Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice (2016)
15, 189–195 © Cambridge University Press 2016
doi:10.1017/S1460396915000540

Literature Review

Palliative radiotherapy for Merkel cell carcinoma: single-centre experience and review of the literature

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(Received 7 July 2015; revised 3 November 2015; accepted 5 November 2015; first published online 25 April 2016)

Abstract

Background and purpose: Merkel cell carcinoma is a rare and aggressive primary cutaneous neuroendocrine carcinoma with a high risk of loco-regional and distant metastasis. It is predominantly seen in the elderly, on the head and neck or extremities. Although treated primarily with surgery, some patients are too frail. A World Health Organization performance status of two or more with co-existing medical co-morbidities, or the site of the disease adjacent to a critical structure, can prevent surgical management. In this cohort of patients, primary palliative radiotherapy has been found to achieve excellent tumour regression and improve quality of life. A new palliative split-course hypofractionated regime has been used in North Middlesex University Hospital in this cohort of patients. The purpose of this case series was to provide supporting evidence on the efficacy of this dose and fractionation regime and review the literature for the palliative management of Merkel cell carcinoma.

Materials and methods: In total, four patients were treated with the palliative split-course hypofractionated regime. The regime consisted of an initial 20 Gray in 5 fractions over 1 week, a 2-week gap and then a further 20 Gray in 5 fractions over 1 week. Tolerability and response to treatment were evaluated by history and clinical examination.

Results and conclusion: The split-course hypofractionated regime was well tolerated, achieved excellent tumour regression and improved quality of life in all four patients. Since then, a further three patients have been successfully treated with the above regime. This case series demonstrates the efficacy of this dose and fractionation in a select group of patients too frail for radical management and adds to the evidence base for the optimal palliative management of Merkel cell carcinoma.

Keywords: hypofractionation; Merkel cell cancer; palliative radiotherapy

CASE 1

A 98-year-old lady presented with a 4-month history of a rapidly growing 8 × 5·5 cm Merkel cell carcinoma (MCC) above her left eyebrow extending on to her upper eyelid causing mechanical obstruction of her vision. When seen in the clinic, the lesion was 8 × 5·5 cm and she had no palpable lymphadenopathy. Staging computed tomography (CT) scan showed no bony involvement or invasion into orbital contents. There was however cervical lymphadenopathy on

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the left side, particularly affecting level 3 nodes. Due to her performance status (PS) of 4 and other co-morbidities, we offered her the split-course palliative hypofractionated radiotherapy regime.

Phase 1 included the primary tumour with a 1·5-cm margin for planning target volume. A dose of 20 Gray (Gy) in 5 fractions using 15 MeV electrons was delivered. Following phase 1 the primary tumour had markedly reduced in size to 5 × 3 cm and she was able to fully open her eye and see clearly. However, her cervical lymphadenopathy had worsened with her left cervical lymph node increasing in size to 5 cm. Phase 2 of 20 Gy in 5 fractions to a reduced volume was commenced after 2 weeks, this time to both the MCC lesion and the left cervical lymph node. Radiation Therapy Oncology Group (RTOG) grade 1 skin toxicity was noted during treatment. This resulted in an excellent response with complete resolution of the primary MCC and the lymph node was no longer clinically palpable (see Figure 1). There were no reported side effects.

At a subsequent 6-month follow-up clinic the treated site still had a complete response but she had a new MCC lesion on her right cheek. However, she deteriorated before she could have any further palliative radiotherapy and died secondary to complications from her end-stage renal disease.

CASE 2

A 92-year-old lady presented with a biopsy confirmed 5 × 5-cm rapidly enlarging MCC on her left cheek. Following multidisciplinary meeting discussions and considering her multiple co-morbidities (PS 3), it was decided to manage the lesion palliatively with radiotherapy. She underwent split-course hypofractionated radiotherapy consisting initially of 20 Gy in 5 fractions using 6-MV photons with bolus to the skin. The lesion responded with complete flattening and minimal scarring. After a 2-week break, she went on to have phase 2 treatment of a further 20 Gy in 5 fractions of superficial radiotherapy. There was minimal RTOG grade 1 skin toxicity during treatment.

