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EDITORIAL

Intraprostatic Urethra: The New Kid on the Block for Prostate Cancer Radiation Therapy?

Thomas Zilli, MD,[a,b] Vérane Achard, MD, PhD,[a,b] and Jennifer Le Guevelou, MD[a,b]

[a]Department of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland; and [b]Faculty of Medicine, Geneva University, Geneva, Switzerland

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The evolving landscape of radiation therapy (RT) for prostate cancer has experienced major breakthroughs in the last decade, marked by a constant decrease in number of fractions, from moderately hypofractionated protocols to ultrahypofractionation, and the widespread implementation of modern delivery techniques, like stereotactic body radiation therapy (SBRT). Although dose-escalated protocols have been significantly associated with improved outcomes, genitourinary (GU) toxicity remains one of the major concerns of these treatments. Understanding the underlying mechanisms for GU toxicity, together with the development of dedicated dose constraints, is a constant effort by the radiation oncology community to make modern RT treatments safer and more tolerable.

In a combined analysis of 23 prospective SBRT clinical trials, Leeman et al demonstrated for the first time the existence of a close association in ultrahypofractionation between the radiation dose delivered to the intraprostatic urethra and the development of GU toxicity.[1] Maximum urethral doses correlated with both acute and late grade 2+ GU toxicities independently from age, prostate size, baseline urinary function, and bladder dosimetry, with a 1.0% late grade 2+ GU toxicity increase for each additional Gy delivered. By limiting the maximal dose to the urethra to 38 Gy in 5 fractions (56 Gy and 80.5 Gy equivalent dose in 2 Gy fractions (EQD_2) for α/β= 10 Gy and 3 Gy, respectively), expected GU toxicity is supposed to remain in a safe range of tolerability, in the order of approximately 20% and 5% of grade 2+ acute and late toxicities, respectively. These findings correlate favorably with data coming from the randomized phase 3 FLAME clinical trial, testing 77 Gy in 35 fractions to the entire prostate with or without a focal boost up to 95 Gy boost to a magnetic resonance imaging-defined dominant intraprostatic lesion. By using a longitudinal dose-effect model, an increased dose to the bladder and urethra resulted in a significant increase in GU toxicity after intensity modulated RT.[2] Incorporation of a urethra dose-constraint of D0.1cc $\leq$ 80 Gy in addition to usual bladder dose-constraint is therefore recommended for focal boost treatment plans to limit long-term GU toxicity, with an estimated rate of grade 2+ GU toxicity below 10% when this dose constraint is respected. The same correlation between the maximal urethral dose and the development of long-term GU toxicity remains valid for other RT schedules, testing conventional fractionation, moderate hypofractionation, or ultrahypofractionation (Table 1).[2-8] Independently from the RT schedule, by limiting the maximal urethral doses to 80 to 85 Gy EQD_2 (α/β = 3 Gy), the cumulative incidences of late grade 2+ GU toxicity are expected to remain below 20% (Fig. 1).

Routine implementation of urethra-sparing techniques in treatment plan optimization deserves nevertheless some specific considerations.

First, because tumor seeding around urethra has been reported by surgical series and a prospective trial of urethra dose reduction (mean dose delivered to the proximal and distal urethra of 48.8 and 65.9 Gy, respectively) has shown a worse biochemical control compared with standard whole prostate irradiation,[9] careful selection of optimal candidates for urethra sparing modalities is mandatory. Development

Corresponding author: Thomas Zilli, MD; E-mail: Thomas.Zilli@hcuge.ch
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Table 1 Selected studies of standard fractionation, moderate and ultrahypofractionation, and related urethral dose metrics and cumulative late grade 2 plus genitourinary toxicities

