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REVIEW - BONADONNA LECTURE SERIES

Understanding urinary toxicity after radiotherapy for prostate cancer: first steps forward

Tiziana Rancati[1], Federica Palorini[1], Cesare Cozzarini[2], Claudio Fiorino[3], Riccardo Valdagni[1,4,5]

[1] Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan - Italy
[2] Department of Radiation Oncology, San Raffaele Scientific Institute, Milan - Italy
[3] Department of Medical Physics, San Raffaele Scientific Institute, Milan - Italy
[4] Department of Radiation Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan - Italy
[5] Department of Oncology and Hemato-oncology, Università degli Studi di Milano, Milan, Italy

ABSTRACT

One of the most relevant achievements of Professor Gianni Bonadonna was the implementation of the methodology of controlled clinical trials in medical oncology. It is valid for all cancer types, oncological disciplines and clinical endpoints, both survival and toxicity. This narrative review reports on the status of the current knowledge of the radiation-induced urinary syndrome after external-beam radiotherapy for prostate cancer. In recent years, the syndrome has been the object of large-scale prospective observational trials specifically devoted to investigating the association of patient and treatment features with acute/late urinary toxicity. The first results of these trials allow initial attempts at predictive modeling, which can serve as a basis for the optimization of patient selection and treatment planning.

Keywords: Prostate cancer, Radiotherapy, Urinary toxicity

Introduction

External-beam radiation therapy is one of the leading options in the curative treatment of prostate cancer, either alone or combined with surgery and hormone therapy. In the past decade, many advances have been made in terms of treatment outcomes and reduction of side effects experienced by prostate cancer survivors. Primarily, the introduction of modern linear accelerators allowed the delivery of highly conformal doses to the tumor target through intensity-modulated beams (IMRT), volumetric arcs (volumetric modulated arc therapy, VMAT) and precise image guidance, while reducing the dose to healthy tissues. In addition, deeper knowledge of tissue response to radiation was acquired, especially for rectal and intestinal symptoms, mainly thanks to the establishment of large clinical trials including hundreds of patients, with systematic scoring and follow-up of patient status. It is now well established that different symptoms, even if representing the expression of damage to the same tissue, may be differently related to the absorbed dose. For example, rectal bleeding arises as a serial effect and is mainly related to the absorption of high doses in small rectal mucosa volumes, whilst fecal incontinence is related to intermediate doses absorbed by large rectal volumes.

The development of reliable models of radiation-induced toxicities along with the available level of technology has determined an efficient improvement of the treatment plans, even in dose-escalated or hypofractionated regimens. This is particularly true for moderate and severe rectal toxicities, which had an incidence close to 20% in the 1990s while in the most recent publications they have fallen below 7%-10%.

However, an analogous result has not yet been reached in urinary symptoms. This is mainly due to the difficulty in sparing the bladder, which is partially but unavoidably included in the target volume, as well as to the clear lack of knowledge concerning the predictors of urinary toxicity. The main reason for this deficiency is probably the difficulty in following for a sufficiently long time a large number of patients whose clinical and dosimetry data need to be individually and prospectively collected with proper evaluation of urinary symptoms. Some important symptoms (e.g., incontinence) may indeed continuously arise after radiation therapy and their incidence reaches a plateau only many years (typically 5-8) after treatment. The fulfilment of reliable models of radiation-induced urinary sequelae is therefore made particularly challenging by the complexity of symptoms, their evolution over time, and the strong dependence on the baseline situation.

It is widely acknowledged that radiation-induced toxicity is a multifactorial problem, depending not only on the delivered

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Corresponding author:
Tiziana Rancati
Prostate Cancer Program
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Venezian 1
20133 Milan, Italy
tiziana.rancati@istitutotumori.mi.it

dose and involving many complex biological processes in the irradiated tissues responding to cellular injury. Individual biological background and expression patterns, premorbid conditions as well as the cell microenvironment are important factors in the development of side effects, although their contributions and interaction are still mostly unknown. The ability to predict which patients are more likely to experience urinary toxicity may improve the potential of individualizing treatment with respect to several aspects concerning the choice of the therapeutic strategy, dose prescription, fractionation, and use of supportive therapies.

