

## CASE STUDY

# Complete clinical response of a neglected cutaneous melanoma with combined radiotherapy and immunotherapy: A case report

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radiotherapy, immunotherapy, cutaneous melanoma, melanoma, complete response

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**Abstract**

The treatment of patients with advanced melanoma has undergone a dramatic change over the past decade. Apart from refining the radiotherapy techniques, the repertoire of systemic treatments expanded from largely futile cytotoxic chemotherapy to substantially more effective MAP kinase and immune checkpoint inhibitors (Immunotargets Ther, 7, 2018)<sup>1</sup>. We report a case which exemplifies the improved efficacy as well as increased complexity of therapeutic decision-making. A 71-year-old man presented with neglected fungating and bleeding malignant melanoma, which resulted in severe anaemia with consequent cardiac dysfunction. There was limited distant spread. Patient was treated with combined radiotherapy and immunotherapy: 55 Gray in 20 fractions over four weeks using 3D-conformal technique followed by an anti-PD1 antibody (pembrolizumab, Keytruda<sup>®</sup> Merck/MSD, Kenilworth N.J.; 2 mg/kg 3-weekly). A surgical approach to provide haemostasis and cosmesis was considered, but would be associated with significant morbidity, prolonged recovery and functional impairment and would not have altered patient survival. The sequential radioimmunotherapy resulted in a complete response. Radiotherapy was completed with only mild skin toxicity. Immunotherapy was complicated by diarrhoea, which necessitated withdrawal of the medication but was controlled with steroids. The non-operative treatment resulted in excellent oncological, functional and cosmetic outcome, with acceptable toxicity. Due to increasing complexity of melanoma therapy, a multidisciplinary approach is of paramount importance.

**Case Presentation**

A 71-year-old man presented with history of dyspnoea and peripheral oedema. He had no past medical or surgical history and no medications. Examination revealed biventricular heart failure and a large (136 × 91 × 56 mm) fungating mass extending over upper back and posterior neck (Fig. 1).

Initial investigations demonstrated severe microcytic anaemia (haemoglobin 35g/L), mitral regurgitation, dilated left heart chambers but preserved ejection fraction of 60%, leading to diagnosis of heart failure from severe anaemia secondary to a bleeding malignant mass. Blood transfusion and medication for heart failure resulted in rapid clinical improvement. Mass biopsy confirmed

malignant melanoma (BRAF and NRAS mutation-negative). Positron emission and computed tomography (PET/CT) showed the fungating primary invading muscles (Fig. 2) with spread to two lymph nodes (left upper neck and axilla) and a separate, isolated metastatic deposit in the small bowel.

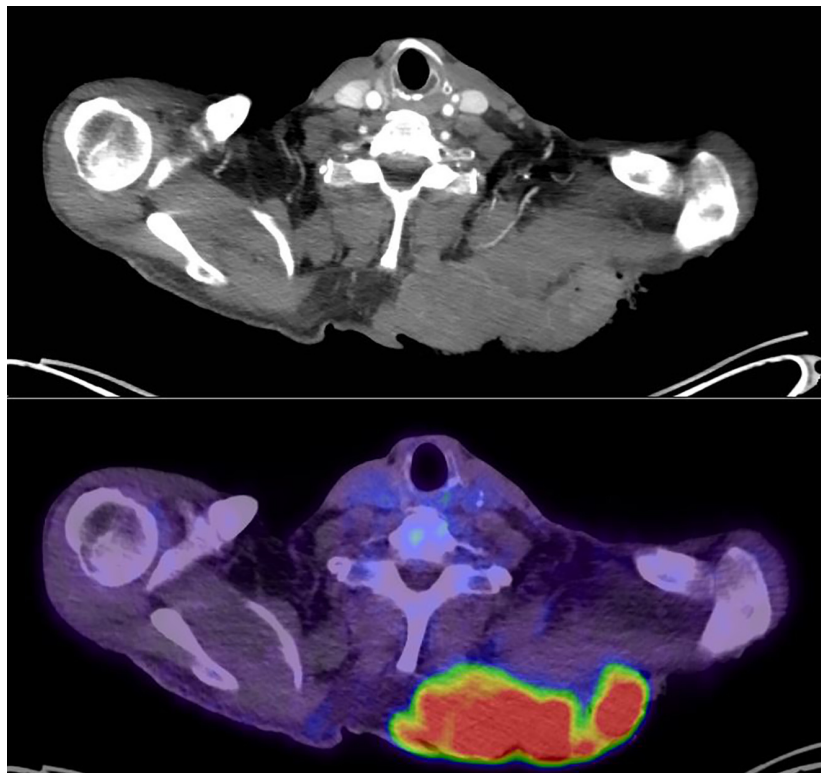
Initially, consideration was given to extensive resection and reconstruction. With rapid correction of heart failure, the patient was cleared for planned surgery. However, at multidisciplinary discussion, which included representatives of head-and-neck surgery, plastic and reconstructive surgery, radiation and medical oncology, metastatic spread was noted and high-dose palliative radiotherapy and systemic treatment were considered more appropriate. He received 55 Gray in 20 fractions