Study	Trial, study design	N	Radiation therapy technique	Prescription dose, Gy (Gy × fraction)	Prescription dose EQD_2 ($\alpha / \beta = 3$ Gy)	Maximal prescription dose constraint	Max urethra dose (EQD_2, $\alpha / \beta = 3$ Gy)	Late grade 2 + GU tox cumulative incidence	Toxicity grading
Groen et al[2]	FLAME, randomized phase 3	276	IMRT, IGRT required	77 (2.2 × 35)	80.1	Dmax <107%	81.6 (Median urethra D0.1cc 78 Gy)	23% (6 y)	CTCAE v.3
		281		77 + 95 (2.2 × 35 + Focal Boost 2.71 × 35)	108.5	Dmax <107%	93.9 (Median urethra D0.1cc 86 Gy)	27.8% (6 y)	CTCAE v.3
Tree et al[5]	PACE-B, randomized phase 3	433	SBRT, IGRT required	36.25 (7.25 × 5)	74.3	V44Gy <20% (Urethra)	103.8	29.1% (2 y)	CTCAE v.4
		441	IMRT, IGRT required	62 (3.1 × 20) 78 (2 × 39)	75.6 78	D2% <107% (66.3 Gy/83.5 Gy)	83.7 83.5	18.8% (2 y)	CTCAE v.4
Widmark et al[6]	HYPO-RT-PC, randomized phase 3	598	3DCRT (80%), IMRT (20%), IGRT required	42.7 (6.1 × 7)	77.7	Dmax <105% (44.8 Gy)	84.3	18% (5 y)	RTOG
		602		78 (2 × 39)	78	Dmax <105%	81.9	17% (5 y)	RTOG
Lee et al[8]	RTOG 0415, randomized phase 3	534	3DCRT, IMRT, IGRT required	73.8 (1.8 × 41)	70.8	Dmax <107%	77.8	22.6 (5.8 y)	CTCAE v.3
		545		70 (2.5 × 28)	77	Dmax <107%	85	29.7 (5.8 y)	CTCAE v.3
Dearnaley et al[3]	CHHiP, randomized phase 3	1065	IMRT, IGRT optional	74 (2 × 37)	74	D1% <105%	77.7	9.1% (5 y)	RTOG
		1074		60 (3 × 20)	72	D1% <105%	77.5	11.7% (5 y)	RTOG
		1077		57 (3 × 19)	68.4	D1% < 105%	73.6	6.6% (5 y)	RTOG
Catton et al[7]	PROFIT, randomized Phase 3	598	IMRT, IGRT required	78 (2 × 39)	78	1 cc ≤105%	81.9	22 (6 y)	RTOG
		608		60 (3 × 20)	72		77.5	22.2 (6 y)	RTOG
Spratt et al[4]	MSKCC, retrospective	1002	IMRT, mix weekly port and IGRT	86.4 (1.8 × 48)	82.9	Dmax <110%	94.6	21.1% (7 y)	CTCAE v.4

Abbreviations: 3DCRT = three-dimensional conformal radiation therapy; CTCAE v.3, v.4 = Common Terminology Criteria for Adverse Events version 3.0, version 4.0; CHHiP = Conventional or Hypofractionated High-Dose Intensity Modulated Radiotherapy for Prostate Cancer; DX = dose delivered to X% of the volume; Dmax = dose maximum; EQD_2= equivalent dose in 2Gy fractions; FLAME = Focal Lesion Ablative Microboost in Prostate Cancer trial; GU = genitourinary; HYPO-RT-PC = Hypofractionated Radiation Therapy of Intermediate Risk Localized Prostate Cancer trial; IMRT = intensity modulated radiation therapy; IGRT = image-guided radiation therapy; MSKCC = Memorial Sloan Kettering Cancer Center trial; PACE = Prostate Advances in Comparative Evidence trial; PROFIT = Prostate Fractionated Irradiation trial; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiation therapy; Vx = % volume that receives more than X Gy.