Only in recent years has the radiation-induced urinary syndrome been the object of large-scale prospective observational trials specifically devoted to investigating the association of patient and treatment features with acute/late urinary toxicity. The preliminary findings allowed a first attempt at predictive modeling which can serve as a basis for optimization of patient selection and treatment planning.

In this narrative review, we report on the current knowledge of the radiation-induced urinary syndrome.

The radiation-induced urinary syndrome – facts and figures

The term "urinary toxicity" comprises a wide variety of symptoms – including urinary frequency, obstruction and stricture, hematuria, dysuria or incontinence – with very different time patterns and different impacts on the individual patient's quality of life (1). Yet, the degree of their effect varies highly among patients and remains uncertain unless patient-reporting tools are used in combination with physician assessments.

The response of the urinary bladder to radiotherapy can be classified into acute/subacute reactions, occurring during radiotherapy and within 3-6 months after treatment completion, and late reactions, which start to appear 6 months after therapy and often occur many years later. The pathophysiology of urinary radiation injury is still not completely understood. The mechanisms of radiation damage affect the urothelium, the vasculature and the detrusor muscles (1). After irradiation, the urothelium exhibits nuclear irregularity and cellular edema, with disruption of the polysaccharide layer; this causes contact between hypertonic urine and isotonic tissue, resulting in tissue inflammation and early urinary symptoms (2). Vascular ischemia, edema and cellular demolition cause depletion of bladder smooth muscle and proliferation of fibroblasts, with consequent decreased bladder compliance and capacity up to hemorrhagic cystitis. Fibrosis leading to occlusion of the urethral lumen is an important factor for the onset of urethral strictures after radiotherapy (3), as well as being likely associated with reduced urinary functionality in terms of urgency and incontinence symptoms.

At the clinical level, urinary toxicity is usually graded using the Common Terminology Criteria for Adverse Events (CTCAE): version 4.03 is the most recent release of these scoring criteria (4). Toxicity is graded from 0 to 5, with grading referring to the severity of the effect. Grade 0 indicates no adverse effect, grade 1 describes mild symptoms with no indication for intervention, grade 2 denotes moderate symptoms requiring minor, local or non-invasive intervention, and grade 3-4 are severe effects requiring hospitalization or urgent intervention and limiting self-care activities of daily living. Any death resulting from late complications of radiation is considered grade 5. Grade 2 toxicities include (a) moderate urinary frequency/urgency with an indication for medical management; (b) symptomatic hematuria requiring the positioning of a urinary catheter or bladder irrigation; (c) urethral obstruction needing dilation and/or the insertion of a urinary or suprapubic catheter; (d) incontinence requiring pads; (e) urinary retention leading to placement of a urinary/suprapubic or intermittent catheter, and (f) fistula requiring non-invasive intervention. Grade 3 effects comprise (a) gross hematuria requiring transfusion, hospitalization, hyperbaric oxygen therapy, radiological or operative intervention; (b) symptomatic urinary tract obstruction with altered organ function needing surgical intervention; (c) urinary incontinence necessitating clamps, collagen injections or surgery; (d) urinary retention with an indication for elective operative or radiological intervention; (e) fistula requiring radiological, endoscopic or surgical intervention or permanent urinary diversion.

The incidence of acute/late radiation-induced urinary toxicity in modern series pertaining to patients treated with radical radiotherapy varies widely, the variation being mainly related to prescription doses, delivery techniques, the presence and frequency of image guidance protocols, hypofractionation, and concomitant hormonal therapies. The rates of grade 1 and grade 2 symptoms in patients followed for up to 10 years are in the range of 20%-43% and 10%-46%, respectively (5-16). Grade 3 urinary toxicity occurs at a rate of 2%-16%. Obstruction, incontinence and radiation cystitis with gross macroscopic hematuria are the most commonly reported grade 3 symptoms. Table I summarizes the urinary toxicity rates as reported by the above-mentioned studies.

