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1 **Nomograms to predict late urinary toxicity after prostate cancer radiotherapy**

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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 (\geq 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),

53 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

56 their calibration plots were generated. Nomogram performance should be validated

57 with 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**

62

63 Radical prostatectomy (RP) and radiotherapy (RT) are cornerstones of localized
64 prostate cancer treatment, leading to relatively similar results in terms of local control
65 ¹. However, the side effects of both are different, mainly concerning the urinary
66 adverse events. If the intensity of this toxicity after RT is relatively well-reported in the
67 literature, the description of the symptoms corresponding to this toxicity is often
68 limited. Moreover, the patient and/or treatment factors related to each of the side
69 effects are not well known. Their identification is crucial. These factors could be used
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
72 therapeutic alternatives. To identify which radiation parameters increase toxicity is
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
77 the strong dose-effect relationship for local control ², while limiting the dose in the
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
80 consistently demonstrated for the rectum, it remains unclear for the bladder ^{3, 4}.
81 Moreover, hypofractionated RT may be more efficient in eradicating prostate
82 adenocarcinoma, but the impact of such modified fractionation on toxicity has not
83 been well-established.

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.

87 We thus analyzed a large group of patients having received prostate cancer RT using
88 different radiation techniques, total doses and fractionations, to accurately quantify
89 and describe late urinary toxicity, identify related risk factors and propose
90 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.

103

104 ***2.2. Patient and tumor characteristics***

105

106 The following data were extracted from each randomized database: age, medical and
107 surgical history (prior abdominal surgery, prior transurethral resection of prostate,
108 anticoagulant treatment, diabetes, hypertension, coronary insufficiency) and tumor
109 characteristics (T stage, Gleason score, pretreatment PSA). Patients were staged by
110 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.

114

115 **2.3. Treatment characteristics**

116

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.

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

131 The 3D radiation technique was carried out following the French GETUG group
132 recommendations, as previously reported ⁷. Patients underwent simulation and
133 treatment in the supine position. Target volume and organs at risk (bladder, rectum
134 and femoral heads) were delineated on CT slices. A bladder wall was generated with
135 a thickness of 7 mm from the external manually-delineated bladder contour according

136 GETUG recommendations. The planning target volume (PTV) was calculated by
137 adding a 10-mm margin in all directions except in the posterior where a 5-mm margin
138 was considered. The dose-volume histogram had to respect the GETUG constraints
139 ⁷. The following bladder dosimetric data were analyzed: volume of the bladder wall,
140 Dmax (maximal dose received in the bladder), D25 (minimal dose received in 25% of
141 the bladder wall) and D50 (minimal dose received in 50% of the bladder wall).
142 Androgen deprivation therapy was given to 23% of the patients, all presenting a high
143 risk 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 incontinence and hematuria (Table 2). Dysuria and decreased stream were
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 (\geq grade 2) was tested
162 at the 5-years mark:

- 163 - Patient parameters: age, diabetes (types 1 and 2), anticoagulant treatment
164 (vitamin K antagonist or antiplatelet drug), prior abdominal or pelvic surgery,
165 prior transurethral resection of prostate, hypertension, coronary insufficiency;
- 166 - Tumor parameters: Gleason Score, T stage, prognostic group (D'amico);
- 167 - Treatment parameters: RT technique (2D technique, 3DConformational
168 technique, with or without IMRT/IGRT), total dose and fractionation, target
169 volume, dosimetric bladder parameters (volume of the bladder wall, maximal
170 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 ≤ 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 the
187 distribution of the parameters between different groups of treatment.

188

189 **3. Results**

190

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

192

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 (\geq 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***

209

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

211 associated to the 5-year risk of urinary toxicity: anticoagulant treatment (RR=2.35),
212 total dose (RR=1.09), age (RR=1.06), D25 (RR=1.03), and Dmax (RR=1.1) received
213 by the bladder (Table 3). Nomogram including pre-treatment factors to predict 5-year
214 risk of global late urinary toxicity (and its calibration plot) is presented in Figure 2.
215 The 5-year risk of urinary frequency was related to total dose (RR=1.07) and
216 diabetes (RR=4). For dysuria, the total dose was the only significant factor (RR=1.1)
217 (Table 3). Figures 3 and 4 present nomograms to predict the 5-year risk of these
218 urinary symptoms. The 5-year risk of hematuria was significantly increased by
219 anticoagulant treatment (RR = 2.9)

220

221 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
227 plateau at three years after RT¹⁰. A longer follow-up is consequently required to
228 properly estimate late urinary toxicity¹⁰. Comparing the risk of urinary toxicity after
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).

