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Patient-reported urinary incontinence after radiotherapy for prostate cancer: Quantifying the dose–effect

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ABSTRACT

Background and purpose: Urinary incontinence following radiotherapy (RT) for prostate cancer (PCa) has a relevant impact on patient's quality of life. The aim of the study was to assess the unknown dose–effect relationship for late patient-reported urinary incontinence (LPRUI).

Methods and materials: Patients were enrolled within the multi-centric study DUE01. Clinical and dosimetry data including the prescribed 2 Gy equivalent dose (EQD2) were prospectively collected. LPRUI was evaluated through the ICIQ-SF questionnaire filled in by the patients at RT start/end and therefore every 6 months. Patients were treated with conventional (74–80 Gy, 1.8–2 Gy/fr) or moderately hypo-fractionated RT (65–75.2 Gy, 2.2–2.7 Gy/fr) in 5 fractions/week with intensity-modulated radiotherapy. Six different end-points of 3-year LPRUI, including or not patient's perception (respectively, subjective and objective end-points), were considered. Multivariable logistic models were developed for each end-point.

Results: Data of 298 patients were analyzed. The incidence of the most severe end-point (ICIQ-SF > 12) was 5.1%. EQD2 calculated with alpha–beta = 0.8 Gy showed the best performance in fitting data: the risk of LPRUI markedly increased for EQD2 > 80 Gy. Previous abdominal/pelvic surgery and previous TURP were the clinical factors more significantly predictive of LPRUI. Models showed excellent performances in terms of goodness-of-fit and calibration, confirmed by bootstrap-based internal validation. When included in the analyses, baseline symptoms were a major predictor for 5 out of six end-points.

Conclusions: LPRUI after RT for PCa dramatically depends on EQD2 and few clinical factors. Results are consistent with a larger than expected impact of moderate hypo-fractionation on the risk of LPRUI. As expected, baseline symptoms, as captured by ICIQ-SF, are associated to an increased risk of LPRUI.

Radiotherapy (RT) is a highly effective option for localized prostate cancer (PCa). Thanks to the accurate tailoring of the dose distribution to the planning target volume (PTV), intensity-modulation (IMRT) combined with in-room image guidance (IGRT) allowed to both increase the delivered dose [1,2] and explore hypofractionated schedules [3,4]; dose escalation definitely led to an improved outcome, confirming the existence of an unequivocal dose–effect for PCa [5,6]. IMRT and IGRT were proved to limit gastro-intestinal (GI) toxicities [7] while urinary toxicity was not substantially affected; on the contrary, an increase of urinary symptoms was reported by several groups when escalating the total and/or daily dose [7–12]. Urgency and incontinence are among the most clinically relevant urinary symptoms: they may occur even years after the treatment and influence the patients' daily health-related quality of life (HRQoL), often permanently. Although the existence of a dose–effect for urinary incontinence is expected [9], it has never been quantified. Several reasons may explain this lack: first of all, the difficulty of collecting an objective, prospectively recorded, evaluation of incontinence in sufficiently large cohorts of patients. The rate of severe late incontinence ranges between 1 and 5% at 3–5 years after RT end, although higher incidences were reported with ultra-high doses and in the post-operative setting [10,11]; then, large series including patients receiving different doses are needed for a reliable quantification. Moreover, a thorough scoring requires a careful baseline assess-

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ment and prospective, longitudinal evaluations for years. In this context, the patient-reported assessment of incontinence, including the patient perception of its impact on HRQoL, should be preferred.

A multi-centric longitudinal cohort study (DUE01) aimed at developing predictive models of patient-reported urinary toxicity and erectile dysfunction is ongoing since 2010 [13]. It is based on the prospective collection of patient-reported toxicity data, clinical and 3D dose–volume information. Incontinence was prospectively assessed by the International Consultation on Incontinence Modular Questionnaire Short Form (ICIQ-SF [14]). The aim of current analysis was to quantify the dose–effect for the risk of 3-year late patient-reported urinary incontinence (LPRUI). The impact of clinical variables was also tested and incorporated into dose–effect relationships by multi-variable logistic models.

Materials and methods

The DUE01 study

The study enrolled patients with localized PCa between April 2010 and December 2014; patients treated post-operatively were not included. Detailed information on ethical issues, power sampling, enrollment criteria, contouring/planning procedures, data collection were previously reported [12,13]. Briefly, patients were treated with conventionally (1.8–2 Gy/fr) or moderately hypofractionated RT (2.2–2.7 Gy/fr) in 5 fractions/week. All patients were treated supine with empty rectum and comfortably full bladder. IGRT was used to set-up the patients in 80% of cases. The treatment of pelvic lymph nodes was at discretion of the treating center, being DUE01 an observational study.

