15 Renal cancer

Background

Primary kidney cancer is the seventh commonest cancer in the UK.[1] Approximately 20% present with metastatic disease and another 20–25% develop metastases after radical treatment to the primary (usually radical nephrectomy/nephron-sparing surgery). Historically kidney cancer has been considered intrinsically radioresistant based on a small amount of experimental data. Two xenograft models have measured α/β ratios as 2.6 and 6.9 Gy.[2] A possible mechanism may be the activation of HIF1α (which is characteristic of clear cell cancers owing to von Hippel-Linda [VHL] mutations) stimulating endothelial cell survival, but preclinical models suggested ablative doses of radiotherapy can overcome this, inducing cell death by alternative means to DNA damage and mitotic catastrophe.[3]

Primary radiotherapy

Neoadjuvant or adjuvant conventional radiotherapy for primary renal cell carcinoma (RCC)

Historical series including small randomised trials of pre- or postoperative radiotherapy gave inconsistent results and used a variety of doses and outdated techniques, with higher doses giving significant toxicity.[3] There is therefore no current role for these approaches.

Stereotactic radiotherapy for primary renal cancer

Surgical resection remains the standard of care in localised disease, but surgery is not feasible in all due to both disease and patient factors including co-morbidities. Stereotactic radiotherapy is less invasive than standard of care surgery, with the potential for faster recovery times and fewer side-effects, though there are no direct comparisons in a trial setting.

In a pooled analysis of 190 patients from 12 international centres, the cumulative 5-year incidence of local failure was 5.5%. Both single and multifraction regimes were used and 29% of patients had a single kidney.[4,5]

In a meta-analysis of 372 patients, median follow-up was 28 months, median tumour size was 4.6 cm, local control 97.2% and glomerular filtration rate reduction 7.7 ml/min; Grade 3–4 toxicity was 1.5%.[6]

Stereotactic radiotherapy is now recommended in the NCCN 2022 guidelines for medically inoperable patients with stage I kidney cancer.[7] Stereotactic radiotherapy can be used for tumours that are not suitable for thermal ablative techniques (cryoablation or radiofrequency ablation), such as larger tumours and those close to the collecting system or major vessels.

15
Renal cancer

Palliative radiotherapy to symptomatic renal primary

For bleeding or pain from a renal primary, embolisation, palliative nephrectomy or systemic therapy are generally preferred to radiotherapy. However, palliative radiotherapy is occasionally used. Dose should be individualised to the patient's circumstances and potential toxicity (proximity of liver, stomach, small bowel etc).

Metastatic renal cancer

Palliative radiotherapy to metastatic disease

A dose response to palliative radiotherapy has been found in some retrospective series but not others.[8,9,10] Radiotherapy is likely to have been underused in palliation of metastatic disease because of preconceptions of radioresistance.[11] Fractionated radiotherapy (30 Gy in 10 fractions/20 Gy in 5 fractions) is recommended particularly for large masses, and 8–10 Gy in a single fraction for those of poor performance status.

Oligometastatic renal cancer

Some favourable-prognosis patients have oligometastatic disease.[12] These patients can have prolonged drug-free survival with treatment of individual metastases, either with surgery or high-dose palliative radiotherapy or stereotactic radiotherapy. Common sites of oligometastases in renal cancer include lung, brain, bone, thyroid, pancreas, soft tissue and head and neck sites including sinuses.

Stereotactic radiotherapy can be used for sites of oligometastases and may be appropriate for oligo-progressive areas in patients responding to systemic therapy. Stereotactic radiotherapy has been shown to have excellent rates of local control in several series. The potential of stereotactic radiotherapy to treat oligometastatic RCC was established through multiple retrospective series and prospective trials, with local control rates >85% at 2 years for metastatic lesions for both clear cell and non-clear cell RCC and a meta-analysis showing 90% local control.[13,14]

See the 'Oligometastases' chapter for treatment principles.

Head of pancreas/duodenum

Pancreatic metastases are common and associated with a favourable prognosis. They are frequently asymptomatic, but metastases at the head of the pancreas may invade the duodenum and cause major gastrointestinal bleeding. High-dose palliative radiotherapy with IMRT (50 Gy in 20–25 fractions), or stereotactic radiotherapy if there is not direct duodenal invasion, can lead to prolonged disease control.[15]

Combination of radiotherapy with systemic therapy

Anti-angiogenic tyrosine kinase inhibitors (TKIs): Caution should be exercised when combining anti-angiogenic TKIs with palliative radiotherapy, particularly when the field encompasses a critical tissue such as brain, spinal cord, liver or small bowel. Although there are no formal guidelines, drug interruption would be advisable when using higher palliative doses over critical structures.[16]

15
Renal cancer

Immunotherapy: Two phase II trials have used the combination of radiotherapy and immunotherapy in metastatic disease and this combination is associated with an acceptable safety profile.[17,18] In the oligometastatic disease setting stereotactic radiotherapy and short-course pembrolizumab is well tolerated, with excellent local control.[19]

