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Original papers

Radiotherapy for Merkel cell carcinoma of the skin

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We examine the impact of radiotherapy in the treatment of Merkel cell carcinoma (MCC) of the skin. Data at two Canadian institutions (Allan Blair Cancer Centre and London Regional Cancer Program) were collected and charts were retrieved from the registry of 1987 to 2005. A total of 79 patients with definite MCC were studied. All except three had a primary skin lesion. Six patients presented with nodal metastases and three patients with distant metastases. Fourteen patients were referred to the cancer centers at the time of recurrence: 2/14 with local recurrence, 8/14 with nodal recurrence, 2/14 with both local and nodal recurrence, and 2/14 with distant recurrence. The series consisted of 40 males and 39 females with a median age of 80 years (range 48-94). The median follow up was 21 months (range 0.5-150.4).

Twenty-two patients (group A) received radiotherapy at the time of presentation,21 being post-operative adjuvant treatment and one being primary treatment without surgery. The 5-year cause-specific survival rate (CSSR) was 42%. The 5-year rates equals the 10-year rate since the CSSR plateaus at a survival of 4.5 years and thereafter, patients died from causes other than MCC. The 5-year overall survival rate (OSR) was 19% for group A.

Fifty-seven patients (group B) had surgery alone without post-operative adjuvant radiotherapy. 5-year and 10-year CSSRs were both 63% (P=0.8, using the logrank test when comparing the two groups of patients). The 5-year OSR was 30% and the 10-year OSR was 13% (P=0.6, group A versus group B). Morbidity from radiotherapy was minimal. Only one patient with an ankle lesion did not take the skin graft well and had drainage for one year before healing. One patient had lymphoedema of the arm (which required a pressure garment) after axillary dissection and radiotherapy of 50 Gy in 25 fractions over 35 days. Radiotherapy after surgical excision is well tolerated. It is recommended if there are high risk factors for recurrence and radiotherapy should be started as soon as possible after referral.

Key words: Merkel cell carcinoma, skin, radiotherapy, prognostic factors

Introduction

Merkel cell carcinoma (MCC) of the skin was formerly called trabecular carcinoma. It is an uncommon, highly malignant primary cutaneous neuroendocrine carcinoma. MCC occurs mostly in white elderly patients, usually with an equal incidence in men and women, although it may be slightly more common in females [1]. About 78% of patients are older than 59 years. Female and male patients are equally involved in the age group below 60 years. After 60 years, MCCs are more often observed in female patients. The tumour is most often located in the head and neck region (50.8%) or the extremities (33.7%). The average size is 29 mm at presentation. Clinically, only a presumptive diagnosis of MCC can be established. The definitive diagnosis is made by histological, especially immunohistological, methods: detection of intermediate filaments and neuroendocrine markers [2]. The exact aetiology of MCC is not known, but it is postulated that it might be related to sunlight. Recent studies demonstrate chromosomal abnormalities in chromosomes 1, 11 and 13 [3].

The immunological aspect of the cancer is interesting, because at least 10 cases of spontaneous remission, complete or partial have been reported in the literature [4, 5]. MCC occurs more frequently in immunosuppressed patients and there are occasional reports of cure with tumour necrosis factor [6] and interferon [7].

There are some controversies in the literature regarding treatment; whether adjuvant treatments should be given and what is the best modality. The appropriate treatment in recurrent and metastatic disease becomes a dilemma due to its occurrence in the elderly who tend to tolerate aggressive treatment poorly. We reviewed cases of this interesting disease which were available in our two institutions and in the literature.

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Materials & methods

From the computerised registry system in the two centres (Allan Blair Cancer Centre, Regina Saskatchewan, and London Regional Cancer Program, London Ontario), a search for MCC was made in order to undertake our retrospective chart review. Data were collected on the extent and location of the disease at presentation, duration of disease, co-existing morbidities, previous irradiation, size of primary/node, timing of treatment, extent of surgery/radiotherapy, resection margin, radiotherapy technique, chemotherapy regimens, recurrent events, survival and final disease status. Actuarial survival was calculated using the Kaplan-Meier method and comparisons were using the logrank test. The Cox proportional hazards model was used for a multivariate analysis of risk factors.

There are 665 cases reported in the literature. In order to give some answers to the current controversies in management with a large enough number of patients, statistical analyses were performed.

