Clinical Oncology 31 (2019) 813–814

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Stereotactic Body Radiotherapy in Metastatic Disease: The Known Unknowns and the Unknown Unknowns

A.C. Tree

The Royal Marsden NHS Foundation Trust, The Institute of Cancer Research, London, UK

Received 24 June 2019; accepted 25 June 2019

Medical reversals are many and frequent, but this should be considered a sign of progress and testament to the evidence-based medicine era that we live in. For most of us, when we were training, we were taught that there was no point irradiating the tumour(s) unless you could give a radical dose to all disease. This was accepted dogma, handed down from generation to generation. The fact that this assertion has been turned on its head in the last few years is testament to how little we still know about cancer and how much we have to learn.

Over the last decade there has been a technological revolution in radiotherapy delivery, moving us from crude two-dimensional fields aimed at skin tattoos, to fiducial- or computed tomography-guided stereotactic body radiotherapy (SBRT) and, latterly, magnetic resonance-guided radiotherapy. In parallel, the evolution of stereotactic radiosurgery (SRS) and SBRT techniques allows high doses to be delivered to the tumour with minimal toxicity in most cases.

It is this precision, giving us the ability to ablate lesions without significant penalty, that has given us the confidence to test radiotherapy in scenarios where previously it would have been considered too risky for the patient. We know that SBRT and SRS rival or exceed surgical outcomes in many primary tumours, but metastatic disease has, until recently, remained impenetrable to the notion of 'radical' radiotherapy.

The first whispers of a possible benefit occurred in metachronous oligometastatic disease; excellent local control was seen with a chance (usually around 25–30%) of distant progression-free survival 2–3 years later [1,2]. Nevertheless, the naysayers claimed that this was case selection and just shrinking cancer was not enough evidence of benefit.

Although this position is not without merit, in contrast, many new targeted drugs are licensed and promoted on the basis of their ability to shrink disease (i.e. progression-free survival). This may require tens of visits to the hospital for the patient and, for many, the risk of significant side-effects. We have, in every radiotherapy department in the UK, the means to shrink cancer with a 'response rate' unrivalled by any drugs, with the possible exception of androgen deprivation in prostate cancer. We have been underselling our speciality for years and it is now time to show the world of oncology what we can do.

We now have trials showing a survival advantage for radiotherapy in low burden metastatic prostate cancer [3], in synchronous metastatic lung cancer [4,5] and in metachronous oligometastatic cancer [6]. It is in the latter scenario, metachronous oligometastases, where the burgeoning literature continues to show that a significant minority of patients remain relapse-free years after a single course (usually three treatments) of SBRT.

In this and a previous issue of *Clinical Oncology* we have a trio of articles exploring three indications for 'radical' (disease-modifying) radiotherapy in metastatic disease. Shiarli *et al.* [7] present the evidence for local consolidation in metastatic non-small cell lung cancer, a disease in desperate need of improved outcomes. Accepting that radiotherapy now has a role in the consolidation of oligometastatic disease, they include a provocative look at whether irradiating the primary alone is enough to obtain most of the benefit or whether irradiation of the primary and all oligometastases is necessary. This is a key point for all of us working in hard-pressed healthcare systems, as contouring and planning multiple lesions with SBRT may be prohibitively resource intense.

Patel *et al.* [8] present the limited but expanding evidence in the arena of oligoprogression, the growth of a limited number of metastases in the context of widespread disease. This state, previously not distinguished from polyprogression, probably reflects limited resistance to current targeted therapy and the heterogenous molecular basis of multiple metastases within the same patient. Hence, the logic of ablation of the resistant clones with SBRT is clear. Two current UK-led trials, HALT [9] and TRAP, seek to test

E-mail address: alison.tree@icr.ac.uk.

https://doi.org/10.1016/j.clon.2019.07.002

this hypothesis in lung and prostate cancer, respectively. The complexities that may be heading our way, in the use of radiation in metastatic disease, are illustrated in Figure 1: where shall we use radiotherapy, when and in whom? Hopefully these trials, and others, will answer whether we should indeed pull up the dandelions or spray weed killer over the whole lawn.

The abscopal effect is a phenomenon that is talked about much more than it actually happens. However, the possibility that radiotherapy, particularly SBRT, with or without the addition of immune checkpoint blockade, can affect distant tumour shrinkage is intriguing. Xing *et al.* [10] combine an excellent introduction to the impact of radiotherapy on immune checkpoint blockade potency in general with a review of current studies combining immunotherapy and radiotherapy. Finally, they discuss whether there is any evidence that the abscopal effect exists 'in real life' or whether it is akin to the fabled Road to El Dorado.

What is clear from all three articles is that SBRT has an expanding role in our treatment of metastatic disease. This is fantastic news for our patients, whose median survival will be improved by this radiation epiphany. But, as always, progress comes at a cost. Our departments need to be ready to cope with an increase in demand, as we have seen in prostate oncology after the publication of STAMPEDE Arm H [3]. We also need to work towards training and empowering all UK centres to deliver SBRT, as surely this is the future of our speciality in many cancers.

A plethora of questions remain: If some radiotherapy is good, is more better? What dose is best? Do we need randomised trials in every tumour type to test the benefit of SBRT in oligometastases/oligoprogression/consolidation (probably not feasible) or can we extrapolate benefit to other 'similar' tumours? Whatever the answers, this is an exciting time to work in clinical (or radiation) oncology.

Conflict of Interest

Research funding was received from Accuray and Elekta. Speaking fees and travel assistance were received from Elekta.

Acknowledgements

I acknowledge NHS funding to the NIHR Biomedical Research Centre at The Royal Marsden and the Institute of Cancer Research, and the support of the Rosetrees Trust. The TRAP and HALT trials are funded by PCUK (RIA16-ST2-006) and CRUK (CRUK/16/020), respectively; their support is gratefully acknowledged.

References

[1] Aitken K, Tree A, Thomas K, Nutting C, Hawkins M, Tait D, *et al.* Initial UK experience of stereotactic body radiotherapy for extracranial oligometastases: can we change the therapeutic paradigm? *Clin Oncol* 2015;27(7):411–419.

[2] Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, *et al.* Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013;14(1):e28–e37.

[3] Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, *et al.* Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018;392(10162):2353–2366, https://doi.org/10.1016/S0140-6736(18)32486-3.

[4] Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, *et al.* Local consolidative therapy versus maintenance therapy/observation for patients with oligometastatic non-small cell lung cancer without progression after front-line systemic therapy: results of a multi-institutional phase II randomized study. *Lancet Oncol* 2016;17(12):1672–1682.

[5] Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, *et al.* Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2018;4(1):e173501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28973074.

[6] Palma D, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, *et al.* Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;393:2051–2058.

[7] Shiarli A-M, McDonald F, Gomez DR. When should we irradiate the primary in metastatic lung cancer? *Clin Oncol* 2019;31:815–823.

[8] Patel PH, Palma D, McDonald F, Tree AC. The dandelion dilemma revisited for oligoprogression: treat the whole lawn or weed selectively? *Clin Oncol* 2019;31:824–833.

[9] McDonald F, Hanna GG. Oligoprogressive oncogene-addicted lung tumours: does stereotactic body radiotherapy have a role? Introducing the HALT trial. *Clin Oncol* 2018;30(1):1–4. https://doi.org/10.1016/j.clon.2017.10.013.

[10] Xing D, Siva S, Hanna GG. The abscopal effect of stereotactic radiotherapy and immunotherapy: Fool's Gold or El Dorado? *Clin Oncol* 2019;31:432–443.