THE ROLE OF RADIATION THERAPY IN CUTANEOUS MELANOMA

Graham Stevens
Melanoma Foundation of New Zealand & Department of Oncology, Auckland City Hospital, New Zealand
Email: gstevens@adhb.govt.nz

Abstract
Melanoma is an aggressive skin cancer with an increasing incidence worldwide. It is particularly common in Australia and New Zealand, where it is a major health issue that is responsible for the deaths of patients of all ages. Although melanomas are cured by surgery alone if they are detected at an early stage, many are diagnosed at more advanced stages. It is in the management of these more advanced melanomas that radiation treatment (RT) has an important role. The commonly-held idea that melanomas are resistant to radiation is an over-simplification, as many melanomas respond well to RT. The role of RT applies to patients treated both for cure and for palliation. In the curative setting, RT is usually combined with surgery, to improve local control at either the primary site or the regional lymph nodes. The precise uses of RT are still being refined, using clinical trials. For patients who have incurable melanoma and receive palliative treatment, RT is used in a wide range of clinical settings to improve quality of life. This review will illustrate some of these situations.

As described elsewhere in this issue of Cancer Forum, the incidence of melanoma is increasing globally. Fortunately, as a result of greater public awareness, many melanomas are detected at an early stage and are treated adequately by surgery alone, without the need for locoregional adjuvant treatment. These thin melanomas have an excellent cure rate and will not be discussed further.

This review of the role of radiation therapy (RT) mainly concerns patients whose melanomas have spread beyond the confines of the primary site. These patients fall into two distinct categories, being i) those for whom cure remains the goal of treatment and ii) those for whom cure is no longer a possibility and whose treatment is aimed at symptom reduction and improvement in quality of life (QOL).

Before describing the roles of RT in various stages of the disease, it is appropriate to consider briefly the radiation response of melanoma. This will provide an explanation of both the previous controversies regarding the value of RT for melanoma and the (apparently) unusual fractionation schedules that have been used.

Radiation response of melanoma
As mentioned above, melanoma has a reputation as a tumour that does not respond to radiation. This idea derived from selective use of clinical data and was supported by early laboratory work using irradiated melanoma cell cultures. In retrospect, it is clear that the irradiated tumours were generally large recurrences that had failed surgical treatment. Good outcomes would be unlikely for any of the common malignancies under these circumstances.

Although the clinical and in vitro cell survival curve responses were generally poor, analysis suggested that the best response was obtained when the total radiation dose was divided into a small number of large fractions (termed hypofractionation), instead of the usual schedule of a larger number of smaller-sized fractions (termed conventional fractionation). However a large in vitro study of human melanomas showed a wide range of radiation responses among xenografts and cell culture lines.

Conventional fractionation is the standard fractionation schedule for curative treatments of most cancers, as hypofractionation tends to increase the risk of serious, late complications caused by RT. In the case of melanoma, however, a number of well publicised clinical series have shown benefit using hypofractionated schedules (see below). Despite the results from these reports, which are discussed below, the case for the superiority of hypofractionation in melanoma treatment remains uncertain, as the single randomised clinical trial comparing conventional versus hypofractionated RT showed equivalence of response.

In summary, the radiation responses of human melanomas show a wide range of radiosensitivities, with some indication of better responses using hypofractionated RT schedules.

Role of RT in management of primary melanoma
In most cases, primary melanomas are managed surgically, with wide excision as the sole treatment. This results in high local control rates if clear margins of excision are obtained. Cure rates are dependent on well documented features including tumour thickness, ulceration and mitotic rate. Postoperative RT should be considered when the risk of local recurrence increases. This includes close or positive margins when re-excision is impractical (eg.closer to critical structures); multiple recurrences; and desmoplastic melanomas, for which recurrence rates exceeding 20% have been reported following surgery. The use of adjuvant RT in these settings reduces local recurrence significantly.

RT has been used also for the definitive treatment of large lentigo maligna and lentigo maligna melanomas. Adequate resection of these large lesions is frequently difficult, particularly in the context of an elderly patient with comorbidities. The results of RT alone for these lesions has shown high rates of local control.

