

Case report: advanced renal cell cancer. When all hope is lost, low dose radiation may help

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ABSTRACT Renal cell cancer is the most common cancer diagnoses. Clear cell carcinoma is the most common form of renal cell cancer. Metastatic RCC is poorly responsive to treatment and has a poor prognosis.

INTRODUCTION

In Australia, renal cell cancer (RCC) is one of the 10 most common cancer diagnoses; the incidence has almost doubled between 1982 and 2007.¹ *Clear cell carcinoma* is the most common form of RCC. One in three cases will present at an advanced stage. Metastatic RCC is poorly responsive to treatment and has a poor prognosis.²

There are a number of targeted agents now approved for clinical use in the treatment of advanced RCC, including tyrosine kinase inhibitors (TKI, e.g., sunitinib and axitinib), multi-kinase inhibitors (e.g., sorafenib), anti-vascular endothelial growth factor monoclonal antibody (e.g., bevacizumab), and the mammalian target of rapamycin (mTOR, e.g., everolimus). In addition, immunotherapy with nivolumab is now approved for advanced disease following failure of one or two lines of anti-angiogenic treatments.

Unfortunately, almost all patients with advanced disease will progress despite these treatments. Renal cell carcinoma has been considered to be radioresistant,³ and many clinicians believe high biologic doses are necessary to achieve meaningful palliation, which may not always be feasible or appropriate. Many patients, therefore, do not have a trial of palliative radiotherapy, especially when volumes are large and potential toxicity may be thought to be high.

CASE

A 66-year-old female presented with a large abdominal mass on a background of metastatic clear cell RCC, which had progressed despite a first-line TKI and immunotherapy. The large mass was recurrent tumor, arising from the surgical bed as well as confluent nodes. It had dramatically increased in size, measuring 110 mm (anterior/posterior) × 149 mm (transverse) × 196 mm (superior/inferior), and extending from the subhepatic space, into the right iliac fossa and across the midline (Images 1 and 2).

She had been diagnosed 1 year previously following resection of a large right sided renal mass. Histopathology was a pathological T3, grade 4 clear cell RCC, 250 mm in maximal dimension, with vascular and lymphatic invasion. A CT scan 3 months following nephrectomy demonstrated retroperitoneal soft tissue deposits up to 34 mm and two suspicious 4 mm lung lesions. Treatment with a TKI (sunitinib) was initiated due to her quick relapse. She had poor tolerance of the sunitinib and her disease advanced over the next 5 months, with progression of the peritoneal disease. She was switched to second line therapy with nivolumab. During the 3 months of immunotherapy, she continued to progress in the abdomen to the size described above (see Images 1 and 2). A second-line TKI, axitinib, was commenced, and she was referred to Radiation Oncology for consideration of palliative RT to the large mass.

At the time, she reported symptoms of malaise and lethargy, with abdominal bloating and some intermittent mild abdominal discomfort. Her abdomen was visibly distended with a firm palpable mass extending from the right upper quadrant to the right iliac fossa. She was tender on examination.

After discussion, she consented to RT treatment, with the understanding that the treatment intent was palliative. The radiation treatment fields were extensive and were designed for symptomatic

stabilization while sparing the remaining kidney. The prescribed dose was 36 Gy in 12 fractions with a low threshold for stopping the RT if she experienced unacceptable side effects, such as nausea or diarrhea. The RT started 3 weeks after her last dose of nivolumab, the axitinib was continued during the RT treatment. The patient had just received her first dose of 3 Gy, when she received news about the sudden death of a family member in another state. Treatment was delayed while she attended the funeral.

On her return 2 weeks later, a re-simulation CT scan demonstrated that the mass had reduced in size by approximately 25% following the single fraction of 3 Gy (Images 3 and 4). The treatment was re-planned, and she completed the remaining 33 Gy in 11 fractions to a smaller treatment volume. She tolerated the remainder of the treatment well with the only side effect being a slight increase in bowel frequency.

A restaging CT scan performed 1 month post the completion of her radiotherapy treatment confirmed stable disease, with the new dimensions of the mass measuring 91 mm × 113 mm × 148 mm (Images 5 and 6). There was ongoing low density change, likely reflecting tumor response. In addition, there had been a reduction in the size of the lung metastases which had not been included within the radiotherapy field. She remained on the axitinib, which

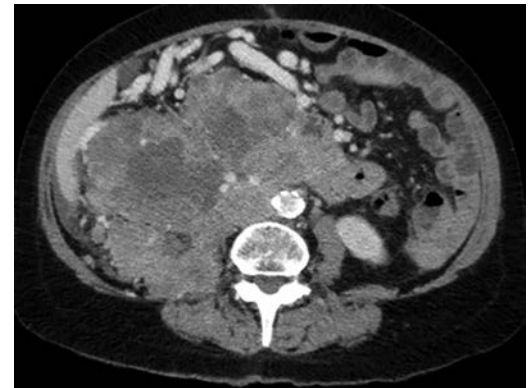
she tolerated well, despite some fluctuation in her blood pressure and an admission due to vomiting and diarrhea secondary to the axitinib.