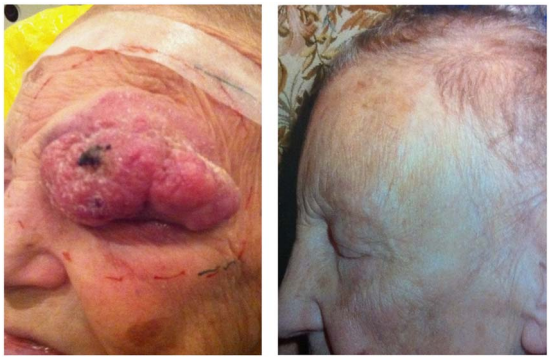

Figure 1. Case 1 pre- and post-treatment photographs.

The patient was reviewed 1 month after treatment and had achieved complete resolution of the primary lesion. She developed a new lesion on the left angle of the jaw measuring 3 × 2·5 cm, which was another biopsy-proven MCC. A CT staging scan showed no definitive evidence of nodal or distant metastases. She underwent a repeat phase 1 treatment of 20 Gy in 5 fractions however, given her progressive frailty and co-morbidities she did not have a phase 2 treatment. Radiotherapy to the new lesion resulted in significant reduction in size by more than 50%, which achieved good local control. She is currently under 2 monthly follow-up sessions with further treatment dictated by symptoms.

CASE 3

An 80-year-old gentleman had been diagnosed by Maxillofacial surgeons with an ~4-cm MCC on the right angle of the mandible invading the parotid. He had a staging CT that showed no lymphadenopathy or distant disease. He underwent a superficial right parotidectomy including skin excision. Histology showed intravascular invasion and extension into the parotid gland. The tumour focally reached the circumferential margin. Clinically within a few weeks of his operation he developed a locally recurrent suspicious nodule measuring 2 cm in the postoperative bed. It was arranged for him to undergo postoperative radiotherapy to the tumour bed and ipsilateral neck.

Due to his multiple co-morbidities and a PS 2 he underwent split-course hypofractionated

https://doi.org/10.1017/S1460396915000540 Published online by Cambridge University Press

radiotherapy with 20 Gy in 5 fractions using 6-MV photons. He tolerated both phases of treatments well with minimal side effects (RTOG grade 1 skin toxicity) and no clinical evidence of recurrence during his follow-up. He died 2 years later from an infective exacerbation of chronic obstructive pulmonary disease.

CASE 4

A 93-year-old gentleman was referred with a 5 × 5-cm skin lesion on the left anterior scalp. This was confirmed to be a MCC on skin biopsy with subcutis and perineural invasion. Due to his significant co-morbidities and a PS of 4 it was planned for him to have palliative radiotherapy alone for local control and thus no staging scans were arranged.

He had 20 Gy in 5 fractions over 5 days using superficial radiotherapy to which the tumour achieved a partial response. He died 2 months later due to urosepsis on a background of chronic kidney disease.

INTRODUCTION

The aim of this case series was to provide evidence on the efficacy of the split-course hypofractionated palliative regime used in the cases presented above and to review the literature on the palliative management of MCC. This will add to the evidence base as currently there is limited evidence on the optimal palliative management of MCC. The methods used for the literature search included PubMed searches with the keywords merkel cell carcinoma, radiotherapy and palliative.

