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35

36 Abstract

37 **Objective:** To analyze late urinary toxicity after prostate cancer radiotherapy (RT):

38 symptom description and identification of patient characteristics or treatment

39 parameters allowing for the generation of nomograms.

40 Methods: 965 patients underwent RT in seventeen French centers for localized

41 prostate cancer. Median total dose was 70 Gy (range, 65-80 Gy), using different

42 fractionations (2 or 2.5 Gy/day) and techniques. Late urinary toxicity and the

43 corresponding symptoms (urinary frequency, incontinence, Dysuria/decreased

44 stream and hematuria) were prospectively assessed in half of the patients using the

45 LENTSOMA classification. Univariate and multivariate Cox regression models

46 addressed patient or treatment-related predictors of late urinary toxicity (\geq grade 2).

47 Nomograms were built up and their performance was assessed.

48 **Results :** The median follow-up was 61 months. The 5-year (≥grade 2) global urinary

49 toxicity, urinary frequency, hematuria, dysuria and urinary incontinence rates were:

50 15%, 10%, 5%, 3% and 1%, respectively. The 5-year (\geq grade 3) urinary toxicity rate

51 was 3%. The following parameters significantly increased the 5 year risk of global

52 urinary toxicity (\geq grade 2): anticoagulant treatment (RR=2.35), total dose (RR=1.09),

age (RR=1.06). Urinary frequency was increased by the total dose (RR=1.07) and

54 diabetes (RR=4). Hematuria was increased by anticoagulant treatment (RR=2.9).

55 Dysuria was increased by the total dose (RR=1.1). Corresponding nomograms and

their calibration plots were generated. Nomogram performance should be validatedwith external data.

58 Conclusions: The first nomograms to predict late urinary toxicity but also specific
 59 urinary symptoms after prostate RT were generated, contributing to prostate cancer
 60 treatment decision.

61 **1. Introduction**

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Radical prostatectomy (RP) and radiotherapy (RT) are cornerstones of localized 63 64 prostate cancer treatment, leading to relatively similar results in terms of local control ¹. However, the side effects of both are different, mainly concerning the urinary 65 adverse events. If the intensity of this toxicity after RT is relatively well-reported in the 66 literature, the description of the symptoms corresponding to this toxicity is often 67 68 limited. Moreover, the patient and/or treatment factors related to each of the side effects are not well known. Their identification is crucial. These factors could be used 69 70 to generate urinary toxicity predictive tools (like nomograms), to guide the physician 71 in deciding the treatment and to inform the patient, in this context of different therapeutic alternatives. To identify which radiation parameters increase toxicity is 72 73 essential in understand how to decrease toxicity, in particular due to new highly-74 conformal radiotherapy techniques, such as Intensity Modulated Radiation Therapy 75 (IMRT) and Image Guided Radiation Therapy (IGRT).

76 These new techniques allow for an increase of the dose in the prostate considering the strong dose-effect relationship for local control², while limiting the dose in the 77 78 bladder and the rectum. Their part in decreasing urinary toxicity has not, however, 79 been clearly shown. If the relationship between dose-volume and toxicity has been consistently demonstrated for the rectum, it remains unclear for the bladder ^{3, 4}. 80 81 Moreover, hypofractionated RT may be more efficient in eradicating prostate 82 adenocarcinoma, but the impact of such modified fractionation on toxicity has not been well-established. 83

84 If nomograms have already been published to predict rectal bleeding and the risk of 85 fecal incontinence ^{5, 6}, to our knowledge no tools have as yet been developed to 86 predict urinary toxicity.

We thus analyzed a large group of patients having received prostate cancer RT using different radiation techniques, total doses and fractionations, to accurately quantify and describe late urinary toxicity, identify related risk factors and propose nomograms.

