

## Advances in the Treatment of Metastatic Melanoma Through Radiotherapy

a report by

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Melanoma is a malignant condition that causes melanocytes in the skin, mucosal surfaces or unusual sites such as the eye or the central nervous system. It is a disease that occurs almost exclusively in patients of Caucasian origin, although rarer forms can occur in other ethnic populations. The incidence may vary but there is a close correlation with the disease. About 10% of patients develop advanced and metastatic disease. The behaviour of melanoma is highly unpredictable, with remissions and relapses occurring without warning during and after therapy. For decades the role of radiotherapy in advanced melanoma has been controversial. Initial impressions among clinicians were that melanoma is a 'radioresistant disease' and that no local therapy other than surgery was of any use.

However, more recently there has been a realisation that melanoma displays a wide variety of radiosensitivity and that in some patients large lesions can respond to modest doses of radiation.<sup>1</sup> Many clinicians have suggested that larger than conventional doses per fraction may have an advantage in treating melanoma because of its large 'shoulder' on the cell-survival curve.<sup>2</sup> Although initial observations have supported this view there is no clinical evidence that hypo-fractionated radiotherapy regimens have any advantage over conventional regimens, with the latter being kinder to sensitive normal tissues.<sup>3</sup> Clinicians now use radiotherapy for a wide variety of indications for metastatic melanoma. Perhaps the greatest progress in advanced disease has been in the management of nodal disease, particularly in the post-operative adjuvant setting. For the purposes of this article metastatic melanoma will be considered as a stage 2-4 disease.

### **The Role of Radiotherapy for Stage II (In-transit Disease) Melanoma**

In-transit metastases from melanoma represent a challenge to both the surgeon and radiation oncologist. Even the identification of in-transit disease as a separate entity from primary melanoma with satellite lesions can be difficult in some cases.<sup>4</sup> However, the prognostic significance is probably similar.<sup>5</sup> The development of in-

transit metastases represents a particularly unpredictable phase of the disease, frequently accompanied by more in-transit recurrences, followed by nodal and systemic metastases. The mechanism of in-transit spread of melanoma is exclusively via cutaneous and subcutaneous lymphatics, which means that there may be large areas of uninvolved skin and subcutaneous tissues between individual tumour deposits. However, in many patients disease can remain confined to a limb or region of the body without distant metastases and may be the cause of considerable morbidity and even mortality. The lower limb is most commonly affected, presumably as a result of its large surface area and extensive system of lymphatics.

Although the primary modality of treatment is surgery, radiotherapy and infusional chemotherapy can play a vital role in the management of in-transit metastases. Radiotherapy can be used for the treatment of excised lesions or the control of bulky disease, where fungating disease may result in bleeding, discharge and local pain. Guidelines regarding exact indications, techniques and doses are poorly described in the literature.

At the Princess Alexandra Hospital in Brisbane we have used high-dose radiotherapy to treat both excised and bulky in-transit disease with reasonable results. It is not necessary to offer radiotherapy to all patients with excised in-transit disease. Single excised lesions occurring for the first time can be observed. Those with recurrences after initial surgery and those with multiple excised deposits should be considered for treatment, particularly if located in the head and neck region. Post-operatively, our policy is to cover the tumour bed with a 3cm margin in all directions apart from depth, where we use a 2cm margin. In this setting, the dose is 48Gy in 20 fractions treating five days per week. For bulky tumours, the extent of the target volume depends on the treatment intent. For localised tumours where the intent is cure, we have recommended a margin of 3cm in all directions apart from depth where a 2cm margin is used. The dose in the curative setting is 50Gy in 20 fractions over four weeks or 36Gy in six fractions over three weeks treating twice weekly, depending on the amount of normal tissue in the field and the treatment intent. In the palliative setting where large areas require treatment, doses are lower, particularly in the lower limb where vascularity to the periphery may be impaired by other causes. In this setting, a dose of 50Gy in 25 fractions (large area) or 36Gy in 12 fractions (smaller area) may be more appropriate. Photons are often the most useful modality but electrons, either as single or conjoined fields, may also be used. In all cases, full skin bolus is essential to ensure the full dose is given to the skin surface. In the palliative setting where extensive in-transit disease is present, it may sometimes be more appropriate to select the most symptomatic area and treat that initially.



