

- 2 Evans SM, Tikellis G, Brooks A, et al. Prostate Cancer Outcomes Registry: Australia and New Zealand report 2018. Reporting on data 2015–2016. Melbourne, VIC: Monash University & The Movember Foundation, 2018.
- 3 Dasgupta P, Baade PD, Aitken JF, Ralph N, Chambers SK, Dunn J. Geographical variations in prostate cancer outcomes: a systematic review of international evidence. *Front Oncol* 2019; **9**: 238.
- 4 Smith DP, Calopedos R, Bang A, et al. Increased risk of suicide in New South Wales men with prostate cancer: analysis of linked population-wide data. *PLoS One* 2018; **13**: e0198679.
- 5 Zajdlewicz L, Hyde MK, Lepore SJ, Gardiner RA, Chambers SK. Health-related quality of life after the diagnosis of locally advanced or advanced prostate cancer: a longitudinal study. *Cancer Nurs* 2017; **40**: 412–19.
- 6 Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2019; **20**: 1518–30.
- 7 Chambers SK, Ng SK, Baade P, et al. Trajectories of quality of life, life satisfaction, and psychological adjustment after prostate cancer. *Psychooncology* 2017; **26**: 1576–85.
- 8 Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2019; **20**: 686–700.
- 9 Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* 2019; **381**: 121–31.
- 10 Crawford-Williams F, March S, Goodwin BC, et al. Interventions for prostate cancer survivorship: a systematic review of reviews. *Psychooncology* 2018; **27**: 2339–48.

Stereotactic beam radiotherapy for prostate cancer: is less, more?

In *The Lancet Oncology*, Douglas Brand and colleagues¹ report an important trial, in which the authors aimed to investigate the fractionation sensitivity of radiotherapy in the curative treatment of low-risk and intermediate-risk prostate cancer. Participants received either conventionally fractionated or moderately hypofractionated radiotherapy, or ultra-hypofractionation (stereotactic body radiotherapy) in five fractions, delivered either daily or every other day. Acute toxicity might be worse when treatments are delivered in few large fractions and an overall treatment time as short as 1–2 weeks, compared with protracted schedules delivered in 6–8 weeks. In this trial, however, stereotactic body radiotherapy was equally well tolerated as conventionally fractionated or moderately hypofractionated radiotherapy. This is an important issue, because stereotactic body radiotherapy is much more patient-friendly in terms of convenience and less costly than are more protracted fractionation schedules. Although the study limits its focus to early tolerance (up to 12 weeks after radiotherapy), this study is the first that was designed to use contemporary radiotherapy delivery techniques—ie, linac-based volumetric modulated arc radiotherapy or CyberKnife.

Dose constraints to the organs at risk (eg, rectal wall, bladder wall, and urethra) were well established, aiming to limit toxicity to acceptable levels. The proportions of patients in the stereotactic body radiotherapy group who had physician-reported

moderate (grade 2) gastrointestinal and genitourinary acute toxicity, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), were 62 (15%) of 415 patients and 121 (29%), respectively, compared with the proportions in the conventionally fractionated or moderately hypofractionated group (33 [8%] of 432 patients and 96 [22%], respectively).

The proportion of moderate gastrointestinal toxicity was higher than those reported by some phase 2 trials using similar stereotactic body radiotherapy scenarios, with proportions ranging from 2% to 8%.^{2–4} To reduce the dose to the rectal wall, the use of gadgets such as endorectal balloons or spacers implanted between the rectum and the prostate have been recommended.^{5,6} Because both procedures are invasive or, at least, uncomfortable, an alternative could be to reduce the dose constraints applied to the rectal wall while keeping the dose prescription to the target unchanged. This method might lead to an optimisation of the final treatment plan by substantially reducing the intermediate and low doses to the rectal wall.⁷ Nowadays, dose distribution optimisation can be substantially and easily improved with software for multicriteria optimisation planning, based on Pareto surface.⁸

Because the prostatic urethra inside the target volume always gets the full prescribed dose, the proportion of patients with moderate genitourinary acute toxic effects was similar to that which has



Burger/PharmScience Photo Library

See [Articles](#) page 1531

been reported elsewhere (26–35%).^{2,3} Nevertheless, in the only trial with a similar treatment schedule, but a dose reduction to the urethra (from 7.25 Gy to 6.5 Gy per fraction), only 14 (17%) of 82 patients had moderate acute genitourinary toxic effects, which favourably compares with the 29% reported by Brand and colleagues.⁴ On the other hand, Zelefsky and colleagues reported genitourinary toxic effects in 24 (18%) of 136 patients, without reducing the dose to the urethra in their dose escalation trial from 32.5 Gy to 40 Gy in five fractions, thus casting doubts about the rationale for partially shielding the urethra, considering, additionally, an increased risk of local relapse.⁹