- 91
- 92 **2. Material and methods**
- 93
- 94 2.1. Patient inclusion criteria
- 95

96 Records from 965 patients who received definitive radiotherapy for localized prostate 97 adenocarcinoma were analyzed. Data were prospectively collected from 470 patients 98 treated in 17 French institutions within two randomized studies: GETUG 06 99 (comparing 70 Gy to 80 Gy) ⁷ and STIC-IGRT (testing IGRT) ⁸, and retrospectively 100 from 495 patients treated in two of them. All patients had a biopsy-proven 101 adenocarcinoma of the prostate. Pretreatment workup included a CT scan and a 102 bone scan.

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104 **2.2.** Patient and tumor characteristics

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The following data were extracted from each randomized database: age, medical and surgical history (prior abdominal surgery, prior transurethral resection of prostate, anticoagulant treatment, diabetes, hypertension, coronary insufficiency) and tumor characteristics (T stage, Gleason score, pretreatment PSA). Patients were staged by digital rectal examination according to the 1992 American Joint Committee on 111 Cancer staging system ⁹. Patients were classified into the three prognostic risk 112 groups defined by D'Amico ¹. Patient and tumor characteristics are presented in 113 Table 1.

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115 **2.3. Treatment characteristics**

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117 The target volume comprised the prostate only in the low risk group (16%), the 118 prostate and the seminal vesicles in the other risk groups. The pelvic lymph nodes 119 were not treated in the two randomized studies, but may have been treated for high 120 risk patients of the two institutions (not treated in the randomized study) (9%). The 121 median total dose of the prostate was 70 Gy (ranging from 65 Gy to 80 Gy), the 122 seminal vesicles receiving 46 Gy, and the pelvic lymph nodes also 46 Gy, if treated. 123 Dose per fraction was 2 Gy/day, 5 fractions/week for 69% of patients, or 2.5 Gy/day, 124 4 fractions/week for 31% of patients.

The radiation technique was 3D conformational for the vast majority of patients (85%) and 2D for 15% of the patients, depending on the treatment period. Intensity Modulated RT (IMRT) and Image Guided RT (IGRT) have been more recently used in patients receiving 80 Gy. Among the 41% of the patients having received 80 Gy, the technique was a standard 3D conformal RT for 63%, IMRT only for 18% and IMRT combined with IGRT in 19%.

The 3D radiation technique was carried out following the French GETUG group recommendations, as previously reported ⁷. Patients underwent simulation and treatment in the supine position. Target volume and organs at risk (bladder, rectum and femoral heads) were delineated on CT slices. A bladder wall was generated with a thickness of 7 mm from the external manually-delineated bladder contour according GETUG recommandations. The planning target volume (PTV) was calculated by adding a 10-mm margin in all directions except in the posterior where a 5-mm margin was considered. The dose-volume histogram had to respect the GETUG constraints ⁷. The following bladder dosimetric data were analyzed: volume of the bladder wall, Dmax (maximal dose received in the bladder), D25 (minimal dose received in 25% of the bladder wall) and D50 (minimal dose received in 50% of the bladder wall).

Androgen deprivation therapy was given to 23% of the patients, all presenting a highrisk cancer.

144 Details of treatment characteristics are presented in Table 1.

145

146 **2.4.** Follow up and toxicity grading

147

148 According to the protocol of surveillance, patients were evaluated every three months 149 for a year and every 6 months thereafter Late urinary toxicity was defined as events 150 occurring more than six months after the beginning of RT. To determine the severity 151 and incidence of main late urinary complaints, records were prospectively extracted 152 from trials database or retrospectively from physicians' reports, at each follow-up 153 visit. Urinary complaints were classified according to the LENTSOMA morbidity 154 scoring system into four categories of symptoms: urinary frequency, dysuria, 155 (Table 2). Dysuria and decreased stream were incontinence and hematuria 156 considered as a single symptom. The analyses were performed for late urinary 157 toxicity and for each of the symptoms, all being considered if \geq grade 2.