233 We identified age, diabetes and anticoagulant treatment as factors increasing the risk
234 of late urinary toxicity by multivariate analysis. Diabetes has already been reported
235 as a strong predictor of late urinary toxicity in prostate cancer radiotherapy¹¹. 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
238 concerns the risk of late rectal toxicity ^{12, 13}. However, anticoagulation has been
239 already associated with gross hematuria in the whole population and could be an
240 independent risk factor of urinary complaints whatever a radiation is performed. Age
241 and diabetes have been previously associated with urinary side effects after radical
242 prostatectomy, especially urinary incontinence ^{14, 15}. Thus, their implications in urinary
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
245 frequency and dysuria). Most of the randomized studies comparing a “standard” dose
246 (68 to 70 Gy) to a higher one (76 to 80 Gy) did not demonstrate such a significant
247 increase in late urinary toxicity ¹⁶⁻¹⁹. However, in a large group of patients who
248 received a dose escalation with 3D-CRT/IMRT, Zelefsky et al reported a significant
249 increase of genitourinary (GU) toxicities after 10 years in patients who received
250 higher doses ²⁰. More recently, the GETUG 06 randomized trial reported such an
251 increase, when escalating the dose from 70 Gy to 80 Gy ⁷. These differences can be
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
254 late GI toxicity, while it was found with a longer follow-up¹⁶. Secondly, studies might
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

260 fractions, so that the planned dose distribution does not represent the actual
261 delivered dose to the bladder.

262 A moderate hypofractionated schedule (2.5 Gy/fr) in our series did not increase late
263 urinary toxicity. These results are concordant with contemporary studies ²¹ and
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
268 bowel dysfunction ^{20, 22, 23}. However, IMRT fails to decrease late urinary toxicity in
269 most studies, as in the present one. Late urinary toxicity could even be partly due to
270 prostatic urethra lesions ²⁴, and modern techniques such as IMRT combined with
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

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

290

291 **5. Conclusions**

292

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

297

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299

300 **References**

301

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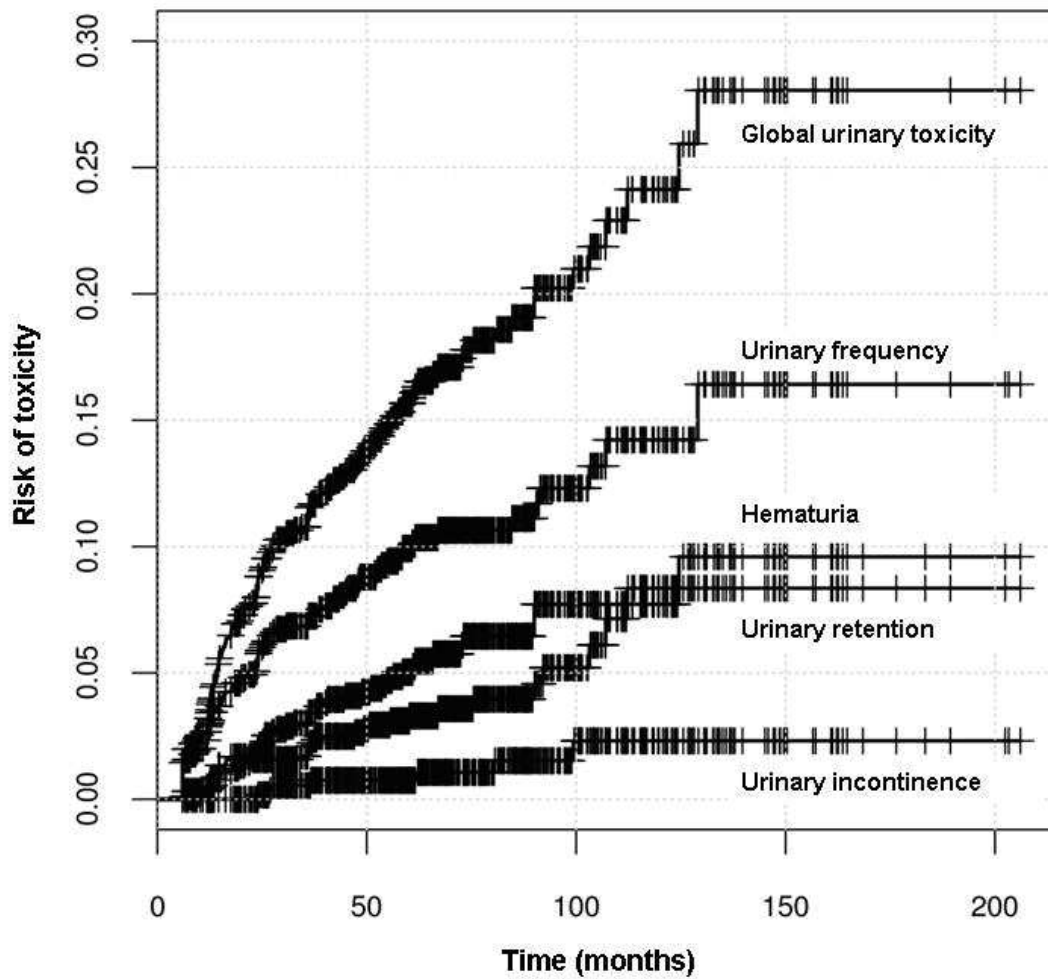
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412 **Figure legends**