With subsequent imaging, 5 months after radiotherapy, the large abdominal mass further reduced in size, now measuring 52 mm × 71 mm × 118 mm (Images 7 and 8). However, there was disease progression in other sites, with a new adrenal metastasis and multiple liver metastases.

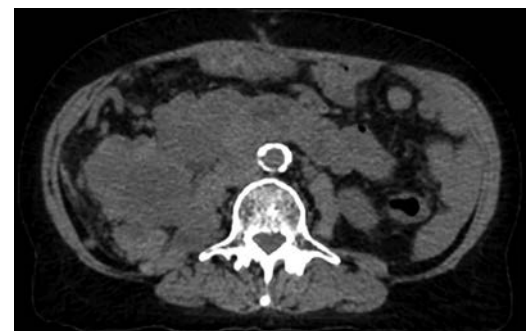
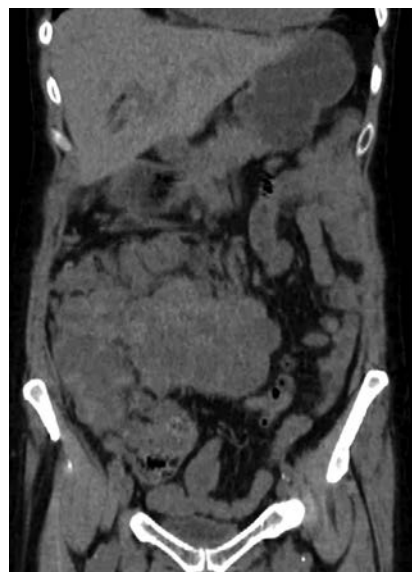
By 7 months after radiotherapy, the mass was demonstrating further regression, with a 40–70% reduction in size from pre-treatment measurements (Images 9 and 10).

By 15 months after radiotherapy, there remained excellent local control of the abdominal mass, despite disease progression in other sites (Images 11 and 12). During this time, due to progressive disease, the patient's axitinib dose was initially increased to a dose of 5 mg mane and 2 mg nocte, and subsequently changed to everolimus 10 mg daily due to poor tolerance. Unfortunately, she continued to progress in the right adrenal gland, liver, and lungs and was referred for further radiotherapy treatment to the large liver metastasis. She received 14 Gy/2F to the large left sided liver lesions which she tolerated well. There was no subsequent abdominal imaging performed to comment on response to treatment.

Images 1 and 2 Coronal and axial views on diagnostic CT of mass before palliative RT.



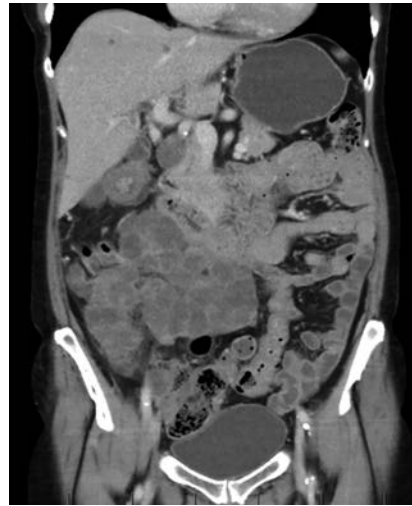
Images 3 and 4 Coronal and axial view on re-simulation CT of mass 2 weeks after 3 Gy of RT.



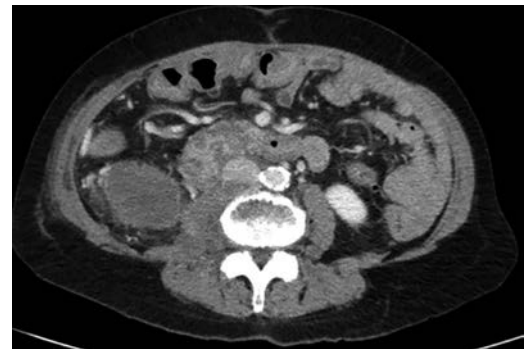
At 17 months after the initial radiotherapy treatment, the patient was admitted with balance and gait disturbance with new weakness of her right hip flexors. An MRI brain and spine confirmed no intracranial or spinal pathology; however, the right retroperitoneal mass was invading the psoas and iliacus muscles with compression

of the right lumbar plexus and right femoral nerve, contributing to the right hip and leg weakness. The patient was referred for further radiotherapy, but her condition declined significantly at this time and therefore did not require the treatment. She died peacefully at a palliative care facility with her family present.