158

159 **2.5.** Statistical analysis

160

161 The impact of the following parameters on late urinary toxicity (≥ grade 2) was tested
162 at the 5-years mark:

Patient parameters: age, diabetes (types 1 and 2), anticoagulant treatment
 (vitamin K antagonist or antiplatelet drug), prior abdominal or pelvic surgery,
 prior transurethral resection of prostate, hypertension, coronary insufficiency;

- Tumor parameters: Gleason Score, T stage, prognostic group (D'amico);

Treatment parameters: RT technique (2D technique, 3DConformational technique, with or without IMRT/IGRT), total dose and fractionation, target volume, dosimetric bladder parameters (volume of the bladder wall, maximal dose, D25, D50) and androgen deprivation.

171 The data-recording modality (prospective versus retrospective collection) was 172 verified as having no significant impact on the risk of toxicity.

173 The Kaplan-Meier method was used to calculate cumulative incidences of late 174 urinary toxicity events (\geq grade 2). The differences between the survival curves 175 were assessed using the log-rank test. Relationships between late urinary toxicity 176 and patient, tumor or treatment parameters were first analyzed using Cox 177 proportional hazard regression at univariate level. Multivariate analyses, including 178 covariates statistically significant in univariate analysis, were carried out using the 179 Cox proportional hazards model. The 5-year late urinary toxicity events were 180 analyzed using logistic regression at univariate and multivariate levels. A p-value 181 \leq 0.05 was considered statistically significant. Nomograms to predict 5-year late 182 urinary toxicity and specific symptoms were built up according to the logistic 183 model. To assess nomogram performance, a nonparametric fit of the predicted 184 probability as regards the actual observed probability was made for each 185 nomogram. The analyses were performed using the SPSS V18 (Chicago, IL) and

186 R with the rms package. Non-parametric tests were used to compare the187 distribution of the parameters between different groups of treatment.

188

189 **3. Results**

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191 The median follow-up was 61 months (range 6-206).

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193 **3.1.** Late urinary toxicity: global quantification and symptom description

194

195 Among the 965 patients, 183 events of late urinary toxicity grade 2 or greater were 196 reported. Among them, only 14 % were toxicity grade 3 or 4. Ninety-two (50%) 197 corresponded to an increase in urinary frequency, 36 (20%) to dysuria, and 48 (26%) 198 to hematuria. Only seven consisted of urinary incontinence grade 2 or greater. The 5-199 year and 10-year rates of grade 2 or higher urinary toxicity, urinary frequency, 200 hematuria, dysuria and urinary incontinence were: 15% (95%CI:12%-18%) and 24% 201 (95%CI:19%-29%), 10% (95%CI: 8%-12%) and 15% (95%CI:11%-19%), 5% (95% 202 CI: 4-6%) and 8% (95%CI:5%-11%), 3% (95%CI: 2%-4%) and 8% (95%CI:4%-12%), 203 and 1% (95%CI: 0%-2%) and 2% (95%CI:0%-4%), respectively. Figure 1 presents 204 cumulative incidence of global late urinary toxicity and the corresponding symptoms 205 (≥ grade 2). The 5 and 10-year rates of grade 3 or higher global urinary toxicity were 206 3% (95%CI: 2%-4%) and 7% (95%CI:5%-9%).

207

208 **3.2.** Nomograms to predict five-year late toxicity

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210 In multivariate analysis, the following pre-planning parameters significantly positive

associated to the 5-year risk of urinary toxicity: anticoagulant treatment (RR=2.35),
total dose (RR=1.09), age (RR=1.06), D25 (RR=1.03), and Dmax (RR=1.1) received
by the bladder (Table 3). Nomogram including pre-treament factors to predict 5-year
risk of global late urinary toxicity (and its calibration plot) is presented in Figure 2.