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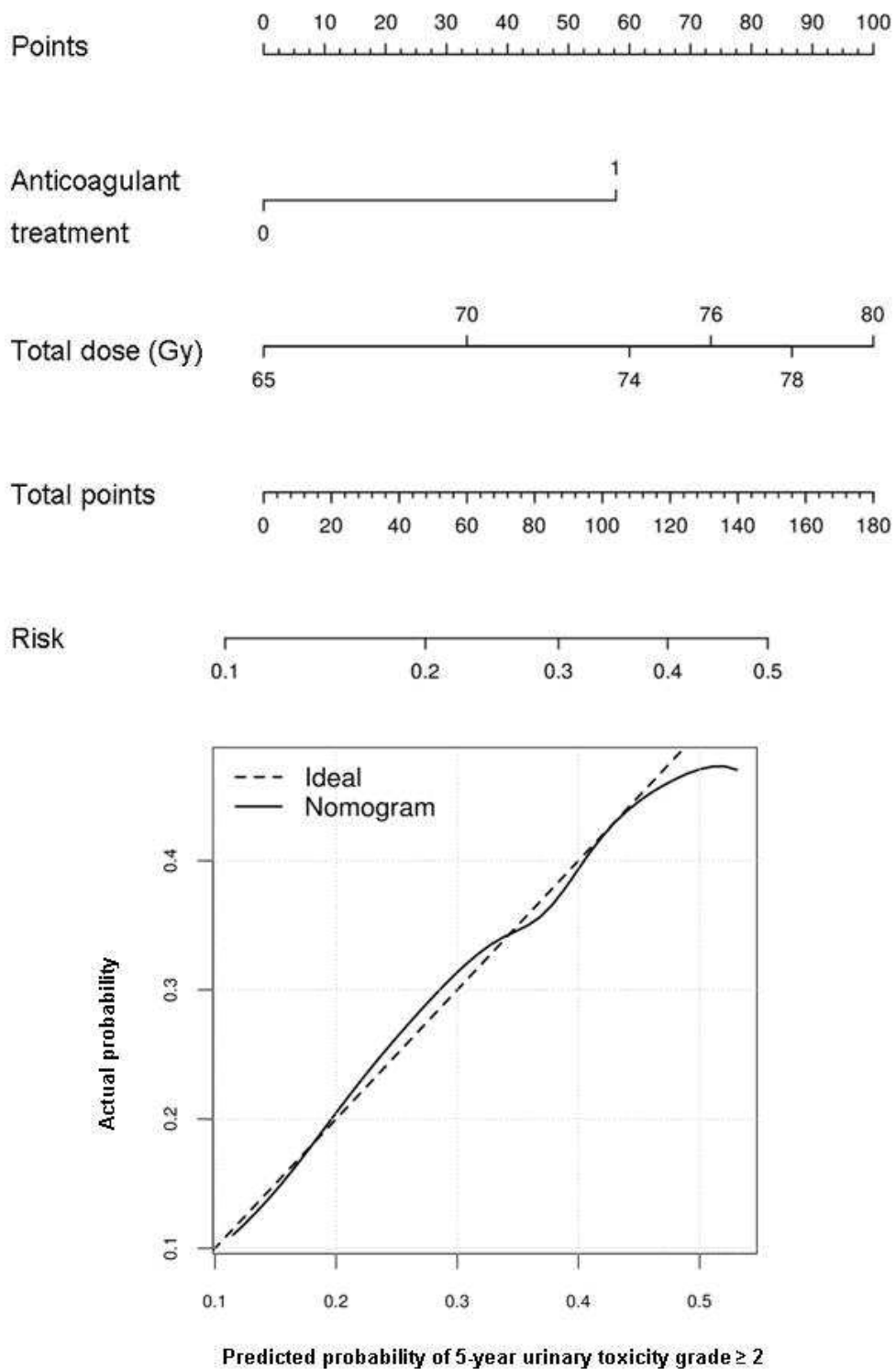