It has to be mentioned that the prevalence of lower urinary tract symptoms increases with age in the general population: moderate to severe symptoms are present in approximately 15% of men aged 50-59 years and approximately 30% of men 70+ years old. The most frequent symptom in the general population is nocturia (17, 18). For this reason the rates of late radiation-induced urinary toxicity could be overestimated.

The pattern of late toxicity is variable, with obstructive symptoms generally resolving with time or intervention, and urinary incontinence worsening with protracted follow-up and increasing patient age (19-21).

A last issue is related to the compelling confirmations of the consequential nature of late radiation-induced urinary toxicity, which were recently reported in large, prospectively followed cohorts (5, 9, 13, 22-27). This suggests that a relevant fraction of late urinary events are a "consequence" of the exuberant repair process following the acute inflammatory phase and it means that any effort to reduce acute toxicity may impact the occurrence of late events.

Is the patient's point of view of interest? Challenges in measuring and reporting radiation-induced urinary symptoms and the importance of patient-reported outcomes

Measuring and reporting radiation-induced urinary symptoms is a demanding task, which must take into account a complex set of symptoms evolving over time and strongly

TABLE I - Summary of trials (modern series pertaining to patients treated with radical radiotherapy) reporting on late urinary toxicity rates

Reference	Pts (N)	RT technique	Prescription dose (Gy)	Follow-up	Scoring type	Toxicity time	Toxicity type	Toxicity rate
Zelefsky et al 1999 (5)	743	3DCRT	64.8-81	Median 3.5 yrs	RTOG	Actuarial 5 yrs	Grade ≥2	10
					RTOG	Actuarial 5 yrs	Grade ≥3	3
Zietman et al 2005 (6)	393	3DCRT mixed^	70.2 vs. 79.2	Median 5 yrs	RTOG	Crude	Grade ≥2	20
					RTOG	Crude	Grade ≥3	2
Talcott et al 2010 (7)	337	3DCRT mixed^	70.2 vs. 79.2	Median 9.4 yrs	PCSI	Crude	Urinary obstruction/irritation	24
					PCSI	Crude	Urinary incontinence	10
Peeters et al 2005 (8)	669	3DCRT	68 vs. 78	Median 2.6 yrs	RTOG/EORTC	Actuarial 3 yrs	Grade ≥2	30
Harsolia et al 2007 (9)	331	3DCRT	70.2-79.2	Median 1.6 yrs	NCI CTC 2.0	Actuarial 3 yrs	Grade ≥2	17
					NCI CTC 2.0	Actuarial 3 yrs	Grade ≥3	3.6
Cahlon et al 2008 (10)	478	IMRT	86.4	Median 4.4 yrs	CTCAE	Crude	Grade ≥2	16
					CTCAE	Crude	Grade ≥3	3
Fonteyne et al 2009 (11)	260	IMRT	74-80	Median 3 yrs	In-house developed scoring system**	Crude	Grade ≥2	21
					In-house developed scoring system**	Crude	Grade ≥3	3
Pederson et al 2012 (12)	296	IMRT	68.5-76.4	Median 3.4 yrs	CTCAE	Actuarial 4 yrs	Grade ≥2	19
					CTCAE	Actuarial 4 yrs	Grade ≥3	2
Wortel et al 2016 (13)	189	3DCRT	78	Median 5.2 yrs	Patient-reported questionnaire*	Actuarial 5 yrs	Grade ≥2	36.4
					Patient-reported questionnaire*	Actuarial 5 yrs	Grade ≥3	16.1
					EORTC-QLQ-PR25	Prevalence at 5 yrs	Any dysuria	6
Wortel et al 2016 (13)	242	IMRT	78	Median 4.8 yrs	Patient-reported questionnaire*	Actuarial 5 yrs	Grade ≥2	46.2
					Patient-reported questionnaire*	Actuarial 5 yrs	Grade ≥3	11.7
					EORTC-QLQ-PR25	Prevalence at 5 yrs	Any dysuria	8
Donovan et al 2016 (14)	545	3DCRT	74	Minimum 6 yrs	EPIC	Prevalence at 6 yrs	Incontinence, use of pads	4
Jolnerovski et al 2017 (15)	277	IMRT	70-80 Gy	Median 6.4 yrs	CTCAE	Actuarial 5 yrs	Grade ≥2	25.3
Byrne et al 2017 (16)	300	IMRT	78-84	Median 4.8 yrs	CTCAE	Actuarial 5 yrs	Grade ≥2	19
					CTCAE	Actuarial 5 yrs	Grade ≥3	3.5

