PROSTATE CANCER

Single dose prostate radiotherapy – a step too far?

Most localized prostate cancer can be cured with radiotherapy. Over the past decade, treatment courses have been shortened with no deterioration in cure rate or adverse effects. Now a small phase II trial has tested whether radiation could be delivered as a single treatment.

Refers to Greco, C. *et al.* Safety and Efficacy of Virtual Prostatectomy with Single-Dose Radiotherapy in Patients with Intermediate-Risk Prostate Cancer: Results from the PROSINT Phase 2 Randomized Clinical Trial. *JAMA Oncol.* http://dx.doi:10.1001/jamaoncol.2021.0039 (2021)

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The techniques used to deliver curative prostate radiotherapy have undergone a revolution in the past decade including the use of daily image-guidance and strict limits on doses to surrounding healthy tissues These iterative improvements have increased cure rates, by increasing precision, and have reduced genitourinary and gastrointestinal adverse effects, owing to better shaping of radiation dose close to the prostate, avoiding surrounding structures.

Hypofractionation— the delivery of fewer sessions of radiotherapy, each with a higher dose than in conventional radiotherapy— can shorten treatment courses from the traditionally used 7–8 weeks down to 4 weeks, with no loss of efficacy or increase in adverse effects [1]. Hypofractionation is more cost-effective to the healthcare system and reduces the burden of treatment to the patient. Research is ongoing into the further shortening of treatment schedules, notably down to five fractions, using stereotactic body radiotherapy (SBRT) techniques. Evidence for the equivalence of this ultrahypofractionated regimen is accumulating, with the large phase III randomized, multicentre PACE B trial— in which men with intermediate-risk prostate cancer are randomly assigned to conventionally fractionated or moderately hypofractionated radiotherapy versus SBRT— expected to report in the next 2 years [2]. The randomised HYPO-RT-PC trial (n=1200) has already demonstrated equivalent outcomes for seven fractions compared with 39 fractions (HR 1.002, p=0.99). [3]. Thus, the radiation oncology community has sought to further decrease the number of fractions, whilst ensuring equivalence in the standard of oncological outcomes and rates of adverse effects .

Greco and colleagues[4] present a randomized phase II study of 30 patients with intermediate-risk prostate cancer treated with either 9 Gy in 5 fractions or 24 Gy in a single dose. The latter regimen is bold and ground-breaking; this paper presents the first publication of long-term outcomes of single-dose external beam radiotherapy.

The researchers report low levels of toxicity, although with only 15 patients in each cohort, the study was not adequately powered to compare outcomes or treatment toxicity. [4] The five fraction dose (45 Gy) was higher than is considered standard (35–40 Gy) and so does not represent a true control. Nevertheless, the idea that 24 Gy can be delivered in a single treatment without significant toxicity causes oncologists to re-examine the benefits of fractionation, which is traditionally thought to reduce side effects and maximise cure rates The lack of reported gastrointestinal toxicity is particularly noteworthy: For the single-dose group the reported rate of acute grade 1 toxicity at 3 months after treatment was 27% (90% CI 6–47%) compared to 7% (90% CI 0-18%) for the 5 fraction group and late ≥grade 2 toxicity was 0% for both groups. This low rate of toxicity validates the researchers' decision not to use a rectal spacer[4].

Acute grade 1 genitourinary toxicity peaked at 1 week post-treatment, and was seen in 27% (90% CI 6–47%) of the 5 fraction group and 40% (90% CI 17–63%) of the single-fraction group. [4] Cumulative late grade 2 genitourinary toxicity rates were similar in both cohorts (15–17%, calculated from graph), which is in accordance with published SBRT data [5] . A single patient had a late grade 3 genitourinary adverse-effect (ureteric stenosis, in the single-dose group), a complication that is rarely seen after radiotherapy delivered in more fractions. [4] Further studies with larger numbers of patients would be needed before any comment can be made about the true incidence of such events after single-fraction treatment.