MCC is a rare primary cutaneous neuroendocrine carcinoma with a propensity to spread to regional lymph nodes and distant sites. It was first described in 1972 by Toker.[1] It frequently affects elderly Caucasian patients with a preference for the head and neck.[2] Risk factors for MCC include sun exposure, immunosuppression and organ transplantation.[2]

The cells of origin is thought to be the merkel cell which are believed to be the slow-acting mechanoreceptors in the basal layer of the epidermis. Clinical appearance of a MCC typically appears as a red, violaceous (violet) nodule with a shiny surface, with overlying telangiectasia. Most lesions are <20 mm in diameter. MCC can spread through the dermal lymphatics system, resulting in the development of multiple satellite lesions.[3]

Table 1. *Tumour, node and metastases staging classification supported by AJCC and UICC*[7]

Stage I	Primary tumour ≤2 cm without evidence of regional lymph node (LN) involvement
Stage II	Primary tumour >2 cm (T2 or T3) or a primary tumour with invasion into bone, muscle, fascia or cartilage (T4)
Stage III	Any primary tumour with regional LN disease
Stage IV	Metastasis beyond the regional LN, regardless of the status of the primary tumour and regional nodes

AJCC = American Joint Committee on Cancer; UICC = Union for International Cancer Control.

On histology, MCC cells are usually ovoid and up to 15 μm in diameter with scanty cytoplasm. Typically, MCC will express both neuroendocrine and cytokeratin markers.[3] In 2008, an association between MCC and Merkel cell polyomaviruses (double-stranded circular DNA viruses) was described.[4]

Between 1999 and 2008, the incidence rate of MCC in England rose from 0·1 to 0·2 per 100,000 persons.[5] The annual incidence of MCC is 0·6 per 100,000 persons and is increasing (~1,600 new cases per year in the United States).[6] The rising incidence is partly due to increased awareness and the introduction of cytokeratin 20 immunostaining. According to the National Cancer Database, the majority of MCCs present with localised disease (66%) followed by nodal disease (27%) and metastatic disease (7%).[6]

Tumour, node and metastases staging classification of MCC is tabulated in Table 1.[7] Along with lymph nodes, common sites of metastases include in transit skin, lungs, central nervous system, bone and liver.[8]

PROGNOSIS

Patients with local disease had a 64% relative survival at 5 years, compared with 39% in regional nodal disease.[9] Although ~70% of patients

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with MCC present with stage one or two disease,[10] the low 5-year survival rates are attributed to high rates of loco-regional and distant recurrence.[11] Time to recurrence is most often reported to occur at around a median of 8 months.[10–12]

TREATMENT

The aim of treatment is to achieve local control in the primary site and the nodes. This is because uncontrolled loco-regional disease has a significant impact on quality of life and increases risk of distant metastasis.[3] Treatment for MCC is primarily surgery. Wide local excision with a 2–3-cm margin is recommended, except for the head and neck region where narrow margins may be acceptable.[6] The use of adjuvant radiotherapy is becoming more prevalent as data show that radiotherapy improves both loco-regional control and survival.[13,14]

In areas where resection is not possible because of the proximity of critical structures or the patient is medically unfit for surgery, or where surgery is refused, radical radiotherapy alone may be offered. Though data regarding radiotherapy alone are limited, high rates of local control have been reported.[15,16] The radical doses used in treating MCC have ranged between 45 to 60 Gy, with higher doses being applied to bulky disease.[3]

A research report published in 2009 identified 19 relevant studies between 1981 and 2008 where the literature on definitive radiotherapy of MCC was reviewed.[17] The studies reported outcome on 65 MCC patients treated with radiotherapy alone. Of the 63 patients who underwent definitive radiotherapy (2 patients had lower-dose schedules) only 9 (14%) were documented to have loco-regional recurrence. The 2 patients who received lower-dose schedules (20 Gy in 5 fractions, 30 Gy in 10 fractions) also achieved complete tumour regression. These studies report high rates of in-field loco-regional control following radiotherapy alone. This in turn supporting a recommendation of moderate-dose radiotherapy alone in select patients unsuitable for surgery and lower-dose palliative dose fractionation schedules to be considered in patients with very poor PS to improve quality of life.