3DCRT = three-dimensional conformal radiation therapy; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; EORTC-QLQ-PR25 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire – Prostate 25; EPIC = Expanded Prostate Cancer Index Composite; IMRT = intensity-modulated radiation therapy; N = number; NCI CTC 2.0 = National Cancer Institute Common Toxicity Criteria 2.0; PCSI = Prostate Cancer Symptom Indices; pts = patients; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; yrs = years.

^ 3DCRT, 50 Gy photons followed by proton boost.

** In-house developed scoring system based on the RTOG, LENT/SOMA (Late Effects on Normal Tissue/Subjective, Objective, Management, Analytic) and Common Terminology Criteria Genitourinary toxicity scoring systems.

* Patient-reported questionnaire based on RTOG/EORTC scoring system.

relying on individual patient characteristics and on pre-radiotherapy urinary functionality.

The previously described CTCAE physician-based score has been found to be much less exhaustive (and often largely different in terms of results) than patient-reported outcomes. This prompted the increasing use of specific patient-reported questionnaires, as it became evident that these instruments can describe and score many different symptoms, allowing nuances and determination of the impact of symptoms on patient-perceived quality of life.

The International Prostate Symptoms Score (IPSS (28)) thus became widely used to score obstructive symptoms and generate an overall assessment of urinary functionality (15, 29-42). Urinary incontinence can be prospectively assessed by the International Consultation on Incontinence Modular Questionnaire Short Form (ICIQ-SF (43)), which also includes the patient's perception of the impact of incontinence on quality of life (14, 44).

The International Consortium for Health Outcomes Measurement (ICHOM (45)) proposed the Expanded Prostate Cancer Index Composite 26-question short form (EPIC-26 (46)), which is already widely used (14, 37, 39, 47-50) and addresses all pertinent domains of prostate cancer treatment side effects including urinary obstructive symptoms, urinary incontinence and hematuria. ICHOM recognized that recommending a single instrument for comprehensive evaluation of side effects was a contentious decision, because centers of excellence already had well-established prospective programs including different patient-reported outcomes and there was no convincing indication for the superiority of one tool over another (45). However, the Consortium strongly recommended the regular use of such patient-reported instruments, from baseline up to 10-year follow-up, as part of high-quality care pathways.

How can we optimize radiotherapy treatment minimizing the risk of urinary toxicity? Established dose-volume effects

One of the most outstanding results achieved in recent years is the acknowledgment of the existence of a dose-volume effect for several urinary symptoms arising after and as a consequence of radiotherapy for prostate cancer.

Several trials reported significant associations between the dose to the urinary bladder and both acute and late urinary injury: a summary of the most relevant studies is reported in the recent review by Landoni and coworkers (51) reporting on the main findings in terms of constraints and relationships. Predominantly, the bladder seems to act as a highly serial organ (52), i.e., its functional subunits are arranged as in a chain and damage to a single subunit causes loss of functionality to the whole organ. An organ with such an architecture is highly sensitive to small volumes receiving high doses. In the particular case of the urinary bladder, reducing the volume that receives more than 75-78 Gy or more than 8-12 Gy per week (5, 9, 11, 12, 15, 26, 27, 34, 53-55) may significantly decrease the risk of acute and/or late urinary toxicity. Table II reports some details of trials highlighting the relationship between acute/late urinary toxicity and bladder doses/prescription dose (with prescription dose being a surrogate for dose to small bladder volumes).