414

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

416 **according to LENTSOMA classification**

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418

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

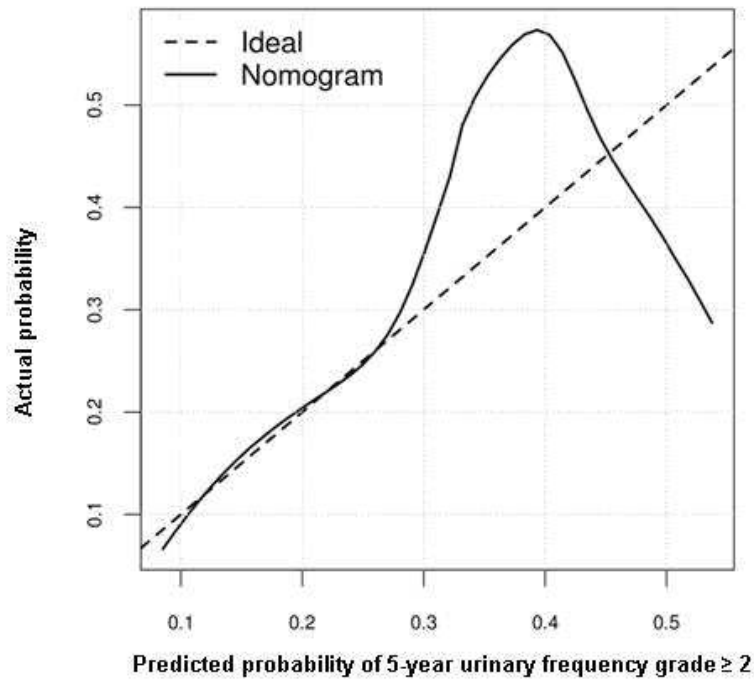
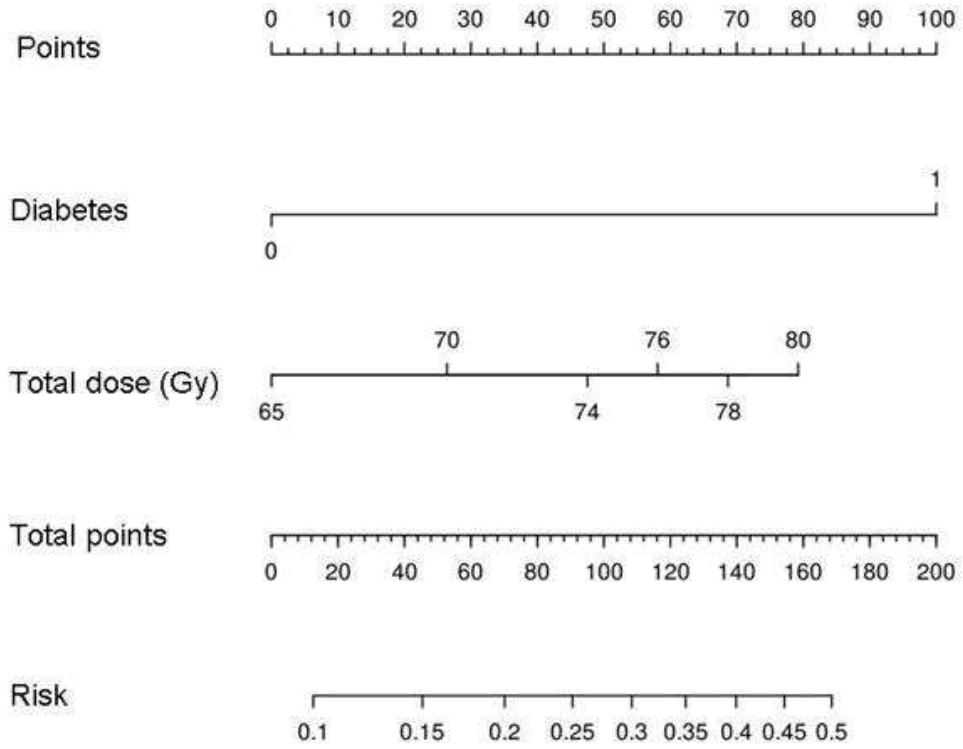
420 **calibration plot**