Five fractions delivered every other day (approximately 10 days overall treatment time) has been the most frequently used schedule in most phase 2 trials of stereotactic body radiotherapy, regardless of the fact that the most convenient procedure for patients and department logistics would be to deliver stereotactic body radiotherapy 5 days in a row. Although no difference in severe genitourinary acute toxicity was observed among the 86 patients treated up to 1 week compared with the 329 treated in more than 1 week, Brand and colleagues¹ found that genitourinary grade 2 acute toxicity was less among those patients treated in the shortest overall treatment time. Was this observation related to selection biases (patients with large prostatic volumes or less favourable baseline genitourinary symptoms being treated over a longer overall treatment time)? Nonetheless, this observation is an invitation to shorten the overall treatment time for stereotactic body radiotherapy in five fractions as much as possible.

Patients in the stereotactic body radiotherapy group were treated with either CyberKnife or volumetric modulated arc radiotherapy. The irradiation time of each fraction was significantly different, much longer (45 min) with CyberKnife and much shorter with volumetric modulated arc radiotherapy (3–5 min). This difference might have had an effect on the incidence of acute toxicity, as was observed in this trial. Furthermore, research has suggested that a long beam-on time with CyberKnife might favour intrafraction repair mechanisms, thus reducing the biologically effective dose for late-responding tissues with high fractionation sensitivity.¹⁰ This effect might have consequences

regarding tumour control and late effects in later follow-up.

Finally, can the number of fractions with stereotactic body radiotherapy further be reduced from five to a single high-dose fraction? There are currently two ongoing monotherapy studies exploring the role of single-fraction stereotactic body radiotherapy for patients with localised prostate cancer: the PROSINT-IGRT phase 2 trial (NCT02570919) investigating 45 Gy in five consecutive fractions versus a single dose of 24 Gy; and the ONE-SHOT trial (NCT03294889), a phase 1–2, multicentre study of the safety and efficacy of a single fraction of 19 Gy with a urethra-sparing approach. Indeed, a change of paradigm towards radiosurgery for prostate cancer seems to be on its way.

Raymond Miralbell

University of Geneva Medical School, Geneva 1260, Switzerland; Institut Oncològic Teknon, Barcelona, Spain; and Centro de Protonterapia Quironsalud, Madrid, Spain
raymond.miralbell@unige.ch

I report personal fees from Bayer and grants from Varian, outside of the submitted work.

Copyright © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

- 1 Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from a randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol* 2019; **20**: 1531–43.
- 2 Meier RM, Bloch DA, Cotrutz C, et al. Multicenter trial of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer: survival and toxicity endpoints. *Int J Radiat Oncol Biol Phys* 2018; **102**: 296–303.
- 3 Fuller DB, Naitoh J, Mardirossian G. Phase 2 multicenter trial of heterogeneous-dosing stereotactic body radiotherapy for low- and intermediate-risk prostate cancer: 5-year outcomes. *Eur Urol Oncol* 2018; **1**: 540–47.
- 4 Zilli T, Jorcano S, Bral S, et al. Urethra-sparing SBRT for prostate cancer: acute toxicity results from a randomized phase II trial. *Radiother Oncol* 2017; **123**: S295.
- 5 Wortel RC, Heemsbergen WD, Smeenk RJ, et al. Local protocol variations for image guided radiation therapy in the multicenter Dutch hypofractionation (HYPRO) trial: impact of rectal balloon and MRI delineation on anorectal dose and gastrointestinal toxicity levels. *Int J Radiat Oncol Biol Phys* 2017; **99**: 1243–52.
- 6 Mok G, Benz E, Vallée J-P, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. *Int J Radiat Oncol Biol Phys* 2014; **90**: 278–88.
- 7 Dubouloz A, Rouzaud M, Tsvang L, et al. Urethra-sparing stereotactic body radiotherapy for prostate cancer: how much can the rectal wall dose be reduced with or without an endorectal balloon? *Radiat Oncol* 2018; **13**: 114–19.
- 8 Craft DL, Hong TS, Shih HA, et al. Improved planning time and plan quality through multicriteria optimization for intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2012; **82**: e83–90.
- 9 Zelefsky MJ, Kollmeier M, McBride S, et al. 5-year outcomes of a phase I dose escalation study using stereotactic body radiosurgery for patients with low and intermediate risk prostate cancer. *Int J Radiat Oncol* 2019; **104**: 42–49.
- 10 Fowler JF, Welsh JS, Howard SP. Loss of biological effect in prolonged fraction delivery. *Int J Radiat Oncol Biol Phys* 2004; **59**: 242–49.