An important consequence of the existence of a dose-volume effect is that any attempt to reduce the fraction of the bladder neck receiving high doses (>75-78 Gy, 2-Gy-equivalent) appears to be justified. This highlights the pivotal role of image-guided radiotherapy (IGRT) in lowering the urinary toxicity risk given its potential to reduce the fraction of bladder that overlays the planning target volume, corresponding to the portion of the bladder that is irradiated at the full prescription dose. The reduction of urinary toxicity with IGRT with respect to non-IGRT reported in several studies (56-59) indirectly supports this argument.

Of note, the role of small bladder volume irradiated at high doses (or of bladder maximum dose) was also established in several trials involving post-prostatectomy settings (24, 27, 60-62).

Does the daily radiation fraction size matter? The impact of altered fractionation

Nowadays the large majority of prostate cancer radiotherapy treatments are performed in fractionated schemes over 7-8 weeks at 2 Gy/fraction, delivered with intensity-modulated modalities with or without IGRT. The choice of delivering radiotherapy treatments in fractionated schedules with small fraction sizes has a sound radiobiological justification. Indeed, fractionation is a key tool for increasing the therapeutic ratio, that is, the separation between tumor control and normal-tissue damage curves which exploits the different ability of normal and tumor tissues to repair the radiation-induced damage.

However, the better sparing of normal tissues achieved with the most recent radiotherapy modalities has reawakened the interest of the radiation oncology community in hypofractionated schemes with the aim of reducing both patient discomfort and treatment costs.

Recently, various protocols including moderately to extremely hypofractionated schemes have been suggested. In particular, the 5-year efficacy results of 4 large randomized phase III trials demonstrated that hypofractionation for localized prostate cancer is non-inferior to conventional fractionation (63-66).

Nevertheless, variations to conventional schedules should be considered with caution, since extreme reduction of the number of fractions without the support of robust data on tissue radiobiological behavior might lead to unacceptably high doses to healthy tissues. This is particularly important for urinary toxicities. In the radical setting, there are some indications that hypofractionation may have a detrimental impact on urinary morbidity compared with conventional fractionation both in the acute and late stages (34, 37, 44, 66-71). On the other hand, in trials prescribing lower 2-Gy-equivalent doses, no significant impact has been reported for acute and late urinary toxicity.

How the bladder responds to variation in fraction sizes is still an open question, with evidence of a higher than previously assumed sensitivity to fractionation starting to appear both in the radical and post-prostatectomy settings (72), which has to be coupled to a steep dose-response after 75-80 Gy.

TABLE II - Summary of trials (modern series pertaining to patients treated with radical radiotherapy) highlighting a relationship between acute/late urinary toxicity and bladder doses/prescription dose (with prescription dose being a surrogate for dose to small bladder volumes)