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

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422 predicted probability versus the actual observed probability.

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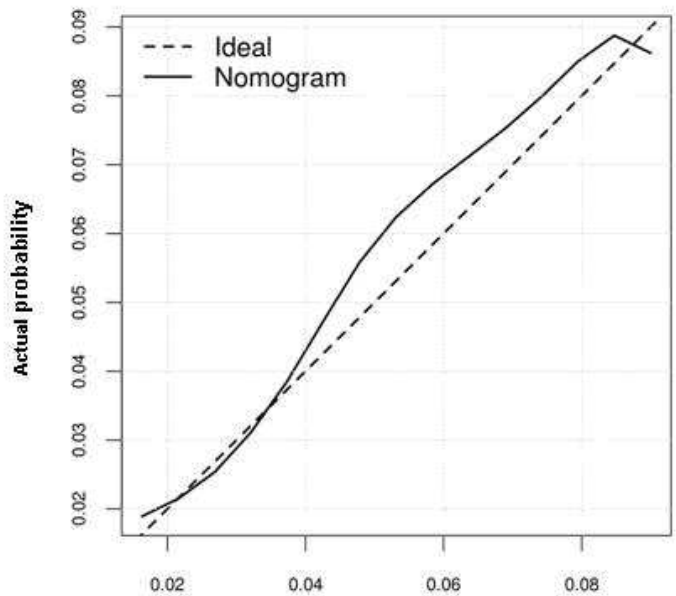
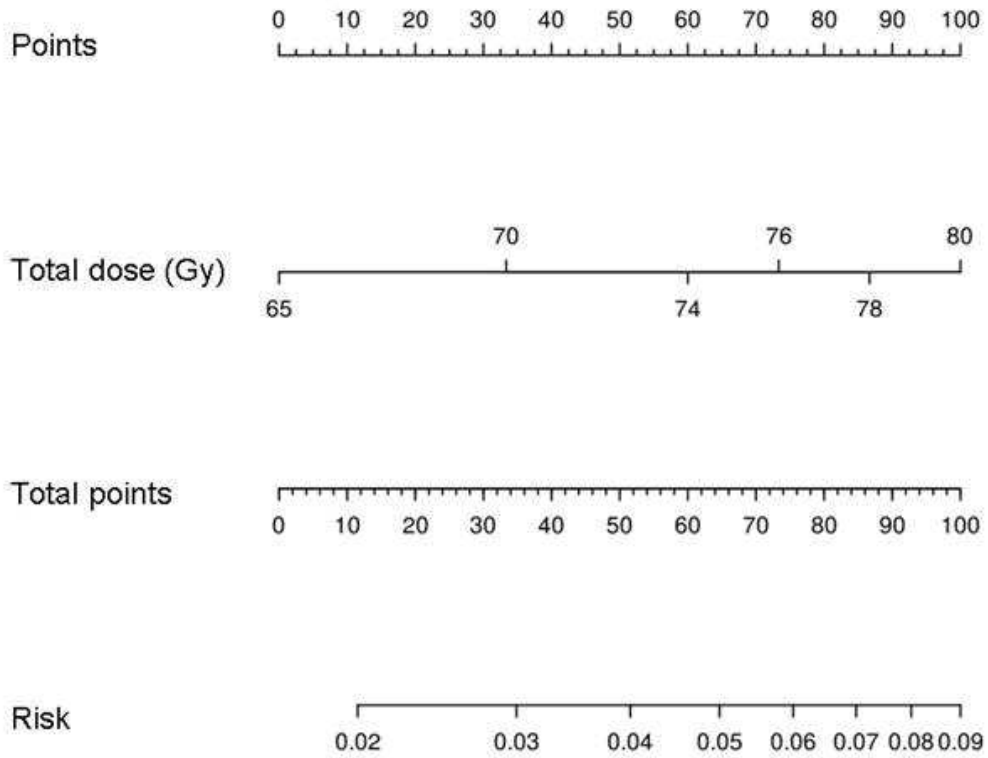
425 **Figure 3: Five-year risk of urinary frequency grade ≥ 2 : nomogram and**