The 5-year risk of urinary frequency was related to total dose (RR=1.07) and diabetes (RR=4). For dysuria, the total dose was the only significant factor (RR=1.1) (Table 3). Figures 3 and 4 present nomograms to predict the 5-year risk of these urinary symptoms. The 5-year risk of hematuria was significantly increased by anticoagulant treatment (RR = 2.9)

220

4. Discussion

222 We showed that the incidence of late urinary toxicity symptoms continuously 223 increases after RT, reaching a rate of 24% and 7% at 10 years, for more than grade 224 2 and grade 3 urinary toxicity, respectively. These rates appear relatively similar to 225 those previously observed after RT⁷. Urinary toxicity events may occur late after RT, 226 later than those observed for late gastro-intestinal toxicity which generally reaches a plateau at three years after RT¹⁰. A longer follow-up is consequently required to 227 properly estimate late urinary toxicity ¹⁰. Comparing the risk of urinary toxicity after 228 229 different treatments should therefore carefully consider the same follow-up. Late 230 urinary toxicity symptoms are mainly characterized by urinary frequency (50% of all 231 events) and, to a lesser extent, by dysuria and hematuria. Incontinence is very rare 232 (<2% at 10 years).

We identified age, diabetes and anticoagulant treatment as factors increasing the risk of late urinary toxicity by multivariate analysis. Diabetes has already been reported as a strong predictor of late urinary toxicity in prostate cancer radiotherapy ¹¹. The

236 fact that anticoagulation or antiplatelet agents increase the risk of late urinary toxicity 237 after prostate cancer radiotherapy has rarely been reported, even if this association concerns the risk of late rectal toxicity ^{12, 13}. However, anticoagulation has been 238 already associated with gross hematuria in the whole population and could be an 239 240 independent risk factor of urinary complaints whatever a radiation is performed. Age and diabetes have been previously associated with urinary side effects after radical 241 prostatectomy, especially urinary incontinence ^{14, 15}. Thus, their implications in urinary 242 243 toxicity after RT should not be underestimated in treatment decision.

244 We found a strong dose-effect relationship in urinary toxicity (global toxicity, urinary frequency and dysuria). Most of the randomized studies comparing a "standard" dose 245 246 (68 to 70 Gy) to a higher one (76 to 80 Gy) did not demonstrate such a significant increase in late urinary toxicity ¹⁶⁻¹⁹. However, in a large group of patients who 247 248 received a dose escalation with 3D-CRT/IMRT, Zelefsky et al reported a significant increase of genitourinary (GU) toxicities after 10 years in patients who received 249 higher doses ²⁰. More recently, the GETUG 06 randomized trial reported such an 250 increase, when escalating the dose from 70 Gy to 80 Gy⁷. These differences can be 251 252 explained by several reasons. The first one is the lack of follow-up. Indeed, the initial 253 MDACC report that compared 78Gy to 70Gy did not show a significant difference in late GI toxicity, while it was found with a longer follow-up¹⁶. Secondly, studies might 254 255 be different in terms of their treatment scheme (dose, target volume, technique), 256 patient characteristics and grading scale. Finally, urinary toxicity might be more 257 related to patient risk factors than dose parameters. The lack of correlation between 258 dose distribution (dose-volume histogram) and urinary toxicity may also be due to the 259 large bladder volume variation occurring at the planning stage and at the different

fractions, so that the planned dose distribution does not represent the actualdelivered dose to the bladder.

262 A moderate hypofractionned schedule (2.5 Gy/fr) in our series did not increase late urinary toxicity. These results are concordant with contemporary studies ²¹ and 263 264 emphasize the interest of hypofractionated schedule in prostate cancer radiotherapy. 265 IMRT and IGRT aim at increasing local control by allowing dose escalation, while 266 reducing toxicity by sparing normal surrounding tissues. Compared to "standard" 3D 267 conformal technique, IMRT clearly reduces the risk of long-term rectal toxicity and bowel dysfunction ^{20, 22, 23}. However, IMRT fails to decrease late urinary toxicity in 268 269 most studies, as in the present one. Late urinary toxicity could even be partly due to prostatic urethra lesions ²⁴, and modern techniques such as IMRT combined with 270 271 IGRT still do not allow for the preservation of this area. A recent non-randomized 272 study of Zelefsky et al reported however that, with a median follow-up of 2.8 years 273 and a high dose (86.4 Gy) delivered to the prostate by IMRT, patients treated with 274 IGRT (using fiducials) experienced significantly less urinary toxicity than non-IGRT 275 treated patients²⁵.