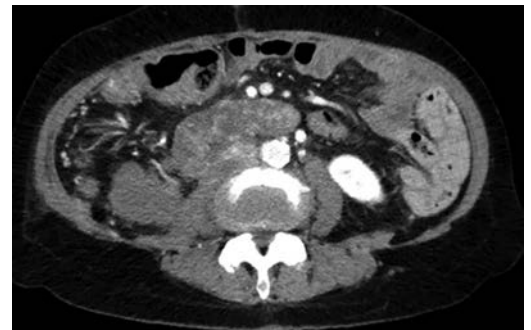
Images 5 and 6 Coronal and axial CT views at 1 month post completion of 36 Gy in 12 fractions of RT.



Images 7 and 8 Coronal and axial CT views at 5 months after completion of RT.



Images 9 and 10 Coronal and axial CT views at 7 months after completion of RT.



Images 11 and 12 Coronal and axial CT views at 15 months after completion of RT.



DISCUSSION

Patients with metastatic RCC have a poor prognosis with demonstrated resistance to cytotoxic chemotherapy agents.⁴ With the discovery of genetic alterations in RCC, there are now a number of targeted therapeutic agents available, which have improved progression free and overall survival for these patients.^{5,6} In addition, immunotherapy has been shown to improve progression free and overall survival.⁷ But despite these new agents, many patients continue to have progressive disease.

There is a preconception of radioresistance in RCC due to the von Hippel-Lindau (VHL) tumor-suppressor gene mutation and hypoxia-inducible factor-1 (HIF-1).⁸ Recently, there has been increased attention given to ablative techniques, delivering doses greater than 10 Gy per fraction safely. This is possible due to the improved capabilities of modern radiotherapy to accurately deliver precise treatment under image guidance. It is thought that with these techniques, the inherent radioresistance of RCC may be overcome.⁹ Unfortunately, these high doses are not always feasible due to large volumes and potential treatment toxicity, as was the case in this patient. But despite a conventional palliative dose regime, this patient achieved an excellent response to her initial 3 Gy of RT treatment.

Concurrent with the palliative RT, the patient received axitinib, an antiangiogenic drug (a small molecule TKI), which has been demonstrated in preclinical studies to radiosensitize tumor endothelial cells, increase apoptosis of endothelial cells, and improve tumor response when used in conjunction with stereotactic body radiotherapy (SBRT).¹⁰ Another preclinical study investigating the enhanced therapeutic efficacy of a single 10 Gy fraction of radiotherapy combined with axitinib in lung cancer, the axitinib augmented the efficacy of the radiotherapy, resulting in complete inhibition of tumor growth, without evidence of significant tissue damage to normal lung.¹¹ While these two studies suggest a benefit with axitinib and stereotactic radiotherapy doses, a further preclinical study confirmed an advantage when combining axitinib with fractionated radiotherapy in standard 2 Gy per fraction doses.¹² Therefore, one possible explanation for the dramatic reduction in the size of the abdominal mass following 3 Gy of radiotherapy could be attributed to the combined effect of the radiotherapy and concurrent axitinib.

Prior to starting the axitinib, the patient had received 3 months of immunotherapy with nivolumab, which was ceased only 3 weeks

prior to the radiotherapy. Nivolumab is an anti-programmed death-1 receptor monoclonal antibody that exhibits checkpoint-mediated immune response against tumor cells. When used in conjunction with RT, the RT can increase quantity and variety of tumoral antigen presentation, enhancing the anti-tumor immune response achieved with these drugs. While this remains investigational and the subject of many clinical trials, retrospective evidence suggests that nivolumab, given within 2 weeks of RT treatment, it is well tolerated with excellent radiological and symptomatic responses.¹³ In this patient, despite progressing on her immunotherapy, when treated with only 3 Gy of RT 3 weeks after her last dose, she experienced a dramatic response in the size of her abdominal mass, leading us to suspect that another possible reason for such a response was that she was primed with her previous nivolumab.

With the use of immunotherapy, radiotherapy is able to induce tumor regression at distant sites which have not been irradiated. The “abscopal effect” is poorly understood, but the immune system is hypothesized to be a key component after the use of radiotherapy.¹⁴ The abscopal effect has been reported following treatment with SBRT; however, a number of case reports have similarly reported abscopal effects following standard fractionation doses of 2 Gy per fraction.^{15,16} Our patient demonstrated a response in her lung metastases on subsequent imaging, following the RT to the abdominal mass, suggesting either an abscopal effect from the immunotherapy or a response to the TKI.

In patients with advanced RCC and progression on immunotherapy, who are not suitable candidates for high dose SBRT due to potential toxicity, our experience suggests that even low doses of RT, which are safe and non-toxic, could provide meaningful and prolonged benefit to patients and should be strongly considered.

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