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Editorial

HERMES: Delivery of a Speedy Prostate Cancer Treatment

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The burden on the National Health Service is more pronounced than ever and there remains a pressing need to reduce the number of patient visits where possible. Not only has the COVID-19 pandemic highlighted the need to consider our resources, but also the livelihood of our patients, the precious nature of life and how we spend the time we have.

The constant tussle between quantity and quality of life has long forced oncology down the route of evidence-based medicine, entwined with clinical experience and patient autonomy. Rapid advances in radiation oncology have welcomed the arrival of more personalised and accurate approaches to radiotherapy delivery. These advances provide the opportunity to re-think our treatment paradigms and facilitate streamlined and efficient departments.

Hypofractionation in Prostate Cancer

When, in 1999, Brenner and Hall [1] hypothesised the α/β ratio of prostate cancer to be 1.5 Gy there began the journey to improve the efficacy and tolerability of prostate treatment through hypofractionation, aiming to deliver a high biologically effective dose in a shorter treatment time without increasing the acute and late toxicities.

CHHiP [2], RTOG-0415 [3] and PROFIT [4] investigated moderate hypofractionation in prostate cancer and safely demonstrated non-inferiority to the conventional 2 Gy fractionation, with an increase in acute gastrointestinal grade 2 toxicity only in CHHiP and PROFIT. 60 Gy in 20 fractions has since been adopted as the standard of care, confirming the low α/β ratio for prostate cancer.

Ultra-hypofractionation in Prostate Cancer

Moving forward to the era of stereotactic body radiotherapy (SBRT) and the ability to deliver ultra-hypofractionated radiotherapy (UHFRT), there is a clear rationale to further exploit the low α/β ratio of prostate cancer. SBRT describes the delivery of high doses of radiotherapy of 5–10 Gy in <10 fractions, with a dose distribution resembling that of high dose rate brachytherapy. A systematic review and meta-analysis of SBRT for localised prostate cancer, including over 6000 patients, found that SBRT is an effective treatment with a favourable toxicity profile [5]. The HYPO-RT-PC trial comparing seven fractions of UHFRT to conventional prostate radiotherapy supported these findings, showing non-inferiority in biochemical recurrence and late toxicity at 5 years [6].

PACE

Complementing HYPO-RT-PC, PACE is a multicentre, international phase III randomised controlled study comparing SBRT with prostatectomy or standard radiotherapy [7]. It is composed of three independently powered sub-trials: PACE-A, PACE-B and PACE-C.

PACE-A compares SBRT with prostatectomy and is focussed on a comparison of aspects of quality of life. PACE-B and PACE-C seek to demonstrate non-inferiority of failure-free survival with SBRT compared with conventional or moderately hypofractionated radiotherapy. Patients in PACE-B have low or intermediate risk disease and do not receive hormonal therapy, whereas patients recruited into PACE-C have intermediate or lower high risk disease and require hormones for 6 months.

The SBRT arm delivers 36.25 Gy in five fractions over 1–2 weeks with an additional secondary clinical target volume dose target of 40 Gy. Treatment can be delivered on the Cyberknife or conventional linear accelerator and in PACE-C treatment on the magnetic resonance-linear accelerator (MR-linac) has been included.

The 12-week toxicity data from PACE-B is reassuring, showing that Radiation Therapy Oncology Group acute toxicity is no worse with SBRT than in the control arm [7]. There was a detriment in the rates of grade 2+ gastrointestinal and genitourinary Common Terminology Criteria for Adverse Events (CTCAE) acute toxicity in the SBRT arm,

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although this was shown to have disappeared by week 12 at the time of analysis.

The recent results from the 24-month PACE-B analysis have continued to show low toxicity in both the conventional radiotherapy and SBRT arms. Genitourinary grade 2+ CTCAE toxicity rates remain higher in the SBRT arm at 11.8% compared with 5.8% in the conventional radiotherapy arm ($P = 0.006$). This is mirrored in the patient-reported outcomes, which show that 32–33% of patients have a clinically significant drop in their urinary quality of life at 2 years post-treatment after SBRT, compared with 22–26% with conventional radiotherapy [8].

The long-term data from PACE-B and outcomes from PACE-C are eagerly awaited. But the question remains, can we go lower than five fractions with radical prostate radiotherapy delivery?

To test more abrupt schedules, additional precision is required. High dose rate brachytherapy has successfully and safely delivered two-fraction radiotherapy [9,10]. Can the same be achieved with external beam radiotherapy? Small studies indicate that it can [11–13] and these abbreviated schedules will probably be popular with patients and departments alike.

The revolutionary integration of a diagnostic magnetic resonance imaging scanner with a linear accelerator (MR-linac) allows the delivery of adaptive radiotherapy by incorporating daily high definition soft-tissue imaging with daily re-contouring and plan adjustment [14]. In the case of prostate cancer, the MR-linac also negates the need for the insertion of fiducial markers, another unwanted invasive procedure for patients.

HERMES

Planning studies have shown that fewer than five-fraction SBRT could potentially be delivered to the prostate with the same organ at risk constraints as high dose rate brachytherapy, when delivered on a linear accelerator [15].

HERMES is a single-centre phase II trial of magnetic resonance-guided SBRT in men with localised prostate cancer (Figure 1). Forty-six men will be treated on the MR-linac and will be randomised between 36.25 Gy in five fractions over 10 days, with clinical target volume target of 40 Gy, and 24 Gy in two fractions over 8 days. Patients randomised to the two-fraction arm will receive an integrated boost to the dominant intraprostatic lesion, escalating the gross tumour volume dose to 27 Gy in two fractions.