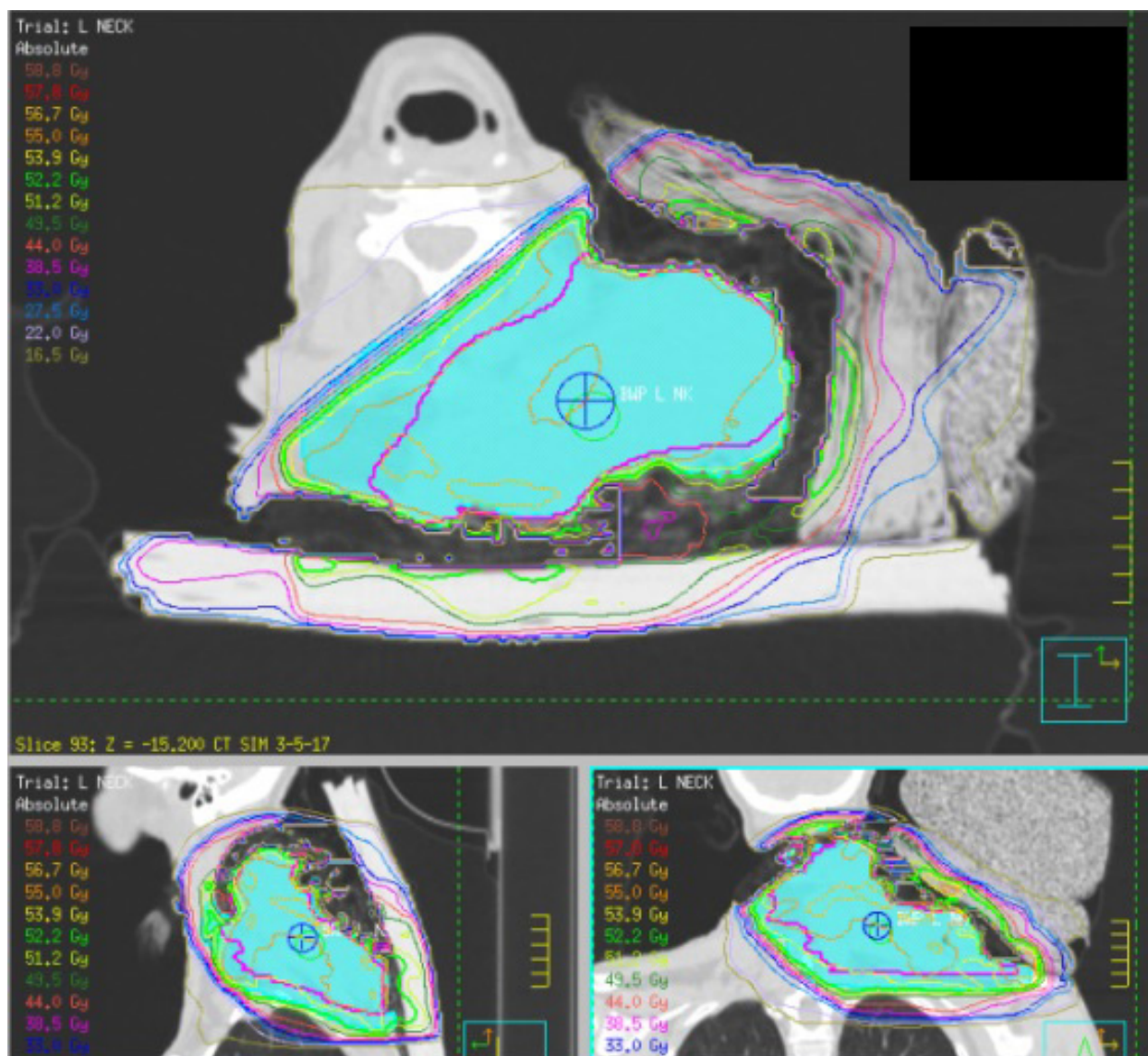
**Figure 1.** Fungating mass before radiotherapy. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