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426 **calibration plot**

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

428 predicted probability versus the actual observed probability.



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=

430 **Figure 4: Five-year risk of dysuria grade ≥ 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

435 **Table 1: Patient, tumor and treatment characteristics**

436

Patient characteristics		
Number of patients		965
Mean age, .yr (range)		68 (45-83)
Diabetes*		7%
Anticoagulant treatment**		21%
Prior abdominal or pelvic surgery		34%
Prior transurethral resection of prostate		6%
Hypertension		19%
Coronary insufficiency		9%
Tumor characteristics		
PSA, ng/ml (range)		15 (0-133)
Gleason Score	<7	53%
	7	38%
	>7	9%
T stage	T1	25%
	T2	62%
	T3	13%
Prognostic group of risk (D'amico) :	Low	18%
	Intermediate	51%
	High	31%
Treatment characteristics		
<i>Radiotherapy technique</i>		
2D Technique		15%
« Standard » 3D Conformational (without IMRT)		66%
IMRT (without IGRT)		7%
IGRT (with IMRT)		12%
<i>Prescribed dose and fractionation</i>		
65 Gy	2.5Gy. 4/w	15%
70 Gy	2.5Gy. 4/w	16%
	2Gy. 5/w	28%
80Gy	2Gy. 5/w	41%
<i>Target volume</i>		
Prostate only		16%
Prostate + Seminal vesicles		75%
Prostate + Seminal vesicles + Pelvic lymph nodes		9%

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

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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

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

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

Table 2: LENTSOMA grading scale (Urinary symptoms)

	grade I	grade II	grade III	grade IV
Subjective				
Dysuria	occasional and minimal	intermittent and tolerable	persistent and intense	refractory and excruciating
Decreased stream	occasionally weak	intermittent	persistent but incomplete obstruction	complete 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 stream		< 1/day self catheterization	dilatation or TUR, > 1/day self catheterization	permanent catheter, surgical intervention
Frequency		occasional antispasmodic	regular narcotic	cystectomy
Hematuria	alkalization iron therapy	single transfusion or cauterization	frequent transfusions or coagulations	surgical intervention
Incontinence	occasional use of incontinence pads	intermittent use of incontinence pads	regular use of incontinence pads or self	catheterization permanent catheter

Table 3: Patient, tumor and treatment factors related to five year risk of late urinary toxicity and corresponding symptoms (multivariate regression logistic analysis)

Factors	Late urinary toxicity		Urinary frequency		Hematuria		Dysuria	
	RR (95.0% CI)	p value	RR (95.0% CI)	p value	RR (95.0% CI)	p value	RR (95.0% CI)	p value
Anticoagulant treatment	2.35 (1.33 - 4.14)	<0.01	-	-	2.89 (1.29 - 6.46)	0.01	-	-
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	-	-	-	-	-	-

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.