

Nomograms to predict late urinary toxicity after prostate cancer radiotherapy.

Romain Mathieu, Juan David Ospina Arango, Véronique Beckendorf, Jean-Bernard Delobel, Taha Messai, Ciprian Chira, Alberto Bossi, Elisabeth Le Prisé, Stéphane Guerif, Jean-Marc Simon, et al.

► **To cite this version:**

Romain Mathieu, Juan David Ospina Arango, Véronique Beckendorf, Jean-Bernard Delobel, Taha Messai, et al. Nomograms to predict late urinary toxicity after prostate cancer radiotherapy.. World Journal of Urology, Springer Verlag, 2013, 32 (3), pp.743-51. <10.1007/s00345-013-1146-8>. <inserm-00911324>

HAL Id: inserm-00911324

<http://www.hal.inserm.fr/inserm-00911324>

Submitted on 7 Jul 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

2

3 Romain Mathieu* a, Juan David Ospina Arango b, Véronique Beckendorf c, Jean-
4 Bernard Delobel d, Taha Messai e, Ciprian Chira d, Alberto Bossi e, Elisabeth Le
5 Prisé d, Stéphane Guerif f, Jean-Marc Simon g, Bernard Dubray h, Jian Zhu b, Jean-
6 Léon Lagrange i, Pascal Pommier j, Khemara Gnep d, Oscar Acosta b, Renaud de
7 Crevoisier b,d.

8

9 a. Dept. of Urology, Centre Hospitalier Universitaire Pontchaillou, Rennes, France

10 b. Inserm U1099, LTSI, Rennes, France

11 c. Centre Alexis Vautrin, Vandoeuvre les Nancy, France

12 d. Centre Eugene Marquis, Rennes, France

13 e. Institut Gustave-Roussy, Villejuif, France

14 f. Centre Hospitalier Universitaire, Poitiers, France

15 g. Hôpital de la Pitié-Salpêtrière, Paris, France

16 h. Centre Henry Becquerel, Rouen, France

17 i. Hôpital Henry Mondor, Créteil, France

18 j. Centre Léon Berard, Lyon, France

19

20 **word count of the text: 2396**

21

22 **word count of the abstract: 244**

23

24 **Keywords** : late urinary toxicity, predictive models, nomograms, prostate cancer,
25 radiotherapy.

26 **Correspondance to:**
27 Romain Mathieu
28 Service d'Urologie
29 Centre Hospitalier Universitaire de Rennes
30 2, rue Henri Le Guilloux
31 35033 Rennes Cedex
32 Phone: + 33 6 63 69 70 30
33 Fax: +33 2 99 28 41 13
34 e-mail: romainmath@yahoo.fr
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 (\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

298 **Acknowledgements:** Marian LEE for her critical review.

299

300 **References**

301

302

303 1. D'Amico, A. V., Whittington, R., Malkowicz, S. B. et al.: Biochemical
304 outcome after radical prostatectomy, external beam radiation therapy, or
305 interstitial radiation therapy for clinically localized prostate cancer. *JAMA*, **280**:
306 969, 1998

307

308 2. Cheung, R., Tucker, S. L., Lee, A. K. et al.: Dose-response
309 characteristics of low- and intermediate-risk prostate cancer treated with
310 external beam radiotherapy. *Int J Radiat Oncol Biol Phys*, **61**: 993, 2005

311

312 3. Fiorino, C., Valdagni, R., Rancati, T. et al.: Dose-volume effects for
313 normal tissues in external radiotherapy: pelvis. *Radiother Oncol*, **93**: 153,
314 2009

315

316 4. Budaus, L., Bolla, M., Bossi, A. et al.: Functional outcomes and
317 complications following radiation therapy for prostate cancer: a critical analysis
318 of the literature. *Eur Urol*, **61**: 112

319

320 5. Valdagni, R., Kattan, M. W., Rancati, T. et al.: Is it time to tailor the
321 prediction of radio-induced toxicity in prostate cancer patients? Building the
322 first set of nomograms for late rectal syndrome. *Int J Radiat Oncol Biol Phys*,
323 **82**: 1957, 2012

324

325 6. Valdagni, R., Rancati, T., Fiorino, C.: Predictive models of toxicity with
326 external radiotherapy for prostate cancer: clinical issues. *Cancer*, **115**: 3141,
327 2009