Patient data and treatment

Incontinence was evaluated through the ICIQ-SF filled in by the patients at start/end of RT and every 6 months until 5 years of follow up. In the current analysis, patients were included if matched the following criteria:

(a) ICIQ-SF available both at baseline and at 36 months;
(b) at least two questionnaires available between 6 and 36 months after RT end.

At current analysis, 298 patients fulfilled these criteria; apart the baseline, the median number of questionnaires per patient was 5 (range: 2–6). The characteristics of the population are shown in Table 1. Patients were treated with IMRT in seven Institutions with conventional (CONV, 74–80 Gy, 1.8–2 Gy/fr, $n = 150$) or moderately hypo-fractionated RT (HYPO, 65–75.2 Gy, 2.2–2.7 Gy/fr, $n = 148$). The prescribed doses D were converted into 2 Gy equivalent doses (EQD2), according to the linear-quadratic model [15]:

$$EQD2 = D(\alpha/\beta + d)/(\alpha/\beta + 2) \quad (1)$$

where d is the daily dose and α/β was set equal to 0.8, 3 and 5 Gy (EQD2(0.8), EQD2(3) and EQD2(5)), according to values reported in the literature [15,16].

ICIQ based "objective" and "subjective" end-points

The ICIQ-SF [14] includes six questions (see Supplementary material S1): questions 1 and 2 (dealing with personal data) and question 6 (describing when the patient experiences leakage) were not here considered. Questions 3 and 4 (ICIQ3, ICIQ4) focus on the frequency of leakage and on the amount of loss respectively. Question 5 (ICIQ5) concerns the interference of these symptoms with normal daily life as perceived by the patient. The total score (ICIQ3 − ICIQ4 + ICIQ5) ranges between 0 (good) and 21 (bad) and includes the patient's perception: due to this, we defined as "subjective" the end-points based on the overall score, and "objective" the end-points only related to ICIQ3 and ICIQ4. The following six end-points of LPRUI were considered:

(a) Subjective, severe: ICIQ-SF > 12 at least once between 6 and 36 months.
(b) Subjective, mild to severe: ICIQ-SF > 5 at least once between 6 and 36 months.
(c) Subjective, mild to severe and persistent: average ICIQ-SF > 5 between 6 and 36 months.
(d) Objective, persistently daily frequency: ICIQ3 > 2 at least once between 6 and 24 months never recovered (average ICIQ3 > 2 after the event).
(e) Objective, daily frequency: ICIQ3 > 2 at least once between 6 and 36 months.
(f) Objective, moderate to severe: ICIQ3 + ICIQ4 > 4 at least once between 6 and 36 months.

Table 1
Summary of patient characteristics. Data are presented as counts (percentages in parenthesis) for categorical variables, and as median values (interquartile range in parenthesis) for the continuous ones.

Age (y)	71 (67–74)
BMI (kg/m^2)	26 (24–29)
PSA (ng/ml)	6.6 (5.2–10.1)
Gleason score:	
<7	109
=7	136
>7	39
n.a.	14
T stage:	
T1	161
T2	100
T3-4	24
TX	10
Diabetes	43 (14%)
Cardiovascular disease	69 (23%)
Hypercholesterolemia	15 (5%)
Urological disease	16 (5%)
Anti-hypertensive	154 (52%)
Anticoagulants	21 (7%)
Cardiovascular drugs	90 (30%)
Antiaggregants	85 (29%)
Antidepressive	12 (4%)
TURP	30 (10%)
Previous abdominal surgery	138 (46%)
Smoke	41 (14%)
Alcohol	153 (51%)
Hormone therapy before/during RT	167 (56%)
Hormone therapy after RT	166 (56%)
Prescribed dose (Gy)	HYPO ($n = 148$): 73.6 (70–74.2) CONV ($n = 150$): 78 (76–78)
Daily dose (Gy/fr)	HYPO: 2.55 (2.5–2.65) CONV: 2.0 (2.0–2.0)
CTV volume (cc)	51 (34–66)
PTV volume (cc)	131 (93–170)
Bladder volume @ planning CT (cc)	188 (123–327)
Pelvic lymph node irradiation	113 (38%)
Seminal vesicles irradiation	236 (79%)

(BMI = body mass index; TURP = transurethral resection of the prostate; CTV = clinical target volume; PTV = planning target volume).

Dose–effect quantification and development of Multi-variable models

The association with each of the six end-points was first tested for EQD2(0.8), EQD2(3) and EQD2(5) by univariable logistic analysis: the value of likelihood was used to assess what EQD2 better fitted the data. The following, prospectively recovered, clinical variables were also considered in the analyses: hormonal therapy before/during RT, hormonal therapy after RT, pelvic lymph-nodes irradiation, seminal vesicles irradiation, age (years), body-mass-

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