over four weeks. A 3D-conformal plan utilising two opposed tangential fields with 10 MV photons and daily image guidance was used with bolus placed over the tumour to ensure full dose to the skin surface (Figs. 3 and 4). In week three, a significant reduction in primary lesion size was observed with complete haemostasis. Treatment was completed, with only mild (grade 2) skin toxicity.

One month after diagnosis, immunotherapy with an anti-PD1 antibody was initiated (pembrolizumab, Keytruda® Merck/MSD, Kenilworth N.J.; 2 mg/kg 3-weekly). The index lesion continued to regress, and twelve weeks after completion of radiotherapy, there was a pigmented patch and residual small ulcer centrally (Fig. 5). During follow-up, an isolated left frontal lobe brain deposit was diagnosed and treated with stereotactic radiotherapy, 24 Gray in 3 fractions. Following the fifth cycle of immunotherapy, the patient developed colitis, which was managed with treatment discontinuation and a prolonged course of prednisolone. Follow-up PET/CT 6 months after diagnosis showed complete resolution of the primary lesion and systemic metastases, with only a cystic, non-enhancing lesion at the treated brain metastasis site. Duration of response was verified 5 months after completion of immunotherapy (10 months after diagnosis) by PET/CT.



**Figure 2.** PET/CT image of the fungating mass with invasion into the muscle. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



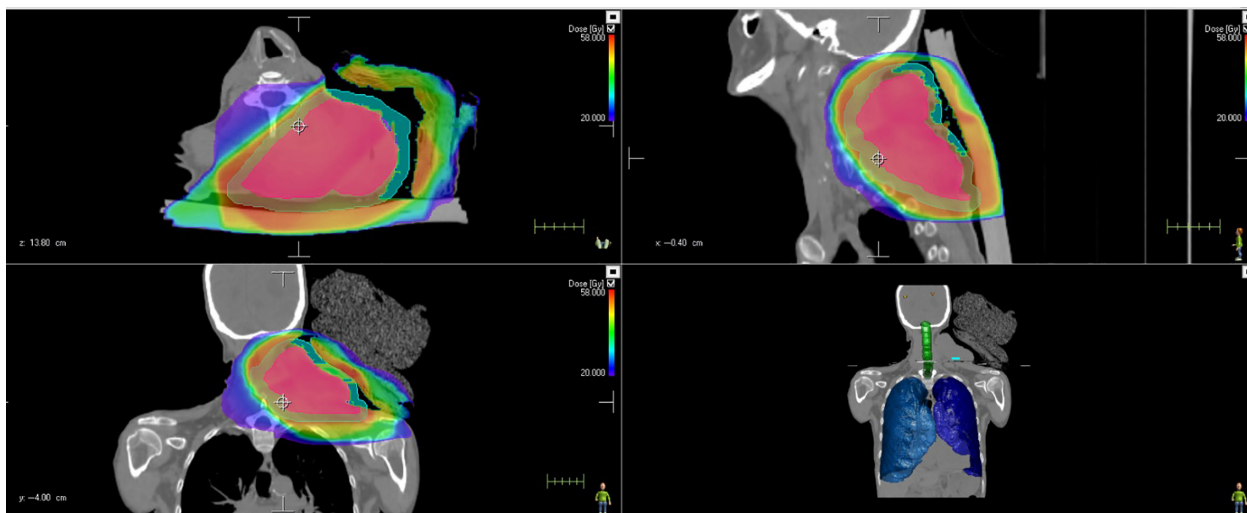
**Figure 3.** Radiotherapy plan. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

