Update: Radiation therapy for skin cancer

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Abstract

Effective management of skin cancer in Australia is important, due to its high incidence and enormous burden on the health system. Radiation therapy (RT) plays an important role in skin cancer management, both as definitive treatment and as a component of multimodal management. This article provides a brief review of the varied roles of radiation therapy in the common skin cancers (basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma and melanoma) in both curative and palliative settings. Biopsy of all lesions is preferred to establish a histological diagnosis. Definitive radiation therapy is commonly delivered to small primary basal cell carcinomas and squamous cell carcinomas, particularly in the elderly with comorbidities and in sites where reconstruction would be difficult. Adjuvant postoperative radiation therapy to the primary site and/or regional lymph nodes has an important role in the management of Merkel cell tumours, larger squamous cell carcinomas and melanomas with adverse clinicopathological features. A major role of radiation therapy in melanoma is the palliation of metastases in stage IV disease.

Radiation therapy (RT or radiotherapy) is widely used in the management of skin cancers.[1-3] Due to the high incidence of skin cancer in Australia, which results in an enormous burden on the nation's health system, a consideration of the role and utility of RT is appropriate. This article provides a brief review of the use of RT in the management of the common skin cancers. It is important to appreciate the significant contributions of Australian researchers to the current understanding of this role. As with all cancers, multidisciplinary discussion is required for optimal outcomes.

Basal cell carcinoma

Basal cell carcinomas (BCCs) are extremely common in the elderly and typically occur on sun-damaged skin, especially in the head and neck region. Most small lesions are nodular, becoming ulcerated (forming 'rodent ulcers') as they grow. Although there is a very low rate of metastasis to regional lymph nodes or distant sites, neglected BCCs may cause major morbidity and extend across large areas, with destruction of adjacent and deeper structures including bone.

While surgical excision of small BCCs in favourable locations is generally preferred, their location often precludes simple excision and requires complex reconstruction.[4] For BCCs in surgically difficult sites in elderly patients, such as the tip of the nose and the inner canthus of the eye, RT is an attractive alternative. BCCs are generally radiosensitive cancers. Short treatment courses with superficial x-rays or electron beams, adding a 5-10mm margin around the tumour, result in high cure rates. Postoperative RT is generally recommended for positive margins, although only a proportion recur following surgery alone.[5]

Larger mobile BCCs remain curable with RT. With deeper infiltration and bone destruction, curative treatment generally involves excision with reconstruction. Postoperative RT is used for close or positive margins. If surgery is contraindicated due to the extent of the BCC or poor patient condition, RT with palliative intent is appropriate to achieve growth restraint and reduce bleeding.

Squamous carcinoma

Squamous cell carcinoma (SCCs) are also common on sun damaged skin. Small SCCs are often excised for convenience and for histological confirmation of the diagnosis. Features predicting local recurrence include: poor differentiation; infiltration of deeper tissues; close or positive margins; perineural spread; and previous recurrence. Re-excision to obtain wider margins, or postoperative RT is appropriate, depending on site.[6]

Following biopsy, definitive RT is commonly delivered to small primary SCCs, particularly in the elderly with comorbidities and in sites where reconstruction would be difficult.[2,4] As for BCCs, short RT courses using superficial X-rays or electron beams are used to treat the tumour with a 5-10mm margin, paying careful attention to the depth of the lesion to ensure adequate dose coverage at depth. Larger margins are needed when there is evidence of perineural spread.

While RT is a valid alternative to excision for many SCCs, there are situations for which surgery is preferred. These include: younger adults, who have many decades to express radiation-related complications; previous RT in that area; sites that will be subject to repeated injury (trauma or sun exposure); lesions with margins that cannot be defined; and tumours eroding into cartilage or bone.

The acute and late adverse effects of RT for small BCCs and SCCs are confined to the treatment volume. The main acute side-effects, either from definitive or postoperative RT, are hair loss within the treated area and a progressive skin reaction, similar to sunburn. This may lead to blistering and crusting, which resolves two to three weeks following the treatment course. As the size of the tumour increases,

more protracted treatment schedules are needed to reduce the intensity of the skin reaction. Late effects include permanent hair loss and progressive atrophy, and depigmentation of the skin. Cartilage and bone necrosis are unlikely with careful patient and tumour selection.

Management of regional lymph nodes is variable.[7,8] Small, well differentiated and superficial SCCs have a low rate of lymph node involvement. In these situations clinical observation is appropriate. For tumours with adverse pathological features, sentinel lymph node biopsy can be used to assess the status of the regional nodes. Alternatively, the regional lymph nodes may be treated electively by surgical lymph node dissection or RT. Palpable or grossly involved regional nodes require a therapeutic node dissection, generally followed by adjuvant post-operative RT.

