-Thanh A, Mariano-Goulart D, Guillot B (2011) Interest of (18)F-FDG PET-CT scanning for staging and management of merkel cell carcinoma: a retrospective study of 15 patients. J Eur Acad Dermatol Venereol 25: 1420-1427.
23. Allen PJ, Zhang ZF, Coit DG (1999) Surgical management of Merkel cell carcinoma. Ann Surg 229: 97-105.
24. Kokoska ER, Kokoska MS, Collins BT, Stapleton DR, Wade TP (1997) Early aggressive treatment for Merkel cell carcinoma improves outcome. Am J Surg 174: 688-693.
25. Victor NS, Morton B, Smith JW (1996) Merkel cell cancer: is prophylactic lymph node dissection indicated? Am Surg 62: 879-882.
26. Willis AI, Ridge JA (2007) Discordant lymphatic drainage patterns revealed by serial lymphoscintigraphy in cutaneous head and neck malignancies. Head Neck 29: 979-985.

27. Boyer JD, Zitelli JA, Brodland DG, D'Angelo G (2002) 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 47: 885-892.

28. Boyer JD, Zitelli JA, Brodland DG, D'Angelo G (2002) 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 47: 885-892.

29. Mendenhall WM, Mendenhall CM, Mendenhall NP (2004) Merkel cell carcinoma. Laryngoscope 114: 906-910.

30. Lawenda BD, Arnold MG, Tokarz VA, Silverstein JR, Busse PM, et al. (2008) Analysis of radiation therapy for the control of Merkel cell carcinoma of the head and neck based on 36 cases and a literature review. Ear Nose Throat J 87: 634-643.

31. Lawenda BD, Arnold MG, Tokarz VA, Silverstein JR, Busse PM, et al. (2008) Analysis of radiation therapy for the control of Merkel cell carcinoma of the head and neck based on 36 cases and a literature review. Ear Nose Throat J 87: 634-643.

32. Garneski KM, Nghiem P (2007) Merkel cell carcinoma adjuvant therapy: current data support radiation but not chemotherapy. J Am Acad Dermatol 57: 166-169.

33. Poulsen MG, Rischin D, Porter I, Walpole E, Harvey J, et al. (2006) Does chemotherapy improve survival in high-risk stage I and II Merkel cell carcinoma of the skin? Int J Radiat Oncol Biol Phys 64: 114-119.

34. Jabbour J, Cumming R, Scolyer RA, Hruby G, Thompson JF, et al. (2007) 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 14: 1943-1952.

35. Poulsen M, Rischin D, Walpole E, Harvey J, Mackintosh J, et al. (2003) 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 21: 4371-4376.

36. Poulsen M, Rischin D, Walpole E, Harvey J, Mackintosh J, et al. (2003) 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 21: 4371-4376.

37. Eng TY, Boersma MG, Fuller CD, Goytia V, Jones WE 3rd, et al. (2007) A comprehensive review of the treatment of Merkel cell carcinoma. Am J Clin Oncol 30: 624-636.

38. Eng TY, Boersma MG, Fuller CD, Goytia V, Jones WE 3rd, et al. (2007) A comprehensive review of the treatment of Merkel cell carcinoma. Am J Clin Oncol 30: 624-636.

39. Eng TY, Naguib M, Fuller CD, Jones WE 3rd, Herman TS (2004) Treatment of recurrent Merkel cell carcinoma: an analysis of 46 cases. Am J Clin Oncol 27: 576-583.