For clinically node-negative patients, sentinel lymph node biopsy (SLNB) is becoming a standard practice. For patients with a negative SLNB, a study showed that 97% (39/40) had no recurrence with the omission of radiotherapy.[18] Clinically node-positive patients go on to have node dissection, and regional control was improved two-fold by the addition of radiotherapy (37 versus 18%).[19] In non-resectable nodal disease, radiotherapy doses up to 60 Gy are recommended.[20] In the United States, Fang et al.[21] prospectively collected data from patients with MCC over a 22-year period, which included data from patients who received radiotherapy alone for positive nodes. Regional control for patients with microscopically involved nodes was 100% regardless of treatment modality. Patients with clinically positive lymph nodes had 2-year regional recurrence-free survival rate of 78 and 73% in the definitive lymph node irradiation ($n = 9$) and completion lymphadenectomy $\pm$ radiotherapy ($n = 15$) groups, respectively ($p = 0{\cdot}8$) with a median follow-up of 16 months. The authors concluded that radiotherapy alone provided similar rates of control as completion lymphadenectomy with or without additional radiotherapy.[21]

Systemic failure remains a big challenge in MCC, with distant failure as the most common site of first disease recurrence.[21] Chemotherapy has been explored with disappointing results.[22]

PALLIATIVE RADIOTHERAPY

Due to the rarity of MCC, there are no randomised controlled trials that address the optimal therapy,[23] and most data on optimal treatment in the literature are supported by retrospective studies or case series. Furthermore there is even more scarcity of data to guide optimal palliative management of MCC.[24] Following a PubMed search, some of the palliative regimes used in the literature for MCC have been tabulated (Table 2).[17,25,26,27] Kilovoltage X-rays, photons and electrons were used in the five cases described by Pacella et al.[25]. The fractionation schedules used included an 8-Gy single fraction, 36 Gy in 9 fractions, 36 Gy in 8 fractions and 25 Gy in 5 fractions. Ashby et al.[26] describes

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Table 2. Palliative radiotherapy regimes used in the literature[17,25–27]

References	sex	Age (years)	Site	Radiotherapy (Gy)	Fractions	Status of field	Loco-regional recurrence after RT (months)	Distant metastases	Status at the time of publication	Survival (months from start of RT)
Pacella et al.[25]	M	60	Right preauricular (1° recurrence)	8	1	CR	Y (3)	Y	Died	7
Pacella et al.[25]	F	74	Left forehead (1° recurrence)	36	9	CR	Y (1)	Y	Alive	52
Pacella et al.[25]	M	84	Nose (1° recurrence)	36	8	CR	Y (8)	N	Alive	5
Pacella et al.[25]	F	83	Left supraorbital region	36	8	CR	N	N	Alive	2
Pacella et al.[25]	F	79	Left forearm	25	5	CR	N	Y	Died	2
Ashby et al.[26]	F	95	Lower eyelid	39	10	NS	N	N	Alive 3 years after rx	NS
Brierley et al.[27]	M	89	Left cheek	26	4	CR	N	N	Died (from other causes)	22
Brierley et al.[27]	F	89	Right inguinal region	8·5	1	CR	N	N	Died (from other causes)	41
Koh et al.[17]	F	86	Trunk	20	5	In-field recurrence	NS	Y	Alive	NS
Koh et al.[17]	F	83	Groin nodes	30	10	CR	NS	Y	Died	NS

Abbreviations: Gy, Gray; RT, radiotherapy; CR, complete response; Y, yes; N, no; NS, not specified.

a case using 39 Gy in 10 fractions using kilovoltage X-rays to a small volume using a lead cut-out. Brierley et al.[27] describes two cases, one was treated with kilovoltage X-rays, a schedule of 26 Gy in 4 fractions (weekly) using lead cut-out, and the other was treated with photons where a single fraction of 8·5-Gy applied dose with a bolus was given. Koh and Veness[17] describes two cases with a fractionation schedule of 20 Gy in 5 fractions and 30 Gy in 10 fractions using either a single large electron or an orthovoltage photon field. Some regimes have reported good loco-regional control (complete response post treatment, no loco-regional or distant metastasis) others not so effective. However, this establishes the wide variety of palliative dose fractionation regimes used with limited data on outcomes.