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### Nodal Metastatic Melanoma

There have been numerous reviews about the role of radiotherapy for nodal melanoma over the past decade; however, little has been prospective. Primarily, this has been because regional outcomes of surgery alone have been reported as being suboptimal, which then

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translates into poorer overall survival. While it is unlikely that radiotherapy after surgery for nodal melanoma improves survival, there may be significant benefits in terms of regional control and its implications for quality of life. Clearly, there are histological features in resected nodal melanoma that are more likely to be associated with regional recurrence. These include multiple node involvement, extracapsular extension and node size.<sup>6-12</sup> Therefore, it would be useful to determine the role of post-operative radiotherapy in this 'high-risk' group, and this has been the subject of controversy for at least a decade, with those for and against radiotherapy arguing without any randomised evidence.

The only published randomised trial involving radiotherapy for metastatic melanoma to lymph nodes was published as far back as 1986.<sup>13</sup> This trial examined the role of post-operative radiotherapy for all node sites but was underpowered to determine any result. Since that time there have been numerous retrospective published studies and reviews examining the role of post-operative radiotherapy to the head and neck region as well as the other nodal basins.<sup>14-21</sup> Most have shown that radiotherapy can reduce the crude rate of regional recurrence to less than 15% without significant complications apart from lymphoedema of the limbs following treatment of the axilla or inguinal region. The Radiation Therapy Oncology Group (RTOG) started a randomised trial in 1990, but this trial was not completed and was probably overshadowed by the emergence of interferon as a possible weapon in the adjuvant treatment of resected nodal melanoma. At the Princess Alexandra Hospital, workers at the Melanoma Clinic started treating both bulky and post-operative nodal melanoma as early as 1989 with a regimen of 50Gy (bulky disease) or 48Gy (post-operative) in 20 fractions over four weeks. This was in contrast to other major melanoma units such as the Sydney Melanoma Unit and the MD Anderson Hospital, Houston, claiming the virtues of hypofractionated regimens such as 30Gy in five fractions or 33Gy in six fractions treating twice weekly.<sup>16-21</sup>

Following the completion of a pilot study that was published in 1995,<sup>14</sup> we started a large prospective study to examine response and toxicity at all three node sites using the same regimen. Patients were eligible if they were considered to be at high-risk of regional recurrence. The study was expanded to include other centres in Australia and New Zealand and became known as Trans-Tasman Radiation Oncology Group (TROG) 96.06. After enlisting 234 patients across the region, the study was completed in 2001 and published in 2006.<sup>22</sup> The study

confirmed low toxicity, a low regional recurrence rate at all sites and significantly worse progression-free and overall survival in those with more than two resected nodes usually implicated with melanoma. Despite all these studies the debate about the benefit of adjuvant radiotherapy has continued.<sup>23,24</sup>

In another recent review, the need for a prospective randomised trial was emphasised as being a priority.<sup>25</sup> After TROG 96.06 was completed plans were under way to perform a randomised trial under the auspices of TROG and the Australian and New Zealand Melanoma Trials Group (ANZMTG). This trial, known as TROG 02.01, is a randomised trial examining the efficacy of regional radiotherapy following nodal surgery where histology of the specimen indicates features predicting a high risk of regional recurrence. This trial was started in late 2002 and completed registration of 250 patients in September 2007. The primary end-point of regional recurrence will be analysed in late 2008.