Results

From 1987 to 2005, a total of 79 patients with definite MCC were found (51 from Regina and 28 from Ontario). This series consisted of 40 males and 39 females with a median age of 80 years (range 48-94). The median follow up was 21 months (range 0.5-150.4). All except three had a primary skin lesion. Six patients presented with nodal metastases and three patients with distant metastases. 14/79 patients were referred to the cancer centres at the time of recurrence: two with local recurrence, eight with nodal recurrence, two with both local and nodal recurrence, and two with distant recurrence. The median time before diagnosis was 4 months (range: 0.5-36).

Twenty-two patients (group A) received radiotherapy at the time of presentation, 21 being post-operative adjuvant treatment and one being primary treatment without surgery. The 5-year cause-specific survival rate (CSSR) was 42%. The 5-year rates equals the 10-year rate since the CSSR plateaus at a survival of 4.5 years and thereafter, patients died from causes other than MCC. The 5-year overall survival rate (OSR) was 19% for group A.

Fifty-seven patients (group B) had surgery alone without post-operative adjuvant radiotherapy. 5-year and 10-year CSSRs were both 63% (P=0.8, using the logrank test when comparing the two groups of patients). The 5-year OSR was 30% and the 10-year OSR was 13% (P=0.6, group A versus group B).

Only two patients in our series received concurrent chemotherapy and radiotherapy. Both were of young age for MCC, 48 and 55 years. The first of these two patients had nodal disease at presentation and died of cancer at 21 months. The second patient had a 0.7 cm primary only and was alive and well at last follow-up at 51 months.

Morbidity from radiotherapy was minimal. Only one patient with an ankle lesion did not take the skin graft well and had drainage for one year before healing. One patient had lymphoedema of the arm (requiring a pressure garment) after axillary dissection and radiotherapy of 50 Gy in 25 fractions over 35 days.

Two patients had rapid progression of their tumour while waiting for commencement of treatment. Two patients had successful salvage of recurrence (one local and one nodal recurrence respectively) by radiotherapy alone without surgery. Two patients had nodal recurrence just outside previous radiotherapy field, emphasising the importance of careful planning for adequate coverage.

Discussion

Diagnosis of MCC

The clinical diagnosis is made with the typical clinical presentation: a rapidly growing, painless, firm, non-tender, shiny, bluish-red, intracutaneous nodule of 0.5-5 cm in diameter, sometimes it can take the form of a plaque. The tumour is usually localised to sun-exposed areas of the head and neck, but does occur in extremities, trunk, genitalia and perianal regions with a random distribution. In our series, the median time before diagnosis was 4 months (range: 0.5-36). Delay in the treatment delivery would result in poorer results. Those patients with rapidly progressive tumour should never be delayed or put on a waiting list for treatment.

Fine needle aspiration enables an early and confident diagnosis of this aggressive tumour and an early planning of surgery [8]. Diagnostic pitfalls include the following. (a) Co-existence of primary cutaneous MCC in association with squamous cell carcinoma and basal cell carcinoma. This has the implication that an ordinary squamous or basal cell carcinoma should be sectioned thoroughly to avoid missing the aggressive MCC component. (b) The presence of desmoplasia may mask the diagnosis of MCC [9]. (c) Malignant lymphoma is an important differential diagnoses for undifferentiated cutaneous round cell tumours. Polymerase chain reaction and sequencing, and immunohistochemistry are instrumental in their evaluation [10].

Pattern of failure & prognostic factors

A typical pattern of failure is a high incidence of distant metastases with an overall rate of 40%, i.e., 25% at presentation, and 15% after radiotherapy; as well as a 30-65% regional recurrence rate. Interestingly in some patients, the tumour was indolent and well controlled by therapy. However in some studies, even stage I patients have a high risk of disease progression, with 53% developing regional lymphadenopathy or visceral metastases. The median survival for all disease stages was 47 months [11].

Prognosis is very poor, particularly when systemic disease is present. Locoregional recurrences result in poor prognosis even after treatment. Nodal involvement at some time has been observed in 65% of reported cases (20% at presentation, subsequently 45%), and distant metastases in 34%. It appears to be distant metastases rather than nodal relapse that accounts for the poor prognosis of this disease [12, 13].

Systemic disease was nearly uniformly preceded by the appearance of nodal metastases and was uniformly fatal regardless of subsequent therapy. This suggests an orderly cascade pattern of spread for this tumour, in which elective regional lymph node dissection may be justified. The recommendations for treatment include a wide excision of the primary tumour and either elective or early therapeutic regional node dissection [14]. The recent literature shows much controversy because adjuvant radiotherapy was reported to have no benefit after adequate surgery [15]. However, another school of thought is that post-operative radiotherapy is the standard of care [16, 17]. There is also the controversy of tumour size greater than 1 cm being put into the high risk group eligible for the Trans-Tasman Radiation Oncology Group (TROG) study. In fact to date, the only one prospective trial that has been completed on MCC, was carried out by the TROG [18]. There is also dispute as to whether statistical non-significance of adjuvant treatment may still be clinically important [19].