276 Based on this predictive factors, we propose the first nomograms to predict late 277 urinary toxicity after radiation therapy. Indeed, many treatments now provide long 278 term survival and the decision of the patient concerning his own treatment is mainly 279 based on expected side effects. These nomograms have been built up according to 280 the pre-treatment parameters, available before any CT simulation, in order to help 281 physician and patient in the decision concerning the different prostate cancer 282 treatments. Consequently, we believe that the corresponding nomograms concerning 283 toxicity after radical prostatectomy should be proposed.

284 One limitation of our study is that both prospective and retrospective data (from 2

institutions) were used to assess our nomograms. However, the effect of data being
retrospectively collected was not found to significantly impact on toxicity risk.
Furthermore, a large number of patients was necessary to identify a maximum
number of reliable toxicity predictors. Finally, nomogram performance has been
validated within our series but should be also confirmed using external data.

290

5. Conclusions

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We were able to identify several parameters increasing the risk of urinary toxicity after prostate cancer radiotherapy. The first nomograms to predict global late urinary toxicity and corresponding symptoms were generated, resulting in new tools for patient management and treatment decision, particularly between RT and surgery.

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412 Figure legends

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415 Figure1: Incidence of global and by symptoms late urinary toxicity (≥grade 2)



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419 Figure 2: Five-year risk of global late urinary toxicity grade \geq 2 : nomogram and

420 calibration plot

421 Calibration plot assessing the nomogram performance by a nonparametric fit of the

422 predicted probability versus the actual observed probability.

423



424



426 calibration plot

- 427 Calibration plot assessing the nomogram performance by a nonparametric fit of the
- 428 predicted probability versus the actual observed probability.



Predicted probability of 5-year urinary retention grade ≥ 2

429

- 430 Figure 4: Five-year risk of dysuria grade \geq 2: nomogram and calibration plot
- 431 Calibration plot assessing the nomogram performance by a nonparametric fit of the
- 432 predicted probability versus the actual observed probability.
- 433
- 434

Table 1: Patient, tumor and treatment characteristics

Patient characteristics				
Number of pati	ients		965	
Mean age,.yr (68 (45-83)			
Diabetes*	7%			
Anticoagulant	Anticoagulant treatment**			
Prior abdomina	al or pelvic su	rgery	34%	
Prior transuret	ral resection o	of prostate	6%	
Hypertension			19%	
Coronary insuf	9%			
		Tumor characteristics	I	
PSA, ng/ml (ra	nge)		15 (0-133)	
		<7	53%	
Gleason Score	;	7	38%	
		>7	9%	
T stage		T1	25%	
T stage		T2	62%	
		13	13%	
Prognostic gro	up of risk	Low	18%	
(D'amico) :		Intermediate	51%	
High 31%				
		Radiotherapy technique		
2D Technique			15%	
« Standard » 3D Conformational (without IMRT)			66%	
IMRT (without	IGRT)		7%	
IGRT (with IMF	RT)		12%	
	Pi	rescribed dose and fractionation		
65 Gy	2.5Gy. 4/w		15%	
70.01	2.5Gy. 4/w	16%		
70 Gy	2Gy. 5/w	28%		
80Gy	2Gy. 5/w			
		Target volume		
Prostate only 16				
Prostate + Seminal vesicles 75%				
Prostate + Seminal vesicles + Pelvic lymph nodes 9%				