Reference	Pts (N)	RT technique	Prescription dose (Gy)	Follow-up	Scoring type	Toxicity time	Toxicity type	Bladder dose descriptor	Dose descriptor cutpoint	Toxicity rate below/above cutpoint (%)
Palorini et al 2016 (34)	171	IMRT	70-80	End of RT	IPSS	Acute, end of RT	DeltaIPSS ≥10	Bladder volume receiving >8.5 Gy/ week	30 cc	13.7 vs. 21
Zelefsky et al 1999 (5)	743	3DCRT	64.8-81	Median 3.5 yrs	RTOG	Late, actuarial 5 yrs	Grade ≥2	Prescription dose	75.6 Gy	7.5 vs. 15
Harsolia et al 2007 (9)	331	3DCRT	70.2-79.2	Median 1.6 yrs	NCI CTC 2.0	Late, actuarial 3 yrs	Grade ≥2	Bladder volume receiving >82 Gy	2.5%	8 vs. 18
Fonteyne et al 2009 (11)	260	IMRT	74-80	Median 3 yrs	In-house developed scoring system**	Late, crude	Grade ≥2	Bladder volume receiving >70 Gy	20%	15 vs. 28
Pederson et al 2012 (12)	296	IMRT	68.5-76.4	Median 3.4 yrs	CTCAE	Late, actuarial 4 yrs	Grade ≥2	Prescription dose	76 Gy	13 vs. 24
Heemsbergen et al 2010 (26)	557	3DCRT	68 vs. 78	Median 5.9 yrs	RTOG/EORTC	Late, actuarial 5 yrs	Grade ≥2 obstruction	Bladder surface receiving ≥80 Gy	0.5 cc	8 vs. 13
Ahmed et al 2013 (53)	503	3DCRT	64-78	Median 5.9 yrs	Modified RTOG/ LENT	Late, crude	Grade ≥2	Mean bladder dose, bladder wall receiving more than 60-70 Gy		
Fleming et al 2011 (54)	180	3DCRT	70-75	Median 5 yrs	RTOG	Late, actuarial 5 yrs	Grade ≥2	Bladder EUD (with n = 0.5)	53.4 Gy	10 vs. 33
Ghadjar et al 2014 (27)	268	IMRT	86.4	Median 5 yrs	IPSS	Late, actuarial 5 yrs	DeltaIPSS ≥10	Maximum dose to bladder trigone	91 Gy	5 vs. 20
Thor et al 2016 (55)	212	3DCRT	78	Median 3.6 yrs	Danish study-specific questionnaire	Late, crude	Moderate/severe obstruction	Maximum bladder dose		
Thor et al 2016 (55)	212	3DCRT	78	Median 3.6 yrs	Danish study-specific questionnaire	Late, crude	Moderate/severe urgency	Maximum bladder dose		
Thor et al 2016 (55)	276	3DCRT	70	Median 6.4 yrs	Swedish study-specific questionnaire	Late, crude	Moderate/severe obstruction	Dose to 20% of bladder volume		
Jolnerovski et al 2017 (15)	177	IMRT	74	Median 6.4 yrs	CTCAE	Late, actuarial 5 yrs	Grade ≥2	Dose to 2% of bladder volume	73 Gy	18.3 vs. 31

3DCRT = three-dimensional conformal radiation therapy; CTCAE = Common Terminology Criteria for Adverse Events; deltaIPSS = variation in IPSS between baseline and follow-up measurements; EORTC = European Organisation for Research and Treatment of Cancer; EUD = equivalent uniform dose; IMRT = intensity-modulated radiation therapy; IPSS = International Prostate Symptom Score; LENT = late effects on normal tissue; N = number; NCI CTC 2.0 = National Cancer Institute Common Toxicity Criteria 2.0; pts = patients; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; yrs = years.
** in-house developed scoring system based on the RTOG, LENT/SOMA (Late Effects on Normal Tissue/Subjective, Objective, Management, Analytic) and Common Terminology Criteria Genitourinary toxicity scoring systems.

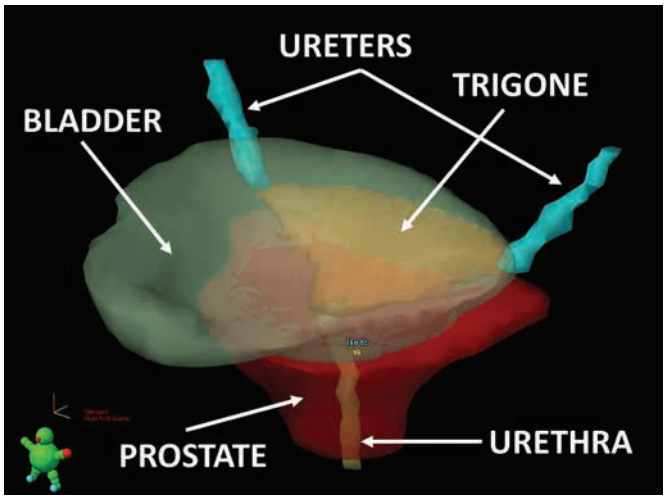

Fig. 1 - Description of bladder substructures.

