EDITORIAL

# Prostate cancer intensity-modulated radiotherapy and long term genitourinary toxicity: an evolving therapeutic landscape



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*"Long Term Genitourinary Toxicity following Curative Intent Intensity-Modulated Radiotherapy for Prostate Cancer: A Systematic Review and Meta-analysis"* by David R et al.

Radiotherapy (RT) is a well-established treatment option for localized prostate cancer, along with radical prostatectomy and active surveillance. Since most of prostate cancer patients can survive longer than 10 years, knowledge of long-term toxicity of each treatment is crucial to help physician and patient determining the most adapted treatment. Because of the combination of technological advances and intrinsic radiobiological properties of prostate cancer, RT treatment modalities have evolved a lot these past 20 years. Intensity-modulated radiation therapy (IMRT) and rotational techniques, compared with 3-dimensional conformal radiation therapy (3D-CRT) have allowed delivering high-dose radiation to the prostate while limiting the radiation dose to the rectum and bladder, thus improving the effective therapeutic ratio.

In order to better characterize the incidence of late genitourinary (GU) toxicity following IMRT, David et al. conducted a systematic review of the literature and performed a meta-analysis of selected studies focusing on the 60-month incidence of Radiation Therapy Oncology Group (RTOG) and Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 GU toxicity, including hematuria, urinary retention, and urinary incontinence. Data was extracted from 6 articles, 1 prospective cohort study and 5 randomized control trials, including the HYPRO, the CHHiP, and the PROFIT trials comparing standard versus moderate hypofractionation [1]. The pooled 60-month cumulative incidence of RTOG and CTCAE Grade ≥2 genitourinary toxicity were 17% (95% CI: 5–20%, $n = 678$) and 33% (95% CI: 27–38%, $n = 153$), respectively. The pooled 60-month cumulative incidence of hematuria was 5% (95% CI: -4-14%, $n = 48$), urinary incontinence 12% (95% CI: 6–18%, $n = 194$), and urinary retention 24% (95% CI: 9–40%, $n = 10$). While these data may suggest that the late GU toxicity is not an uncommon finding following IMRT and highlight the paucity of high-quality studies reporting long-term GU toxicity, some specific considerations are nevertheless needed in interpreting these results.

First, differentiating grade 2 versus grade ≥3 severe toxicities is essential in understanding the real impact of a treatment, being grade 2 events moderate by definition and requiring only minimal non-invasive interventions often prescribed at the discretion of the treating physician. In more than half of the trials included in this study, grade 3 or more toxicities were rarely observed, with cumulative incidence rates below 3% [2–5]. On the other hand, evaluation of long-term patient-reported outcomes (PROs) may be a better discriminator of long-term toxicities and a helpful instrument to confirm safety and enhance patient information. Of note, long-term PROs results in the CHHiP trial confirmed a continued low incidence of moderate or high bother on all urinary, bowel and sexual domains for both fractionation arms [6]. The 5-year prevalence of moderate or worse urinary symptoms was below 10% for the three treatment schedules, confirming moderate hypofractionation as standard of care for intermediate-risk localized prostate cancer.

Second, mechanisms underlying the occurrence of GU toxicity may be complex and multifactorial. While the benefit of IMRT in reducing GU side effects compared to 3D-CRT techniques may be overall less evident than the expected benefit in limiting rectal toxicity [7], it is certain that modern technologies can help to better spare structures involved in long-term urinary toxicity. Optimization of doses delivered to the intraprostatic urethra [8] or to the bladder trigone [9] may represent an appealing strategy to further reduce urinary toxicity. Urethra-sparing techniques currently tested in some trials [10] have shown promising results in terms of GU toxicity and quality of life, despite long-term results for biochemical disease control have not yet been reported.

Third, important developments have been integrated in the standard clinical practice in terms of image guidance. Modern image-guides RT techniques (IGRT) were not routinely implemented in all studies of the present meta-analysis. In the CHHiP trial, use of IGRT was associated with a lower rate of grade ≥2 RTOG GU toxicity at 2-year compared to patients treated without (3.9% vs. 8.4%) [11]. Similarly, in the PACE-B phase III trial randomizing patients between moderate and extreme hypofractionation, use of intrafractional motion control with robotic radiotherapy was clearly associated with a better GU toxicity profile compared to patients treated without this technology [12]. Last but not least, the interim analysis of the phase III MIRAGE trial presented at the ASCO GU 2022 meeting confirmed the added value of online adaptive RT technologies, with a statistically significant reduction in acute grade ≥2 GU toxicity for prostate SBRT delivered with MRI-linacs compared to a standard CT-based solutions [13].

In conclusion, the study by David et al. provides useful benchmarking data on long-term GU toxicity following IMRT. Nevertheless, modern RT is an evolving field with many important technological developments integrated in the last years. Optimization of doses delivered to the intraprostatic urethra and bladder neck, routine integration of IGRT modalities, and adaptive RT solutions will certainly be an important step forward in improving tolerance and reducing the impact on long-term quality of life of prostate cancer patients treated with definitive RT.

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## DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

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## AUTHOR CONTRIBUTIONS

TZ and VA: paper writing.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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