Role of RT in management of locoregional melanoma
The value of RT and its appropriate use as an adjunct to surgery in the management of regional lymph nodes represents the most uncertain aspect of the role of RT in melanoma. Quite apart from the misconceptions regarding the sensitivity of melanoma to radiation (discussed above), there are other considerations mitigating against RT. First, there is a strong correlation between nodal involvement with melanoma and survival. Thus, patients with sufficient indication for
postoperative RT to the regional nodal basin have a poor prognosis due to development of systemic metastasis. Second, the morbidity of lymph node dissection followed by postoperative RT may exceed the potential gain in local control. Third, there is no indication that any improvement in local control impacts on survival. On the other hand, uncontrolled locoregional melanoma is frequently an irretrievable and devastating condition.

Currently there are no data from randomised clinical trials (RCTs) to assess adequately the merit of adjuvant RT following regional lymph node dissection. The sole reported RCT used an unusual RT schedule and did not report on local control. A RCT addressing this issue is being conducted as an intergroup study by the Australian and New Zealand Melanoma Trials Group (ANZMTG) and the Trans Tasman Radiation Oncology Group (TROG). The trial was opened in 2003 and has accrued approximately half of the 270 patients required. The randomisation is between surgery alone versus surgery plus postoperative RT for patients with fully resected nodal regions in which the histopathology report indicates nodal involvement with melanoma. Inclusion criteria include the number of involved nodes, nodal size and the presence of extracapsular spread.

In the absence of high level evidence, current practice outside the clinical trial is based on the available published data. Many surgical series over the past two to three decades have provided a good indication of factors influencing regional recurrence. Most of these factors are adverse histopathological features, the dominant ones being number of involved nodes, maximum size of involved nodes and the presence of extracapsular extension of melanoma into connective tissue. Regional recurrence rates averaging 20-30% have been reported for any of these adverse findings, with higher recurrence rates for combinations. Not surprisingly, these adverse features tend to occur together. Non-histological factors influencing regional recurrence include the indication for lymph node dissection (therapeutic versus elective) and the site of the nodal basin (higher recurrence rates for cervical nodes versus axilla or groin).

The addition of adjuvant postoperative RT to lymph node dissection has been reported in retrospective or prospective non-randomised studies by a number of groups. These include series in which limited neck dissections were performed. The RT fractionation schedules in these studies have varied considerably, although most investigators have used hypofractionated schedules. These include 30 Gray in five fractions (treating twice weekly), 33 Gray in six fractions (treating twice weekly) and 48 Gray in 20 daily fractions.

Despite the large range of recurrences reported in surgical series and the differing fractionation schedules used in the RT series, the local relapse rates following post operative RT fall close to 10% in all series. These local relapse rates are markedly less than the historical surgical series and imply that RT is effective in controlling microscopic deposits of melanoma. By contrast, local recurrence rates of dissection and postoperative RT increase to approximately 50% following incomplete surgery and gross residual disease.

Patients are referred for postoperative RT on the basis of adverse pathological features. This places them at high risk for metastatic disease. However, survival was 37% at five years in the Sydney Melanoma Unit (SMU) series, attesting to the benefit of local control for one third of patients at least. Similarly, the late effects and complications of combined dissection and postoperative RT are important to evaluate. The anticipated late effects are soft tissue fibrosis and induration within the radiation field, with the potential for lymphoedema following irradiation of the axilla or groin. For anatomical reasons, the risk of serious complications is less for neck irradiation than for treatment of other nodal regions. Although the radiation fields in neck irradiation often extends from the temporal region to the clavicle, the depth of treatment is limited to several centimetres. However, when treating the axilla and groin, larger volumes of tissue are irradiated, including the lymphatics draining an entire limb. To minimise the risk of complications, careful attention to radiation field placement is mandatory, to ensure maximum sparing of normal tissues without compromising the target volume. Lymphoedema rates ranging 20-50% have been reported.

**Role of RT in management of metastatic melanoma**

Despite the trend to earlier diagnosis, many patients develop metastases from melanoma. The spectrum of metastatic presentation is wide, with regard both to the location(s) of metastasis(es) and to the rate of progression. As systemic treatments have limited efficacy in metastatic melanoma, local treatments, including RT, become important for palliation of distressing symptoms. A brief assessment of the value of RT in various scenarios follows.

The incidence of brain metastases in patients with metastatic melanoma is high, reaching 75% in autopsy series. Clinically, the diagnosis of brain metastases is highly variable, from the initial presentation of melanoma to the final episode of widespread metastatic disease. Diagnosis is made by CT or MRI brain scans. Irrespective of the time of onset, the median survival from the diagnosis of brain metastases is several months.