These data are consistent with a very low alpha/beta ratio, a parameter describing the tissue sensitivity to fractionation. However, it must be emphasized that the confidence intervals of alpha/beta ratios that can be derived from modern practice observational clinical trials are very large, since in patients it is not possible to systematically span a wide range of fractionation schemes or prescribed doses. For this reason, the ultimate statement on bladder alpha/beta ratio will probably have to be based on new animal studies. These experiments still represent a necessary step for accurately determining the sensitivity of the bladder to fractionation.

Are there exceptionally sensitive and critical substructures in the bladder? Evidence of spatial effects

Some studies from the literature underlined the need to overcome the assumption that the urinary bladder is uniformly sensitive to radiation (26, 27, 31, 35, 36, 73). As a matter of fact, the bladder comprises several substructures which may have distinct radiobiological behaviors and sensitivities, leading to different impacts on distinct urinary symptoms (see Fig. 1 for a summary description of these structures). The main attempt of these studies was to identify specific bladder subregions associated with urinary toxicity after radiotherapy. This could have profound consequences for treatment planning optimization to reduce the toxicity risk.

Several published results (26, 27, 31, 35, 36, 73) converged in the identification of the trigone dose as strongly associated with worsening of symptoms and an increased risk of severe acute and late injury. The exact mechanisms controlling the trigone are still unclear; however, as this muscle is actively involved in sphincter opening, it is realistic to claim that its damage might elicit frequency, urgency and/or incontinence symptoms. Some trials also suggested the possible presence of a threshold effect at 2-Gy-equivalent doses of 80-82 Gy (31, 35).

The work by Yahya et al (36) also identified the dose to the anterior-inferior portion of the bladder surface as being strongly associated with the incidence of dysuria, hematuria, and worsening of symptoms as measured by IPSS.

All these findings point to the need for refined optimization of treatment planning based on the explicit definition of critical/sensitive bladder substructures and on specific dose constraints for each bladder portion.

Of course, also the dose received by the urethra may play a role: the currently available data do not allow to distinguish the relative contribution due to bladder and urethra irradiation. A major impact of urethra irradiation (mostly associated with urethral stenosis) is expected for very high dose schedules, as reported in brachytherapy series (74).

Does the individual patient matter? Clinical features as modulators of dose effects

Many recently published studies reported relevant patient-related features that are significantly associated with an increased risk of urinary toxicity. An extensive review of these studies can be found in references 51, 75 and 76. These clinical features act as individual dose-response modifying factors, making some patients more sensitive or resistant to radiation.

A first essential risk factor for urinary toxicity, consistently described by different trials, is the baseline urinary functionality (8, 13, 15, 44, 77, 78), with patients having an already impaired functionality being at higher risk of experiencing severe acute and late urinary toxicity. For this reason, an evaluation of the baseline situation should be mandatory before treatment planning, also considering the possibility of stricter dose limits for some patients.

Other patient-related characteristics have been emphasized as being associated with an increased risk of worsening of acute and late symptoms: previous transurethral resection of the prostate (8, 11, 16, 26, 44, 60) as well as smoking (30, 79-82), age (13, 30, 34, 44, 53, 62, 78), vascular comorbidities and use of cardiovascular drugs (34, 62, 78), diabetes (15, 62, 78, 79), and use of antihypertensive medication (30, 34). These last patient-related characteristics are indirect markers of possible damage to the microcirculation leading to impairment of tissue oxygenation, a key step in the repair of radiation-induced tissue damage. Table III presents details on patient-related features which were found to be associated with an increased risk of acute or late urinary toxicity.