A feature of a small percentage of SCCs is perineural spread, in which the tumour can infiltrate the perineurium and extend for considerable distances along nerves.[9] In this manner, SCC can enter the cranial cavity, leading to cranial nerve palsies. Cranial nerves V and VII are most commonly involved. Although mostly incurable, high dose RT to the course of the involved nerves can reverse nerve palsies and improve quality of life.

Merkel cell carcinoma

Although much less common than BCCs or SCCs, and often regarded as a rare tumour, Merkel cell carcinoma is not a rare cancer in Australia. It also occurs on chronically sun exposed skin in the elderly, often as a rapidly growing nodule with a propensity for early spread, both locoregionally and to distant sites. Merkel cell carcinoma is a radiosensitive and chemosensitive skin cancer. A number of recent reviews have been published.[10-13]

The management of the primary tumour is wide excision if possible, though definitive RT results in a high local control rate if excision is not possible. Postoperative RT is commonly used following excision of Merkel cell carcinoma, although the benefits are uncertain if wide excision margins have been obtained.

The management of regional nodes remains uncertain. For clinically negative nodes, management options include: observation; sentinel lymph node biopsy and subsequent management depending on sentinel lymph node status; and elective dissection or elective RT. When regional lymph nodes are clinically involved, options include regional node dissection, with postoperative RT for multiple involved nodes or extracapsular spread, or high dose RT alone. A dose response and volume relationship has been demonstrated and chemoradiation improves control rates in Merkel cell carcinoma considered to be at high risk due to size, recurrence or nodal involvement.[14,15] In the event of distant metastases, RT is useful for palliation in a number of sites, due to the radiosensitivity of Merkel cell carcinoma.

Overall there are many unanswered questions relating to the management of Merkel cell carcinoma, and clinical trials are hampered by its low incidence. Recent identification of a polyomavirus associated with Merkel cell carcinoma (but not necessarily causative) adds to the uncertainties in management.

Melanoma

There is limited use of RT in the management of primary melanoma, which is generally well managed with wide excision, with or without sentinel lymph node biopsy. Exceptions are adjuvant postoperative RT for the desmoplastic neurotropic subtype, which is being investigated currently, and definitive RT to treat large areas of lentigo maligna in the elderly.[3]

Melanoma has previously been considered to be poorly responsive to RT, despite good evidence for a wide spectrum of radiosensitivity.[1] The value of postoperative RT following therapeutic regional lymph node dissection has been a matter of controversy for several decades. A recent phase III clinical trial has helped to define this role, showing a statistically significant reduction in locoregional relapse with the addition of postoperative RT, compared with dissection alone in patients with stage III melanoma.[16] As anticipated, there was no survival advantage to the combination, with many patients progressing to systemic metastatic disease. Until the long-term complications of combined treatment (particularly lymphoedema) are reported, the net value of adjuvant RT remains unresolved.

The major role of RT in melanoma has been palliation of metastases in patients with stage IV disease.[3] Until the recent development of effective systemic therapies (BRAF inhibitors and immunomodulators), palliation of metastatic melanoma relied largely on surgery and RT. Although initial responses to targeted therapies (eg. BRAF inhibitors) are frequently spectacular, they are currently limited to tumours with the appropriate mutation (approximately 50% of metastatic melanomas) and response duration appears to be limited.

Recent technical developments are expanding both the role and effectiveness of RT in stage IV melanoma. Of particular interest is the management of cerebral metastases, due their high incidence and poor prognosis. The traditional treatment of cerebral metastases was dependent on the number of cerebral lesions, their locations and the patient's performance status. Single accessible metastases were resected surgically, postoperative whole brain RT was generally used, with phase III clinical trial evidence (not specific for melanoma) of a significant reduction in subsequent intracranial relapse.[17] Multiple brain metastases were treated with steroids alone or steroids plus whole brain RT.

Since the development and widespread use of stereotactic radiosurgery, the paradigm for the management of cerebral metastases has changed markedly.[18] Stereotactic radiosurgery involves a high single (ablative) dose of radiation, delivered with submillimetre precision to a defined intracranial target. Due to the steep dose gradient at the periphery of the treated metastasis, normal surrounding brain is spared potentially damaging effects of high dose radiation. By contrast with neurosurgery, stereotactic radiosurgery is a non-invasive outpatient procedure which can be used to treat multiple brain metastases in a single session, largely independent of their locations within the brain.[19] The response rates exceed 80% and seem comparable to the results following surgical excision, though no randomised trials have been undertaken. As

for neurosurgical excision, the addition of whole brain RT to stereotactic radiosurgery reduces the risk of further intracranial recurrence.[20] Unlike whole brain RT, stereotactic radiosurgery may be repeated for new metastases.

