In this edition of *European Urology*, Cozzarini et al. report their experience with postprostatectomy radiotherapy for prostate cancer (PCa), focusing on the impact of daily fraction size on late urinary toxicity [1]. The authors retrospectively compare the toxicity of two groups of fractionation schedules used at their institution: a conventionally fractionated regimen (1.8 Gy per fraction) and a collection of regimens using a larger dose per fraction or hypofractionation (2.35, 2.5, 2.6, or 3.6 Gy per fraction).

Hypofractionated postprostatectomy radiotherapy is a particularly attractive treatment strategy because it has several potential advantages.

The potential advantages of hypofractionation are (1) increased convenience for patients because of fewer treatment days, (2) reduced cost to patients because of reduced travel and out-of-pocket expenses (eg, copays), (3) improved resource use for physicians because of the fewer number of treatments per patient and overall, and (4) consequently reduced cost to society. All of these factors may increase the use of adjuvant and early salvage postprostatectomy radiotherapy [2]. For example, it is estimated that <20% of patients with pT3 disease and positive margins receive adjuvant radiotherapy despite its being the most likely to benefit them [3,4].

Hypofractionation can also be exploited to achieve radiation dose escalation, which is a proven effective strategy for intact PCa. Dose escalation with hypofractionation is achievable because of the favorable radiobiological nature of PCa relative to the adjacent rectum and bladder (ie, lower α/β ratio) that may result in greater cell killing for a given level of toxicity. For intact PCa, hypofractionation over approximately 5 wk appears to be at least as effective as, and not more toxic than, conventional fractionation with fraction sizes of 2.5 Gy from the Cleveland Clinic [5], 2.7 Gy from the Fox Chase phase 2 trial [6], or 3.1 Gy from the Italian phase 3 trial [7]. It is logical, therefore, to imagine that similar results may be possible after prostatectomy.

The current paper by Cozzarini et al. [1] emphasizes the need for caution as results from intact PCa are extrapolated to the postprostatectomy setting because there are important differences compared with radiotherapy for intact PCa. The volume of bladder irradiated is greater postoperatively compared with intact prostate radiotherapy. And while the rectum is widely accepted as the dose-limiting structure for intact PCa, the vesicourethral anastomosis and bladder are of equal, if not greater, concern postoperatively because they are contained within the clinical target volume. A dose–volume relationship is believed to exist, in which the tolerance of the bladder is a balance between the total radiation dose and bladder exposure. For a given portion of bladder, doses above a “tolerance dose” are expected to increase the risk toxicity. This is a very important concept to consider when critically evaluating the results of Cozzarini et al.

Cozzarini et al. [1] report an increased rate of genitourinary toxicity with the use of hypofractionation, but it is possible that the excess toxicity is simply related to a relative increase in the bladder dose, which is dependent on fraction size. Biological modeling can be used to equate physical dose with a biologically equivalent dose when varying fraction sizes are used. While the authors do report equivalent doses in 2-Gy fractions (EQD2) for the various fraction schedules used, the EQD2 doses used may underestimate the total radiation dose used because they
assumed a bladder $\alpha/\beta$ ratio ($\alpha/\beta_{\text{bladder}}$) of 5. The $\alpha/\beta_{\text{bladder}}$ is not as well defined and may range from 3 to 10 Gy [8,9]. The most conservative estimate would be $\alpha/\beta_{\text{bladder}}$ of 3, which is commonly used for late-responding tissue such as the bladder.

Using an $\alpha/\beta_{\text{bladder}}$ of 3, the EQD2$_{\text{bladder}}$ was 70 Gy for the 2.35-Gy fraction group ($n = 117$), 77 Gy for the 2.5-Gy fraction group and 82 Gy for the 2.6-Gy fraction group ($n = 80$, combined), and 68 Gy for the 2.9-Gy fraction group ($n = 50$), compared with 67 Gy for the 1.8-Gy control group that received conventional fractionation. Therefore, assuming that the only difference in the radiotherapy technique between the conventional and hypofractionation groups was the dose per fraction, it is possible that the bladder and vesicourethral anastomosis received much higher biologically equivalent doses when hypofractionation was used. Unfortunately, the authors did not vary the assumption of the $\alpha/\beta_{\text{bladder}}$ to learn if it significantly altered the results of the multivariable analysis for late genitourinary toxicity. Perhaps in light of the potential for an escalation of total dose as high as 10–15 Gy (28 fractions of 2.5–2.6 Gy)—which is unprecedented postoperatively to date—in one-third of the hypofractionation group (80 patients), observing an increase in toxicity is not unexpected.

The EQD2 model can be used to arrive at more moderate schedules that may provide modest dose escalation on the order of 8–10 Gy, in line with the magnitude of dose escalation proven effective for intact PCa. For example, the University of Wisconsin has used 65 Gy in 26 fractions of 2.5 Gy (EQD2$_{\text{bladder}}$ = 72 Gy), which is more in line with conventional doses of 64–70 Gy in 2-Gy fractions, and toxicity rates have been low, with encouraging efficacy, after 4–5 yr [10].

Understanding the bladder’s tolerance of radiotherapy, whether it be for prostate, bladder, or gynecologic cancers, has historically been elusive because variation in bladder filling and location during radiotherapy likely means that the actual dose received by the bladder is not identical to the dose in the treatment plans used for clinical study. And perhaps consequently, toxicity has often not been fully explained by dosimetric modeling alone [11]. Further dosimetric studies are needed to better define the dose-volume relationship that predicts toxicity, to derive an ideal biological model for estimating the effect of dose and fraction size on bladder function, and to firmly establish the portions of the bladder that may be most sensitive to the effects of radiotherapy.

Hypofractionated postprostatectomy radiotherapy is a promising avenue of clinical research with many potential benefits. Further study is warranted, ideally with well-designed, prospective clinical trials testing a moderate schedule of hypofractionation with the aim of shortening treatment time, improving outcome with dose escalation, and minimizing the risk of toxicity with a radiotherapy technique that incorporates fraction size–dependent dose limits for the bladder and other sensitive organs to enable a fair and balanced comparison with conventional fractionation.

Conflicts of interest: Mark K. Buynousski has been a consultant for General Electric and has received royalties from Up-To-Date and Amersys.

References