Studies from conventional fractionation have shown that in 89–100% the site of local recurrence occurs at the dominant intraprostatic lesion [16]. The MR-linac offers the unique ability to visualise and target areas within the prostate. Dose escalation and side-effects are usually traded-off against one another, but we hope that by boosting the site where local relapse is most commonly seen we will be able to maximise cure while keeping toxicity to a minimum.

In HERMES the primary end point is short-term genitourinary toxicity and the aim is to show that rates of early grade 2+ toxicity in the two-fraction arm are no more than twice as high as we saw in PACE. Gastrointestinal toxicity and patient-reported outcomes measures, with urinary bother as a key interest, will be measured at 12 weeks, 1, 2 and 5 years post-treatment. Prostate-specific antigen kinetics will be measured at 2 and 5 years post-treatment.

HERMES: Promises and Potential Pitfalls

We hope our enthusiasm for HERMES is easy to comprehend. Patients will receive radical radiotherapy with only two sessions of treatment, significantly reducing their

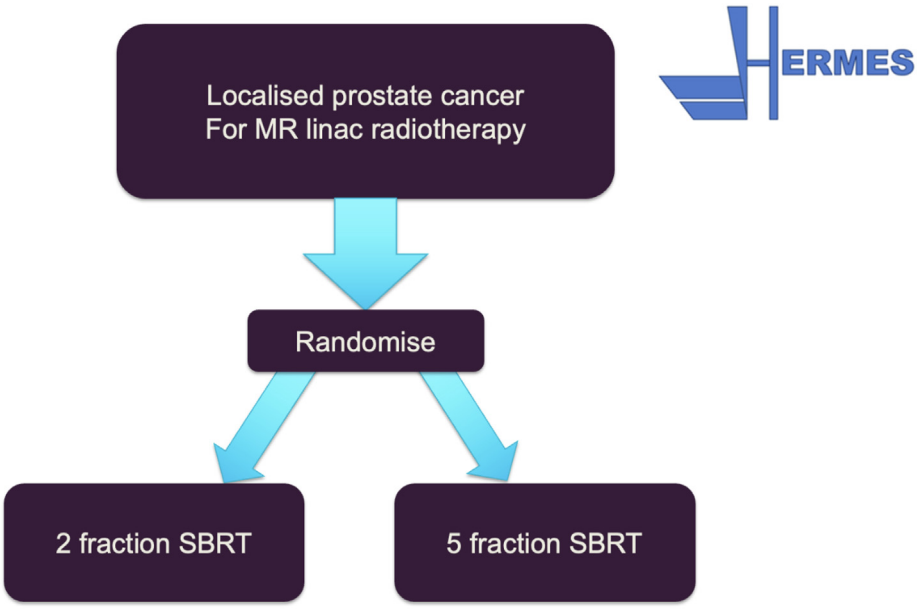

Fig 1. Randomisation schema for HERMES. MR-linac, magnetic resonance-linear accelerator; SBRT, stereotactic body radiotherapy.

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time spent commuting to hospital and in the radiotherapy department. This offers psychological and physical advantages to patients compared with the daily trips seen with conventional radiotherapy, while also reducing the burden on our radiotherapy departments.

Despite the significant reduction in overall treatment time when only receiving two fractions of radiotherapy there may be some nervousness over the time the patient will spend on the treatment couch in one sitting. In our department, patients receiving five-fraction treatment remain on the MR-linac couch (at each fraction) for around 55 min, with the beam on for around 9 of those minutes. In our experience, this is well-tolerated by patients, backed by findings from our Prostate Radiotherapy Integrated with Simultaneous MRI (PRISM) study, in which only one patient in 27 requested that the workflow be interrupted. For HERMES, however, the treatment time will be longer. To mitigate this we will deliver each fraction in two sub-fractions, therefore allowing patients to get off the bed and empty their bladder half way during the treatment. This process has been successfully integrated and tested within the workflow.

Second, with only two fractions, any small under- or overdose at each treatment will have a significant effect on disease control and/or side-effects. With SBRT, notably in the recent PACE-B data, we have seen that genitourinary side-effects predominate over gastrointestinal side-effects [7] and this effect may be amplified when we reduce to two fractions. Careful sparing of overdose to the urethra and potentially bladder neck is needed, as with high dose rate brachytherapy, to mitigate this effect. With SBRT studies, reducing dose around the urethra shows better long-term genitourinary side-effects [13,17]. The MR-linac allows us to accurately contour and introduce urethral dose constraints in an attempt to learn more about tolerance and minimise genitourinary side-effects.

Conclusion

With our increasing wealth of knowledge and discovery comes the potential to push the boundaries of radiotherapy and evade the restrictions imposed by existing standard techniques. The advent of the MR-linac and the delivery of SBRT have provided us with the tools to ask new questions while hopefully improving the patient journey.

HERMES offers the ability to test the capabilities of the MR-linac and will give us an initial assessment of the safety of two-fraction treatment. This trial is a logical next step following on from the PACE trial. We hope that it will show the potential of how far we can go with UHFRT for men with prostate cancer.

Conflicts of interest

A. Tree reports financial support from the JP Moulton Foundation and Elekta. A. Tree reports a relationship with Elekta that includes: funding grants, speaking and lecture fees, and travel reimbursement. A. Tree and E. Hall report a relationship with Accuray Inc that includes: funding grants (both) and speaking and lecture fees (A. Tree). A. Tree and E. Hall report a relationship with Varian Medical Systems Inc that includes: funding grants.

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