Males are reported to have a worse prognosis independent of stage and extent of therapy [12]. Young age, defined as less than 70 years, was found to be a good prognostic factor in the Australian study where the above prospective TROG study was compared with historical controls which fulfilled the same eligibility criteria [20].

A literature review on 665 reported cases was therefore undertaken by us in order to give some answers to the current controversies in management. Univariate analysis showed age of less than or equal to 65 years (P=0.009), size of less than or equal to 1 cm (P=0.02), and female rather than male (P=0.002), to be good prognostic factors. Among the three groups of patients, i.e., with or without post-operative radiotherapy, and primary radiotherapy without surgery, we performed univariate analyses. The group without postoperative radiotherapy fared the best, and the group with post-operative radiotherapy fared second-best for CSSR (P=0.019). For OS, there was borderline significance among the groups of patients (P=0.067). Again, the group without post-operative radiotherapy fared the best and post-operative radiotherapy second-best.

Multivariate analysis for CSSR showed that the group without post-operative radiotherapy (P=0.03), female (P=0.004), and size less than or equal to 1 cm (P=0.01) were significantly good prognostic factors. Multivariate analysis for OSR showed that the lack of co-morbid conditions (P=0.002), female (P=0.002), age less than or equal to 65 years (P=0.004) and size less than or equal to 1 cm (P=0.01) were significantly good prognostic factors.

The data in the literature were consistent with our own series of 79 patients. This study showed that 5-year OSR without post-operative radiotherapy patients have a trend to fare better, 30% versus 19%, than those with post-operative radiotherapy. Possible reasons which might explain why the group without post-operative radiotherapy fared the best include potential bias from earlier stage, fewer co-morbid conditions or other good prognostic factors.

Other prognostic factors have been used as basis for treatment recommendation. These include small cell size and high mitotic rate which were associated with a low survival rate [20]. When cell size was excluded, males and depth of invasion were associated with a worse survival, although these were not statistically significant [20]. Post-operative radiation or chemotherapy may reduce the risk of recurrences. It should be given for patients with poor prognostic features. In the literature, bad prognostic features include the following: lymph node metastasis, size greater than 1 cm (in the TROG study [18]), size greater than 2 cm [15], male rather than female [2], positive nodes, recurrent disease or gross residual disease after surgery [18]. TROG used the subgroup greater than 1 cm as one of the eligibility criteria for the chemoradiation study and other authors have questioned this [15]. Our present study showed that 1 cm may be a good dividing line for use in clinical studies of MCC.

Surgery is the mainstay of initial treatment for MCC and surgery alone is effective for small tumours and adequate resection margins. Complete regression with primary radiotherapy in inoperable elderly patients [21-23] has been reported. Gross disease of 3 cm size was effectively treated by radiotherapy alone although the follow-up was only 18 months at the time of reporting [22]. This was contrasted by other reports where primary radiotherapy achieved partial regression only [24, 25]

The importance of post-operative radiation therapy in the treatment of MCC has been addressed by Meeuwissen et al [16], Shaw et al [26], Hasle [27], and Savage et al [11]. In the Meeuwissen et al [16] series the total number of patients was 80. All 38 patients treated with surgery alone relapsed, with a median time to recurrence of 5.5 months, compared with 10/34 relapses in patients treated with combined surgery and radiotherapy, with a median time to recurrence of 16.5 months.

Conclusions

Since the rate of progression of MCC is unpredictable, referred patients should be assessed and treated without delay. Careful radiation therapy planning to avoid any geographical miss is recommended. The management of MCC remains controversial, particularly in the adjuvant settings. Due to the rarity of this disease further investigations with prospective controlled trials may require international multicentre collaborations. We suggest that it is probable that a 1 cm tumour size might be a good dividing line for eligibility criterion. This should be investigated further.