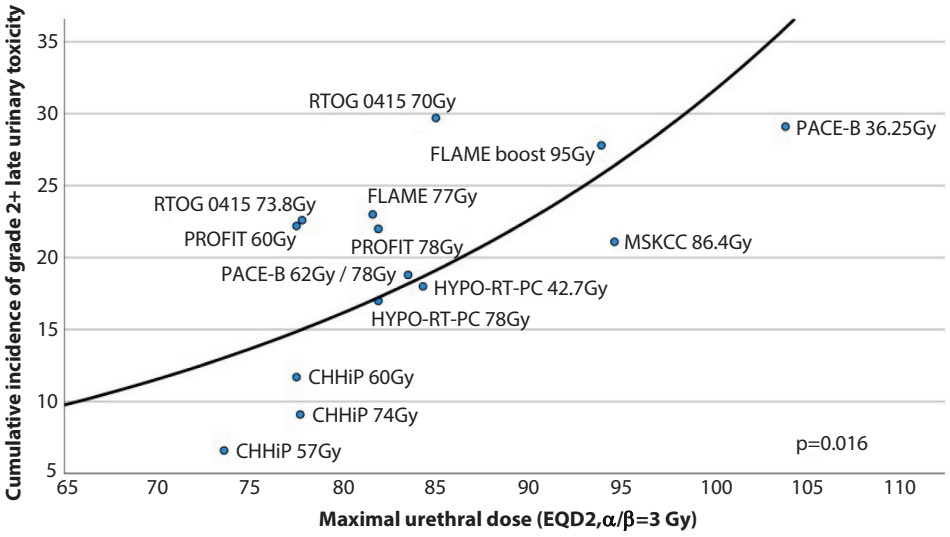

Fig. 1. Dose-toxicity curves of cumulative incidence of late grade 2+ urinary toxicity according to maximum urethral doses (equivalent dose in 2 Gy fractions, equivalent dose in 2Gy fractions, α/β = 3 Gy for late toxicity) of trials testing conventional fractionation, moderate and ultrahypofractionation (see Table 1).

of SBRT techniques trying to maintain a minimal therapeutic dose to the urethra and the surrounding peri-urethral tissues and limiting at the same time doses exceeding the threshold of 38 to 40 Gy in 5 fractions may represent a safe way to limit GU toxicities. Delivery of a homogenous dose to the urethra (ie, 32.5 Gy in 5 fractions, 74 Gy EQD_2 α/β = 1.5 Gy for microscopic peri-urethral disease control) as used in a phase 2 prospective trial may represent an appealing strategy to minimize GU toxicity while maintaining an acceptable long-term tumor control.[10] After 18 months of follow-up, toxicities were among the lowest reported from SBRT series, with a late grade 2 GU toxicity rate of 4%, no grade 3 toxicities, and minimal rates of biochemical failures. Long-term outcomes of these urethral-sparing techniques are nevertheless awaited to confirm the safety of this approach.

Second, delineation of this organ at risk remains challenging, as to date no consensus has been reached on the definition of urethra for RT treatments. Urethral catheter placement has been defined by the Groupe Européen de Curiethérapie/ European Society Radiation Oncology-European Association of Urology (GEC/ESTRO-EAU) consensus guidelines as the gold standard method to identify the prostatic urethra, although the procedure is invasive and associated with an increased risk of iatrogenic urethral strictures. Coregistration with multiparametric magnetic resonance imaging may represent an alternative noninvasive option, limiting urethral deformation but with some delineation challenges, especially in patients with large hypertrophic glands. Use of 2 to 3 mm margins around the urethra should be considered to account for catheter-related anatomic distortions and/or daily repositioning.[11]

Third, optimization on urethra should require the implementation of a robust image guided RT technology. In the 24-month results of the Prostate Advances in Comparative Evidence trial,[5] SBRT patients treated with intrafractional tracking on fiducial markers using a robotic-based delivery system showed better grade 2+ GU toxicity rates compared with patients treated with conventional linacs and no mandatory fiducial implant (5.9% vs 15.4%). Violation of dose constraints to the urethra and other structures involved in GU toxicity (bladder, trigone) by less accurate daily repositioning and lack of intrafractional motion control can probably explain the worse GU toxicity observed in patients treated with linac-based systems. Use of adaptive RT delivery modalities implementing magnetic resonance-guided RT techniques can represent a promising modality to further decrease GU toxicity by sparing urethra and limiting daily repositioning incertitude.

In conclusion, the study by Leeman et al provides useful benchmarking data for future studies. Dose-effects relations for the dose to the urethra on GU toxicity are observed independently from the fractionation, with probably a 80 to 85 Gy EQD_2 (α/β = 3 Gy) dose threshold to maintain late grade 2+ GU toxicity below a 20% rate. Although open questions still remain on urethra definition, specific dose constraints and optimal urethra-sparing techniques as well as integration of intraprostatic urethra as additional organ at risk should be considered in treatment optimization of dose escalated RT protocols. Approaches trying to limit urethral doses are therefore highly encouraged in future clinical trials to reduce both acute and late GU toxicity.

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