Recommendations

Primary renal cancer:

- Stereotactic radiotherapy is safe and effective for medically inoperable patients with primary renal cancer; either single-fraction (26 Gy in 1 fraction) or multifraction regimens (42 Gy in 3 fractions/40 Gy in 5 fractions) are recommended (Grade B, Level 2a)

Oligometastases:

- Stereotactic radiotherapy has a role in treating oligometastatic renal cancer (Grade B, Level 2a)

Palliative radiotherapy for symptom relief:

- Fractionated radiotherapy (30 Gy in 10 fractions/20 Gy in 5 fractions) is recommended particularly for large masses; consider 8–10 Gy in a single fraction for those of poor performance status (Grade C, Level 4)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[20]

References:

1. Cancer Research UK. www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer (accessed Jul 2022).
2. Ning S, Trisler K, Wessels BW, Knox, SJ. Radiobiologic studies of radioimmunotherapy and external beam radiotherapy *in vitro* and *in vivo* in human renal cell carcinoma xenografts. *Cancer* 1997; **80**: 2519–2528.
3. Siva S, Kothari G, Muacevic A *et al*. Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach. *Nat Rev Urol* 2017 Sep; **14**(9): 549–563.
4. Siva S, Louie AV, Warner A *et al*. 5-year outcomes stereotactic ablative radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (International Radiosurgery Oncology Consortium for Kidney). *Lancet Oncol* 2022; **23**: 1508–1516.
5. Siva S, Ellis RJ, Ponsky L *et al*. Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma. *Future Oncol* 2016; **12**: 637–645.
6. Correa RJM, Louie AV, Zaorsky NG *et al*. The emerging role of stereotactic ablative radiotherapy for primary renal cell carcinoma: a systematic review and meta-analysis. *Eur Urol Focus* 2019; **5**(6): 958–69.
7. National Comprehensive Cancer Network. Kidney Cancer (version 2.2023). www.nccn.org/professionals/physician_gls/pdf/kidney.pdf (accessed 10 June 2022).
8. DiBiase SJ, Valicenti RK, Schultz D *et al*. Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: support for dose escalation based on a biological model. *J Urol* 1997; **158**(3): 746–749.

15
Renal cancer

9. Onufrey V, Mohiuddin M. Radiation therapy in the treatment of metastatic renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 1985 Nov; **11**(11): 2007–9.
10. Wilson D, Hiller L, Gray L, Grainger M, Stirling A, James N. The effect of biological effective dose on time to symptom progression in metastatic renal cell carcinoma. *Clin Oncol (R Coll Radiol)* 2003 Oct; **15**(7): 400–7.
11. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment. *Cancer* 2005; **104**: 1129–1137.
12. Heng DYC, Xie W, Regan MM *et al*. Prognostic factors for overall survival in patients with MccRCC treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009; **27**(34): 5794–5799.
13. Zaorsky NG, Lehrer EJ, Kothari G, Louie AV, Siva S. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. *Eur Urol Oncol* 2019 Sep; **2**(5): 515–523. doi:10.1016/j.euo.2019.05.007. Epub 2019 Jul 11. PMID: 31302061.
14. Kothari G, Foroudi F, Gill S, Corcoran NM, Siva S. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. *Acta Oncologica* 2015; **54**(2): 148–157.
15. Maund I, Bowzyk Al-Naeeb A, Welsh SJ, Eisen T, Fife K. Intensity modulated radiotherapy is a well-tolerated and effective treatment for the long-term control of intra-abdominal and retroperitoneal oligometastatic renal cell cancer. *Kidney Cancer* 2018; 103–113.
16. Fife K, Bang A. Combined radiotherapy and new systemic therapies: have we moved beyond palliation? *Clin Oncol (R Coll Radiol)* 2020 Nov; **32**(11): 758–765. doi:10.1016/j.clon.2020.07.021. Epub 2020 Aug 27. PMID: 32863071.
17. Hammers HJ, Vonmerveldt D, Ahn C *et al*. Combination of dual immune checkpoint inhibition (ICI) with stereotactic radiation (SBRT) in metastatic renal cell carcinoma (mRCC) (RADVAX RCC). *J Clin Oncol* 2020; **38**: 614.
18. Masini C, Iotti C, De Giorgi U *et al*. Nivolumab (NIVO) in combination with stereotactic body radiotherapy (SBRT) in pretreated patients (PTS) with metastatic renal cell carcinoma (mRCC): first results of phase II NIVES study. *J Clin Oncol* 2020; **38**: 613.
19. Siva S, Bressel M, Wood ST *et al*. Stereotactic radiotherapy and short-course pembrolizumab for oligometastatic renal cell carcinoma: the RAPPORT trial. *Eur Urol* 2022 Apr; **81**(4): 364–372.
20. www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (last accessed 28/11/2023).

Acknowledgements

With thanks to lead authors Dr Kate Fife and Dr Will Ince (Cambridge University Hospitals NHS Foundation Trust) for reviewing and updating this chapter of the guidance.