Greco and colleagues[4] entitle their paper 'virtual prostatectomy' but we would contend that with quality-of-life metrics favouring radiotherapy over surgery in randomized trials [6] 'virtual prostatectomy' might not be something to which oncologists should aspire. The patient-reported outcomes described in this study are good, with no patient recording major bother for either gastrointestinal or genitourinary symptoms. The latter could relate to the urethral-sparing method described in the protocol, which reduces the dose to the urethra below 19.2 Gy (compared to 24 Gy to the rest of the prostate). A similar urethral-sparing method is also used in the only other publication of single fraction external beam radiotherapy (n=6) where there was no remaining emergent toxicity at 12 weeks, although 50% of patients recorded Grade 2 genitourinary toxicity immediately following treatment [7]. Genitourinary toxicity from prostate radiotherapy should be the focus for toxicity reduction as it now predominates over gastrointestinal toxicity [1,2,3] Additionally, a significant proportion of men met the criteria for clinically important deterioration in sexual quality of life (defined as a drop of 0.5 times the baseline standard deviation of the sexual domain scores on the EPIC-26 scale) at 12 months: 46% in the 5 fraction cohort, and 62% in the single-fraction group .[4] Thus, preservation of erectile function should also be a key aim for radiotherapy treatment.

However, adverse effects are only one side of the equation. Biochemical relapse-free survival with single-dose radiation (19 Gy) delivered with brachytherapy has been universally disappointing and has now been largely abandoned as an idea[8]. In a study of 44 patients with intermediate-risk prostate cancer treated with single-dose brachytherapy. analysis of dose delivered in patients whose cancer recurred demonstrated that the dominant area of cancer received an even higher dose than prescribed: 90% of the predominant cancer-containing regionof the prostate actually received 21.5Gy due to the way brachytherapy doses are prescribed [9] Some areas of the cancer would have received doses even higher than this However, despite these high radiation doses approximately one-third of patients developed

biochemical recurrence by 5 years.[8] In the trial by Greco and co-workers[4] , the radiotherapy was not prescribed as per International Committee for Radiological Units (ICRU) 91 guidelines for either group, hence the actual doses delivered were not much higher than the prescription doses of 24 Gy and 45 Gy respectively Thus, the dose delivered to 95% of the planning target volume was only 22.1 Gy,[4] which is similar to the aforementioned brachytherapy data[8]; hence similar long term outcomes could be expected.

Why such high radiation doses are not sufficient to cure localized prostate cancer is unclear – perhaps we need to return to two of the four 'Rs' of radiobiology we learned as trainees (repair of DNA damage, re-distribution of cells in the cell cycle, re-population and re-oxygenation of hypoxic tumour areas) and focus on whether re-oxygenation and re-distribution, which are promoted by fractionation, need to be somehow augmented with such small numbers of doses . Biochemical failure occurred in 20% (3/15) of patients in the single-fraction group by 48 months[4] (compared with 10% at 60 months in the CHHiP trial (60 Gy in 20 fractions) [1]). The nadir PSA at 3 years was also higher in patients in the single-fraction cohort (0.4 ng/ml) than in patients in the 5-fraction group (0.3 ng/ml)[4]. A nadir of ≤0.2 ng/ml at 4 years is highly correlated with long-term disease control and portends a better prognosis than even a slightly higher PSA of 0.2-0.5 ng/ml [10]. This raises the possibility that biochemical failure in the single dose cohort may be worse than that seen after more fractionated courses.

Greco and colleagues[4] present an important study that adds to our knowledge about the far reaches of hypofractionation. That such extreme radiation doses can be delivered with low levels of toxicity is reassuring, but the weight of evidence at present suggests that single-fraction radiotherapy, regardless of delivery modality, achieves less favourable biochemical outcomes and does not seem to be a promising strategy for further trials. Studies are ongoing to determine whether two or three fractions are sufficient to achieve cure in localized prostate cancer or whether, when the early pioneers stumbled across five fraction SBRT, they achieved the zenith of effective hypofractionation.

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Competing interests

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