The expansion of these stereotactic and image-guided techniques to the treatment of systemic metastases has been fruitful. Vertebral metastases, which are a common cause of pain and possible spinal cord compression, have a 90% durable response rate following treatment with single fractions of 24 Gray, with good pain control for the remainder of the patient's life.[21] Careful immobilisation and sculpting of dose, which are essential for these high single doses, protect the spinal cord from damage. Similarly, high response rates are achieved in liver and lung metastases using these techniques.[22] The recent development of effective systemic agents will undoubtedly modify the role of RT in patients with stage IV melanoma. Several drugs have intracranial activity, such that studies of combination therapy will be required.[23]

In conclusion, RT plays an important role in the management of all the common skin cancers, although the role varies between the different cancers. Despite the generalities outlined above, it is important to individualise treatment and to manage patients in a multidisciplinary setting wherever possible.

References

1. Stevens G, McKay MJ. Dispelling the myths surrounding radiotherapy for treatment of cutaneous melanoma. Lancet Oncol. 2006;7(7):575-83.
2. Veness MJ. The important role of radiotherapy in patients with non-melanoma skin cancer and other cutaneous entities. J Med Imaging Radiat Oncol. 2008;52(3):278-86.
3. Hong A, Fogarty G. Role of radiation therapy in cutaneous melanoma. Cancer J. 2012;18(2):203-7.
4. Mendenhall WM, Amdur RJ, Hinerman RW, Cognetta AB, Mendenhall NP. Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. Laryngoscope. 2009;119(10):1994-9.
5. De Silva SP, Dellon AL. Recurrence rate of positive margin basal cell carcinoma: results of a five-year prospective study. J Surg Oncol. 1985;28(1):72-4.
6. LeBoeuf NR, Schmults CD. Update on the management of high-risk squamous cell carcinoma. Semin Cutan Med Surg. 2011;30(1):26-34.
7. Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. Head Neck. 2007;29(7):621-31.
8. D'Souza J, Clark J. Management of the neck in metastatic cutaneous squamous cell carcinoma of the head and neck. Curr Opin Otolaryngol Head Neck Surg. 2011;19(2):99-105.
9. Mendenhall WM, Amdur RJ, Hinerman RW, Werning JW, Malyapa RS, Villaret DB, Mendenhall NP. Skin cancer of the head and neck with perineural invasion. Am J Clin Oncol. 2007;30(1):93-6.
10. Henness S, Vereecken P. Management of Merkel tumours: an evidence-based review. Curr Opin Oncol. 2008;20(3):280-6.
11. Nicolaidou E, Mikrova A, Antoniou C, Katsambas AD. Advances in Merkel cell carcinoma pathogenesis and management: a recently discovered virus, a new international consensus staging system and new diagnostic codes. Br J Dermatol. 2012;166(1):16-21.
12. Rao NG. Review of the role of radiation therapy in the management of Merkel cell carcinoma. Curr Probl Cancer. 2010;34(1):108-17.
13. Zhan FQ, Packianathan VS, Zeitouni NC. Merkel cell carcinoma: a review of current advances. J Natl Compr Canc Netw. 2009;7(3):333-9.
14. Foote M, Harvey J, Porceddu S, Dickie G, Hewitt S, Colquist S, Zarate D, Poulsen M. Effect of radiotherapy dose and volume on relapse in Merkel cell cancer of the skin. Int J Radiat Oncol Biol Phys. 2010;77(3):677-84.
15. Poulsen M, Rischin D, Walpole E, Harvey J, Mackintosh J, Ainslie J, Hamilton C, Keller J, Tripcony L; Trans-Tasman Radiation Oncology Group. 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(23):4371-6.
16. Burmeister BH, Henderson MA, Ainslie J, Fisher R, Di Iulio J, Smithers BM, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol. 2012;13(6):589-97.
17. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280(17):1485-9.
18. Carlino MS, Fogarty GB, Long GV. Treatment of melanoma brain metastases: a new paradigm. Cancer J. 2012;18(2):208-12.
19. Chang WS, Kim HY, Chang JW, Park YG, Chang JH. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases? J Neurosurg. 2010;113 Suppl:73-8.
20. Patil CG, Pricola K, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database Syst Rev. 2010;(6):CD006121.
21. Shin JH, Chao ST, Angelov L. Stereotactic radiosurgery for spinal metastases: update on treatment strategies. J Neurosurg Sci. 2011;55(3):197-209.
22. Greco C, Zelefsky MJ, Lovelock M, Fuks Z, Hunt M, Rosenzweig K, et al. Predictors of local control after single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases. Int J Radiat Oncol Biol Phys. 2011;79(4):1151-7.
23. Gonsalves Shapiro D, Samlowski WE. Management of Melanoma Brain Metastases in the Era of Targeted Therapy. J Skin Cancer. 2011;845863.