All these patient-related factors should be combined to determine the dose to critical bladder structures when developing predictive models for urinary toxicity, in order to obtain tools which have the power to individualize treatment planning and optimization. Some examples are given in references 30, 34 and 62, and on the website of the Maastro Clinic, http://www.predictcancer.org/Main.php?page=UreProstateModel.

Coming to conclusions: what can we expect from the near future?

Although much remains to be understood and investigated, our knowledge of radiation-induced urinary toxicity, and of the main dosimetry and clinical factors involved in its appearance and persistence, has increased dramatically in recent years. The key success factor leading to these first steps can surely be found in the increased awareness of the

TABLE III - Summary of trials (modern series pertaining to patients treated with radical radiotherapy) highlighting a relationship between acute/late urinary toxicity and patient-related features

Patient-related features	Reference	Odds ratio/hazard ratio	Acute/late toxicity
Baseline urinary symptoms	Peeters et al 2005 (8)	2.2	Late
	Heemsbergen et al 2010 (26)	2.7	Late
	Barnett et al 2011 (77)	2.1-4.2^	Late
	Yahya et al 2015 (78)	2.1-3.6^	Late
	Wortel et al 2016 (13)	2.4	Late
	Jolnerovski et al 2017 (15)	2.4	Late
	Cozzarini et al 2017 (44)	2.4	Late
TURP	Peeters et al 2005 (8)	1.7	Late
	Fonteyne et al 2009 (11)	1.4	Late
	Heemsbergen et al 2010 (26)	3.6	Late
	De Langhe et al 2014 (60)	1.4	Late
	Byrne et al 2017 (16)	2.5	Late
	Cozzarini et al 2017 (44)	1.3-2.3^	Late
Smoking	Cozzarini et al 2015 (30)	2.0-4.0^	Acute
	Stankovic et al 2016 (79)	17.3	Acute
	Solanki et al 2013 (82)	1.5-3^	Late
	Steinberger et al 2015 (81)	1.8	Late
	Bagalà et al 2016 (80)	14.0	Late
Age	Cozzarini et al 2015 (30)	0.94*	Acute
	Palorini et al 2016 (34)	0.94-0.96*	Acute
	Ahmed et al 2013 (53)	1.45**	Late
	Mathieu et al 2014 (62)	1.06*	Late
	Yahya et al 2015 (78)	0.91-0.96^	Late
	Wortel et al 2016 (13)	1.62***	Late
	Cozzarini et al 2017 (44)	1.2*	Late
Vascular comorbidities/use of cardiovascular drugs	Palorini et al 2016 (34)	2.2	Acute
	Mathieu et al 2014 (62)	2.35-2.9^	Late
	Yahya et al 2015 (78)	4.8	Late
Diabetes	Mathieu et al 2014 (62)	4.0	Late
	Yahya et al 2015 (78)	6.0	Late
	Stankovic et al 2016 (79)	3.0	Late
	Jolnerovski et al 2017 (15)	2.0	Late
Use of antihypertensives	Cozzarini et al 2015 (30)	1.8	Acute
	Palorini et al 2016 (34)	1.6	Acute

TURP = transurethral resection of the prostate.
^ Depending on urinary symptom.
* Continuous variable in years.
** Dichotomized at 70 years.
*** Dichotomized at 68 years.

relevance of the problem, which affects a large fraction of the older population of high-income countries, where prostate cancer is endemic and where most patients diagnosed with prostate cancer receive radiotherapy treatment.

The continuous effort towards improving our ability to predict the risk of urinary toxicity should translate into refinement of our therapeutic approaches, aiming to reduce urinary toxicity while preserving the high rates of cure for these patients. The increasing availability of information from huge databases, also coming from large international collaborations and including standardized patient-reported outcome measurements, will further boost this relevant field of research in the coming years. This will allow continuing reduction of urinary side effects and the consequent improvement

of quality of life and reduced risk of patient regret about the choice of radiotherapy (83) in long-surviving prostate cancer patients.

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