## Discussion

Herein, we report a case of neglected fungating malignant melanoma treated with combined radiotherapy and immunotherapy, resulting in excellent oncological, functional and cosmetic outcome, with acceptable toxicity. A surgical approach to provide haemostasis and cosmesis was considered. The patient was optimised medically for the extensive resection planned. Further discussion amongst the two surgical teams and representatives of the oncology teams was undertaken. The patient would require the resection of the large primary together with the underlying muscle, neck and

axillary dissections as well as segmental small bowel resection to be rendered clear of disease. Long-term survival of patients with resected oligometastatic disease has been reported; however, the results are affected by selection bias and the survival achieved with modern systemic treatments is longer<sup>2,3</sup>. Ultimately, the surgical management was thought to be associated with significant morbidity, prolonged recovery and functional impairment and would not have altered patient survival.

Modern radiotherapy using conformal techniques allows for precise delivery of high doses to tumour targets with excellent sparing of normal tissue and organs at risk. High-dose palliative radiotherapy is an option for patients



**Figure 4.** Radiotherapy plan. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**Figure 5.** Residual pigmented patch after three months of combined therapy. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

with symptomatic areas of disease, who are of relatively good performance status and have limited or stable metastatic disease. Radiotherapy can result in durable

local control in the majority of patients with favourable side effect profile. Radiotherapy is a useful treatment modality for palliative indications, adjuvant irradiation of primary tumour beds at high risk of local recurrence and for select patients at high risk of nodal recurrence. Stereotactic radiotherapy is a particularly effective technique.<sup>4,5</sup>

Systemic therapy for melanoma has changed dramatically in the past decade. Use of immune checkpoint inhibitors has resulted in unprecedented improvement in survival for patients with stage IV melanoma. Median survival of six months observed with chemotherapy has increased to over three years with immunotherapy. Objective response rate to immunotherapy in phase III studies is between 33% and 57%, with reports of complete responses ranging from 5% to 16%. Importantly, immunotherapy differs from other forms of systemic therapy in that immune cells are able to recognise and eradicate micro-metastases wherever they are in the body. Hence, most responses are durable and often ongoing after discontinuation of therapy.<sup>6,7,8</sup>

Abscopal effect occurs when a local therapy, most often radiation, not only achieves a response of the targeted tumour but also leads to shrinkage of untreated tumours elsewhere in the body. The abscopal effect of radiotherapy combined with immunotherapy is an area of active study. The synergistic effect of combined radiotherapy and immunotherapy is characterised by regression of metastatic disease distant to the site of local radiotherapy, mediated by activation of the immune system. There are prospective clinical trials examining combination radiotherapy and immunotherapy to identify subsets of patients who may benefit from this approach.<sup>9,10,11,12</sup>

## Conclusion

Sequential radiotherapy and immunotherapy treatment modalities are often used together in metastatic disease. Herein, we report a case of neglected fungating malignant melanoma treated with combined radiotherapy and immunotherapy, resulting in excellent oncological, functional and cosmetic outcome, with acceptable toxicity. Due to increasing complexity of melanoma therapy, a multidisciplinary approach is of paramount importance.

## Disclaimers

The views expressed in the article are the authors own and are not an official position of the Gold Coast University Hospital. Neither of the authors is a recipient of a research scholarship, and the paper is not based on previous communication to a society or a meeting.

## Ethical approval

Ethical approval (low-risk application) was obtained from our institution for this case report. Consent for publication has been obtained.

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