The initial management of patients with multiple brain metastases is immediate commencement of high dose steroids. In many cases this will settle the presenting symptoms. This is followed by whole brain irradiation (WBRT) if the patient’s condition is adequate. The usual RT schedules are 20-30 Gray in 5-10 daily fractions. Response rates are generally poor, with the addition of WBRT adding one to two months to the median survival compared with steroids alone. Of patients with multiple brain metastases, subgroups with minimally different survivals have been identified from an analysis of prognostic factors.

Despite the dismal prognosis for most patients, small subgroups should be considered for more aggressive treatment. This includes patients with single or oligo brain metastases without extracranial metastasis or with minimal, slowly progressive extracranial disease. Surgical resection of a single cerebral metastasis improves survival compared with WBRT alone. Conversely, addition of WBRT to surgical resection reduces dramatically the incidence of further intracranial relapse, although survival is unchanged.

Stereotactic radiation (SRT) is a non-surgical alternative for aggressive treatment of metastases. SRT is a high precision technique that utilises a number of radiation beams that focus on the metastasis. This produces a very high radiation dose in the target, with a sharp dose fall-off outside the target volume. These characteristics are well suited to the treatment of brain metastases. SRT is usually delivered in an outpatient setting and does not require a surgical procedure or general anaesthetic. In general there are few side effects and patients are able to walk out of the treatment room and resume their pre-treatment activities immediately.
Limitations on the use of SRT are a maximum tumour diameter of approximately 3cm. Many centres offering SRT also impose a limit of approximately three metastases, all of which may be treated at the same episode. Multiple reports indicate that single doses of approximately 15-20 Gray lead to control of a metastasis in approximately 90% of cases. It is often possible to repeat the procedure if new brain metastases develop at a later date. Although surgical resection and SRT have not been compared in a RCT, case matching suggests that both methods have similar results. SRT has an advantage for lesions that are deeply placed and surgically inaccessible. Conversely, surgical resection provides pathological confirmation of malignancy. This is essential if doubt exists regarding the diagnosis, as clinical and radiological suspicion is incorrect in approximately 10% of cases.33

The skin is a common site of both locoregional and distant metastasis. RT is used extensively for isolated lesions which are inappropriate for local excision. However toxicity limits RT in the treatment of extensive areas of infiltrated skin. Short courses of palliative RT are used for bone metastases causing pain and for stabilisation following orthopaedic intervention and internal fixation of bone metastases. Vertebral metastases that threaten or cause spinal cord compression should be considered for initial surgical decompression followed by RT. If surgery is not possible, due to either the patient’s condition or extensive vertebral metastases that preclude internal fixation, RT is delivered under steroid cover. Palliative RT is used to shrink masses causing a variety of symptoms. Large, dominant mediastinal masses causing vascular, oesophageal and bronchial obstruction often respond to RT. Nodal masses and soft tissue masses in unusual sites (eg. muscle, tongue, etc) may respond also. Unfortunately, responses tend to be transient, although occasional responses are durable.

Melanoma spreads commonly to lung, liver and the gastrointestinal tract. RT is useful for individual symptomatic lung lesions, but is of limited value for infradiaphragmatic metastases.

The future

The science and technology of RT are advancing rapidly. This is most evident in the fusion of developments in the accuracy of treatment delivery and radiobiological knowledge of tumour cell killing. These developments are enabling the concepts of intracranial SRT to be extended to the remainder of the body. Real time imaging during delivery of radiation, coupled with techniques for gating and/or tumour immobilisation, enable higher doses to be delivered with greater safety. Methods for tracking and targeting tumours during treatment are being developed. The importance of dose inhomogeneity within the tumour is being explored. The ability to increase the radiation dose to regions of hypoxia or decreased radiation sensitivity, due to intrinsic genetic variability, is being investigated. This is possible due to the integration of advanced treatment delivery techniques and sophisticated imaging such as positron emission tomography, using molecular probes.

Conclusion

It is evident that RT has a significant role in all phases of the management of melanoma, from the primary tumour to widespread metastatic disease. When melanoma is localised, RT has its main role as a surgical adjuvant, to decrease the risk of local recurrence. Until definitive evidence is available from RCTs, the finding of adverse pathological features should guide the use of postoperative RT to the primary site and regional nodal basin. RT has an indispensable role in palliation. In particular, the development of stereotactic techniques has had a dramatic impact on the management of many patients with brain metastases. Current developments in RT, combined with developments in imaging, should improve the efficacy of RT and increase its scope and role to encompass visceral metastases.

References