Currently, pending the results of TROG/ANZMTG 02.01 the indications for post-operative radiotherapy following nodal surgery can be divided into two groups, i.e. absolute and relative. The following are absolute indications where radiotherapy is strongly recommended:

- macroscopic or microscopic disease after surgery;
- previous nodal surgery; and
- tumour spill at surgery.

The following are relative indications where radiotherapy could be considered:

- more than one node involved;
- extracapsular extension or total nodal replacement by tumour;
- an involved node larger than 4cm in maximum diameter;
- parotid node involvement; and
- a suboptimal lymph node dissection.

Again, the technique of nodal basin radiotherapy has been poorly described in the literature. In principle, the target volume should cover the surgical bed including any scars. An exception is the pelvis, where the scar and the nodes make the volume large. In the head and neck region, the volume normally extends from the skull base to the

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clavicles. In this region, a large electron field is easiest to use but a three-field photon technique may be better where the neck is thick. The axilla and supraclavicular nodes should be treated in continuity with a large anterior and posterior photon combination to avoid an excessive dose to the lungs. In the groin, a three-field photon plan is useful to spare the femoral neck and treat pelvic nodes if required.

Further information regarding treatment techniques are described in the report on TROG 96.06.<sup>22</sup>

The definition of a suboptimal lymph node dissection may vary from a simple node excision to the removal of fewer than 15 nodes in the head and neck basin, 10 nodes in the axilla or six nodes in the groin. The role

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of radiotherapy for elective nodal irradiation – where no nodes have been sampled or dissected – is unclear, although there is a suggestion from one study that it may be of benefit.<sup>26</sup>

The role of radiotherapy in the pre-operative setting is even more controversial, with little information in the literature. Nevertheless, there are patients who present with bulky technically unresectable nodal disease who require treatment. If the patient has no or minimal metastatic disease there is a case for the use of pre-operative radiotherapy followed by possible surgery in order to maximise regional control. Similar doses to those used in the post-operative setting are effective with the ultimate response being variable.<sup>3,14,15</sup> Almost all patients demonstrate some tumour shrinkage that may be maximal three to three months after therapy. Follow-up computed tomography (CT) and positron emission tomography (PET) scans should be considered prior to surgery to evaluate the response and reassess the patient for other metastatic diseases. If there is significant progression at distant sites the

surgery could be cancelled and the patient left with the benefit of palliative radiotherapy. It is likely that more patients are likely to undergo this approach in future.

## Metastatic Melanoma to Distant Sites

The management of melanoma to distant sites with radiotherapy is similar to that involving other primary sites. One of the challenges to the treating radiation oncologist is the variety of sites that melanoma can metastasise to, ranging from some common sites such as brain, bone and skin to more unusual sites such as heart, bowel and eye. Nevertheless, most of the doses used are the same as used at metastatic sites for other malignancies, e.g. 8Gy in a single fraction for bone metastases and 20Gy in five fractions for brain metastases. The treatment of symptomatic intra-abdominal metastases involving the liver, adrenal gland or small bowel should be according to the volume of normal tissue involved and the aim of the therapy, e.g. pain relief, cessation of bleeding, etc. Typical doses are 10Gy in two fractions (liver) or 18Gy in five fractions (adrenal).

More controversy surrounds the role of radiotherapy following the resection of one or few cerebral metastases. Currently, there is no randomised trial of benefit in terms of intracranial failure involving melanoma, but there are some data from a randomised trial involving cerebral metastases from all sites. In 1998, Patchell et al. published a randomised controlled trial of 95 patients with single brain metastases and showed the addition of post-operative radiotherapy resulted in a lower intracranial recurrence rate and patients were less likely to die of neurological causes.<sup>27</sup> Stereotactic radiosurgery (SRS) has become a useful tool in the management of cerebral metastases that are not suitable for surgery. There are a number of single-institution reviews of the role of SRS for single or few brain metastases from melanoma with encouraging results.<sup>28,29</sup> However, there are no trials comparing this modality with surgery or conventional radiotherapy in this setting. ■

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