A split-course hypofractionated regimen has been used palliatively in squamous cell cancer (SCC) of head and neck patients in whom the tumour stage, PS and co-morbidity makes radical treatment unsuitable.[28] The schedule comprises of an initial 20 Gy in 5 fractions over 1 week followed by a 2-week gap, and then a further 20 Gy in 5 fractions over 1 week if the patient is able to tolerate the treatment. The radiation field encompassed the gross tumour volume with a 1–2-cm margin, using 6-MV photons and a surface bolus in cases of skin infiltration. Out of the 33 patients treated, 26 (79%) reported symptomatic improvement at the 4–6-week follow-up, 13 (39%) patients had complete tumour response and 11 (33%) had a partial response as assessed clinically and in some cases radiologically. The median overall survival was 9 months (range 3–43 months). Progression-free survival at 1 and 2 years was 35 and 25%, respectively. Treatment was well tolerated, and admission for nasogastric feeding and/or supportive management was required in only six patients. The above retrospective analysis showed that split-course hypofractionated radiotherapy is an effective palliative regimen for head and neck SCC with acceptable toxicity. The same split-course hypofractionated regime used by Kancherla et al.[28] has been adopted for MCCs treated at the North Middlesex University Hospital with palliative intent. Most patients were elderly and had multiple co-morbidities

https://doi.org/10.1017/S1460396915000540 Published online by Cambridge University Press

Table 3. World Health Organization performance status[29]

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about for more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

with a World Health Organization PS score of 2 and above (Table 3).[29] Although the numbers treated with this regime are small, good local control was seen in all the patients treated at this centre and are presented in this case series.

CONCLUSION

MCC is a rare, aggressive, radiosensitive tumour with a high propensity for loco-regional and distant metastasis. There is a lack of randomised controlled trials that address the optimal therapy, particularly palliative management. A review of the literature revealed varying palliative regimes with varying outcomes. The split-course hypofractionated regime of 20 Gy in 5 fractions, a 2-week gap and then a further 20 Gy in 5 fractions (if tolerated) was used in North Middlesex University Hospital. The aim of this case series was to present further evidence on this schedule in the palliative setting of MCC. The outcome of the case series demonstrates that these aims were met as the regime was well tolerated and achieved excellent local control. This is especially important in a select group of frail patients with MCC, who without treatment can potentially become very symptomatic from this disease. Further accrual of patients treated with the above regime in North Middlesex University Hospital will add to the evidence base and strengthen the case for this dose and fractionation.

Acknowledgements

None.