Dosimetric parameters					
	Volume (cc) +/- SD	70,7 +/- 39,5			
Bladder	Dmax(Gy) +/- SD	75,8 +/- 4,7			
(wall***)	D25 (Gy) +/- SD	64,8 +/- 11,6			
	D50 (Gy) +/- SD	43,1 +/- 15,2			
	PTV prostate and SV (cc) +/- SD	234,5 +/- 60,9			
Target	PTV prostate only (cc) +/- SD	174,2 +/- 55,6			
	V95 (%)+/- SD	93,1 +/- 10,8			
Androgen deprivation (concomitant and adjuvant) 23%					

437 438

439 Yr: year, * type 1 or 2, ** vitamin K antagonist and antiplatelet drugs, W: week, SD:

440 Standard Deviation, ***thickness of bladder wall = 7mm, Dmax: maximum dose, D25:

441 minimal dose received in 25% of the bladder wall volume, D50: minimal dose

received in 50% of the bladder wall volume, PTV: planning target volume, V95:

volume of the prostate-PTV (in %) receiving 95% of the prescribed dose.

Table 2: LENTSOMA grading scale (Urinary symptoms)
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	grade I	grade II	grade III	grade IV
Subjective				
Dysuria	occasional and minimal	intermittent and tolerable	persistent and intense	refractory and
				excruciating
Decreased	occasionally weak	intermittent	persistent but incomplete	complete obstruction
stream			obstruction	
Frequency	3–4-h intervals (6–8/day)	2–3-h intervals (9–12/day)	1–2-h intervals (13–24/day)	hourly (>24/day)
Hematuria	occasional	intermittent	persistent with clot	refractory
Incontinence	< weekly episodes	< daily episodes	pads/undergarments/day	refractory
Management				
Dysuria	occasional, nonnarcotic	regular nonnarcotic	regular narcotic	surgical intervention
Decreased		< 1/day self catheterization	dilatation or TUR, > 1/day self	permanent catheter,
stream			catheterization	surgical intervention
Frequency		occasional antispasmodic	regular narcotic	cystectomy
Hematuria	alkalization iron therapy	single transfusion or	frequent transfusions or	surgical intervention
		cauterization	coagulations	
Incontinence	occasional use of	intermittent use of	regular use of incontinence	catheterization
	incontinence pads	incontinence pads	pads or self	permanent catheter

Table 3: Patient, tumor and treatment factors related to five year risk of late urinary toxicity and corresponding symptoms

	Late urinary toxicity	inary toxicity Urinary f		Irinary frequency		Hematuria		Dysuria	
Factors		р		р		р		р	
	RR (95.0% CI)	value	RR (95.0% CI)	value	RR (95.0% CI)	value	RR (95.0% CI)	value	
Anticoagulant	2 35 (1 33 - 4 14)	<0.01	_	_	2 89 (1 29 - 6 46)	0.01	_	_	
treatment	2.00 (1.00 - 4.14)	\$0.01			2.00 (1.20 0.40)				
Total dose	1.09 (1.05 - 1.14)	<0.01	1.07 (1.02 - 1.13)	0.01	-	-	1.10 (1.02 - 1.17)	0.01	
Diabetes	-	-	4.00 (1.42 - 11.27)	0.01	-	-	-	-	
D25	1.03 (1.00-1.06)	0.04	-		-	-	-	-	
Dmax	1.10 (1.04-1.17)	<0.01	-		-	-	-	-	
Age	1.06 (1.01-1.11)	0.02	-		-	-	-	-	

(multivariate regression logistic analysis)

CI: confidence interval, RR: relative risk, p value ≤ 0.05 was considered statistically significant. D25: minimal dose received in 25% of the bladder wall volume.

Following parameters have been tested in the model: age, diabetes, anticoagulant treatment, prior abdominal surgery, prior

transurethral resection of prostate, hypertension, coronary insufficiency, gleason score, T stage, prognostic group of risk (D'amico),

RT technique (2D, Conformational 3D with or without IMRT/IGRT), total dose and fractionation, target volume, dose received by the bladder (maximal dose, D25, D50), and androgen deprivation.