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References

1. Akosa AB, Nield DV, Saad MN. Merkel cell carcinoma: a clinico-pathological report of 3 cases. *Br J Oral Maxillofac Surg* 1994; 32: 111-3.
2. Meyer-Pannwitt U, Kummerfeldt K, Boubaris P et al. Merkel cell tumor or neuroendocrine skin carcinoma. *Langenbecks Arch Chir* 1997; 382: 349-58.
3. Leonard JH, Leonard P, Kearsley JH. Chromosomes 1, 11, and 13 are frequently involved in karyotypic abnormalities in metastatic Merkel cell carcinoma. *Cancer Genet Cytogenet* 1993; 67: 65-70.
4. Takenaka H, Kishimoto S, Shibagaki R et al. Merkel cell carcinoma with partial spontaneous regression: an immunohistochemical, ultrastructural, and TUNEL labeling study. *Am J Dermatopathol* 1997; 19: 614-8.
5. Connelly TJ, Kowalcyk AP. Another case of spontaneous regression of Merkel cell (neuroendocrine) carcinoma. *Dermatol Surg* 1997; 23: 588-90.
6. Hata Y, Matsuka K, Ito O et al. Two cases of Merkel cell carcinoma cured by intratumor injection of natural human tumor necrosis factor. *Plast Reconstr Surg* 1997; 99: 547-53.
7. 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: 315-23.
8. Perez-Guillermo M, Sola-Perez J, Abad-Montano C et al. Merkel cell tumor of the eyelid and the cytologic aspect in fine-needle aspirates: report of a case. *Diagn Cytopathol* 1994; 10: 146-51.
9. Kossard S, Wittal R, Killingsworth M. Merkel cell carcinoma with a desmoplastic portion. *Am J Dermatopathol* 1995; 17: 517-22.
10. Miettinen M. Keratin 20: immunohistochemical marker for gastro-intestinal, urothelial, and Merkel cell carcinomas. *Mod Pathol* 1995; 8: 384-8.
11. Savage P, Constenla D, Fisher C et al. The natural history and management of Merkel cell carcinoma of the skin: a review of 22 patients treated at the Royal Marsden Hospital. *Clin Oncol R Coll Radiol* 1997; 9: 164-7.
12. Crown J, Lipzstein R, Cohen S et al. Chemotherapy of metastatic Merkel cell cancer. *Cancer Invest* 1991; 9: 129-132.
13. Leong AS, Philips GE, Pieterse AS et al. Criteria for the diagnosis of primary endocrine carcinoma of the skin (Merkel cell carcinoma). A histological, immunohistochemical and ultrastructural study of 13 cases. *Pathology* 1986; 18: 393-9.
14. Yiengpruksawan A, Coit DG, Thaler HT et al. Merkel cell carcinoma: prognosis and management. *Arch Surg* 1991; 126: 1514.
15. 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.
16. Meeuwissen J, Bourne R, Kearsley J. The importance of postoperative radiotherapy in the treatment of Merkel cell carcinoma. *Int J Radiat Biol Phys* 1995; 31: 325-31.
17. Bouren R, O' Rourke ME. Management of Merkel Cell tumor. *Aust NZ J Surg* 1988; 58: 971-4.
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.
19. Allen PJ, Bowne WB, Jaques DP et al. Merkel cell carcinoma: improved outcome with the addition of adjuvant therapy. J Clin Oncol 2005; 23: 7235; author reply 7237. Comment on: *J Clin Oncol* 2005; 23: 2300.
20. Skelton HG, Smith KJ, Hitchcock CL et al. Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. *J Am Acad Dermatol* 1997; 37: 734-9.
21. Ashby MA, Jones DH, Tasker AD et al. Primary cutaneous neuro-endocrine (Merkel cell or trabecular carcinoma) tumour of the skin: a radioresponsive tumour. *Clin Radiol* 1989; 40: 85-7.
22. Pople IK. Merkel cell tumour of the face successfully treated with radical radiotherapy. Eur J Surg Oncol 1988; 14: 79-81.
23. Schnabel T, Glag M. Breast metastases of Merkel cell carcinoma. *Eur J Cancer* 1996; 32A: 1617-8.
24. Dini M, Lo Russo G. Merkel cell carcinoma of the eyelid. *Eur J Ophthalmol* 1997; 7: 108-12.
25. Kacker A, Thaker A, Singh M et al. Primary neuroendocrine carcinoma of the skin arising from the post aural region. *J Laryngol Otol* 1992; 106: 258-60.
26. Shaw JH, Rumball E. Merkel cell tumour: clinical behaviour and treatment. *Br J Surg* 1991; 78: 138-42.
27. Hasle H. Merkel cell carcinoma: the role of primary treatment with radiotherapy. *Clin Oncol R Coll Radiol* 1991; 3: 114-6.

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