References

1. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972; 105 (1): 107–110.
2. Suarez C, Rodrigo J P, Ferlito A, Devaney K O, Rinaldo A. Merkel cell carcinoma of the head and neck. Oral Oncol 2004; 40: 773–779.
3. Poulsen M. Merkel-cell carcinoma of the skin. Lancet Oncol 2004; 5: 593–599.
4. Feng H, Shuda M, Chang Y, Moore P S. Clonal integration of a polyomavirus human Merkel cell carcinoma. Science 2008; 319 (5866): 1096–1100.
5. National Cancer Intelligence Network. Rare skin Cancer England. http://www.ncin.org.uk. Accessed on 20 October 2015.
6. Hughes M P, Hardee M E, Cornelius L A, Hutchins L F, Bercker J C, Gao L. Merkel cell carcinoma: epidemiology, target, and therapy. Curr Dermatol Rep 2014; 3: 46–53.
7. Edge S B, Byrd D R, Compton C C et al. (eds). Merkel cell carcinoma. AJCC Staging Manual, 7th edition. New York: Springer, 2010: 315–323.
8. Bichakijan C K, Lowe L, Lao C D et al. Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. Cancer 2007; 110 (1): 1–12.
9. Paulson K G, Iyer J G, Byrd D R, Nghiem P. Pathologic nodal evaluation is increasingly commonly performed for patients with Merkel cell carcinoma. J Am Acad Dermatol 2013; 69 (4): 653–654.
10. Allen P J, Bowne W B, Jaques D P, Brennan M F, Busam K, Coit D G. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol 2005; 23 (10): 2300–2309.
11. Gillenwater A M, Hessel A C, Morrison W H 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 (2): 149–154.
12. Eng T Y, Naguib M, Fuller C D, Jones W E 3rd, Herman T S. Treatment of recurrent Merkel cell carcinoma: an analysis of 46 cases. Am J Clin Oncol 2004; 27 (6): 576–583.
13. Mojica P, Smith D, Ellenhorn J D. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. J Clin Oncol 2007; 25 (9): 1043–1047.
14. Lewis K G, Weinstock M A, Weaver A L, Otley C C. Adjuvant local irradiation for Merkel cell carcinoma. Arch Dermatol 2006; 142 (6): 693–700.
15. McAfee W J, Morris C G, Mendenhall C M, Werning J W, Mendenhall N P, Mendenhall W M. Merkel cell carcinoma: treatment and outcomes. Cancer 2005; 104 (8): 1761–1764.
16. Mortier L, Mirabel X, Fournier C, Piette F, Lartigau E. Radiotherapy alone for Merkel cell carcinoma. Arch Dermatol 2003; 139 (12): 1587–1590.
17. Koh C S, Veness M J. Role of definitive radiotherapy in treating patients with inoperable Merkel cell carcinoma: the

Westmead Hospital experience and a review of the literature. Australas J Dermatol 2009; 50: 249–256.

18. Mehrany K, Otley C C, Weening R H, Phillips P K, Roenigk R K, Nguyen T H. A meta-analysis of the prognostic significance of sentinel lymph node status in Merkel cell carcinoma. Dermatol Surg 2002; 28 (2): 113–117.
19. Veness M J, Perera L, McCourt J et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. ANZ J Surg 2005; 75 (5): 275–281.
20. Veness M J, Palme C E, Morgan G J. Merkel cell carcinoma: a review of management. Curr Opin Otolaryngol and Head Neck Surg 2008; 16 (2): 170–174.
21. Fang L C, Lemos B, Douglas J, Iyer J, Nghiem P. Radiation monotherapy as regional treatment for lymph node-positive Merkel cell carcinoma. Cancer 2010; 116 (7): 1783–1790.
22. Poulsen M G, 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 (1): 114–119.
23. 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.
24. Khan L, Barnes E A. Radiotherapy for metastatic Merkel cell carcinoma: a review of the literature. J Skin Cancer 2012; 2012: Article ID 654981, 5pp.
25. Pacella J, Asby M, Ainslie 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.
26. Ashby M A, Jones D H, Tasker A D, Blackshaw A J. Primary cutaneous neuroendocrine (Merkel cell or trabecular carcinoma) tumour of the skin: a radioresponsive tumour. Clin Radiol 1989; 40: 85–87.
27. Brierley J D, Stockdale A D, Rostom A Y. Merkel cell (trabecular) carcinoma of skin treated by radiotherapy. Clin Oncol (R Coll Radiol) 1991; 3: 117–118.
28. Kancherla K N, Oksuz D C, Prestwich R J et al. The role of split-course hypofractionated palliative radiotherapy in the head and neck cancer. Clin Oncol (R Coll Radiol) 2011; 23: 141–148.
29. Oken M M, Creech R H, Tormey D C et al. Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol 1982; 5: 649–655.

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