328

329 7. Beckendorf, V., Guerif, S., Le Prise, E. et al.: 70 Gy versus 80 Gy in
330 localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J*
331 *Radiat Oncol Biol Phys*, **80**: 1056, 2011

332

333 8. de Crevoisier, R., Pommier, P., Bachaud, J. et al.: Image-guided
334 Radiation Therapy (IGRT) in Prostate Cancer: Preliminary Results in Prostate
335 Registration and Acute Toxicity of a Randomized Study. *Int J Radiat Oncol*
336 *Biol Phys*, **75**: 99, 2009

337

338 9. Beahrs, O. H.: American Joint Committee on Cancer: Manual for
339 Staging of Cancer. 4th edition ed. Philadelphia, PA JB Lippincott 1992

340

341 10. Gardner, B. G., Zietman, A. L., Shipley, W. U. et al.: Late normal tissue
342 sequelae in the second decade after high dose radiation therapy with
343 combined photons and conformal protons for locally advanced prostate
344 cancer. *J Urol*, **167**: 123, 2002

345

346 11. Herold, D. M., Hanlon, A. L., Hanks, G. E.: Diabetes mellitus: a
347 predictor for late radiation morbidity. *Int J Radiat Oncol Biol Phys*, **43**: 475,

348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397

1999

12. Takeda, K., Ogawa, Y., Ariga, H. et al.: Clinical correlations between treatment with anticoagulants/antiaggregants and late rectal toxicity after radiotherapy for prostate cancer. *Anticancer Res*, **29**: 1831, 2009

13. Choe, K. S., Jani, A. B., Liauw, S. L.: External beam radiotherapy for prostate cancer patients on anticoagulation therapy: how significant is the bleeding toxicity? *Int J Radiat Oncol Biol Phys*, **76**: 755

14. Novara, G., Ficarra, V., D'Elia, C. et al.: Evaluating urinary continence and preoperative predictors of urinary continence after robot assisted laparoscopic radical prostatectomy. *J Urol*, **184**: 1028, 2010

15. Teber, D., Sofikerim, M., Ates, M. et al.: Is type 2 diabetes mellitus a predictive factor for incontinence after laparoscopic radical prostatectomy? A matched pair and multivariate analysis. *J Urol*, **183**: 1087, 2010

16. Pollack, A., Zagars, G. K., Starkschall, G. et al.: Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys*, **53**: 1097, 2002

17. Zietman, A. L., DeSilvio, M. L., Slater, J. D. et al.: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA*, **294**: 1233, 2005

18. Dearnaley, D. P., Sydes, M. R., Graham, J. D. et al.: Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol*, **8**: 475, 2007

19. Al-Mamgani, A., van Putten, W. L., Heemsbergen, W. D. et al.: Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*, **72**: 980, 2008

20. Zelefsky, M. J., Levin, E. J., Hunt, M. et al.: Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*, **70**: 1124, 2008

21. Leborgne, F., Fowler, J.: Late outcomes following hypofractionated conformal radiotherapy vs. standard fractionation for localized prostate cancer: a nonrandomized contemporary comparison. *Int J Radiat Oncol Biol Phys*, **74**: 1441, 2009

22. Namiki, S., Ishidoya, S., Ito, A. et al.: Five-year follow-up of health-related quality of life after intensity-modulated radiation therapy for prostate cancer. *Jpn J Clin Oncol*, **39**: 732, 2009

23. Alicikus, Z. A., Yamada, Y., Zhang, Z. et al.: Ten-year outcomes of

398 high-dose, intensity-modulated radiotherapy for localized prostate cancer.
399 Cancer, **117**: 1429, 2011

400

401 24. Wallner, K., Roy, J., Harrison, L.: Dosimetry guidelines to minimize
402 urethral and rectal morbidity following transperineal I-125 prostate
403 brachytherapy. Int J Radiat Oncol Biol Phys, **32**: 465, 1995

404

405 25. Zelefsky, M. J., Kollmeier, M., Cox, B. et al.: Improved Clinical
406 Outcomes with High-Dose Image Guided Radiotherapy Compared with Non-
407 IGRT for the Treatment of Clinically Localized Prostate Cancer. Int J Radiat
408 Oncol Biol Phys, *in press*, 2012

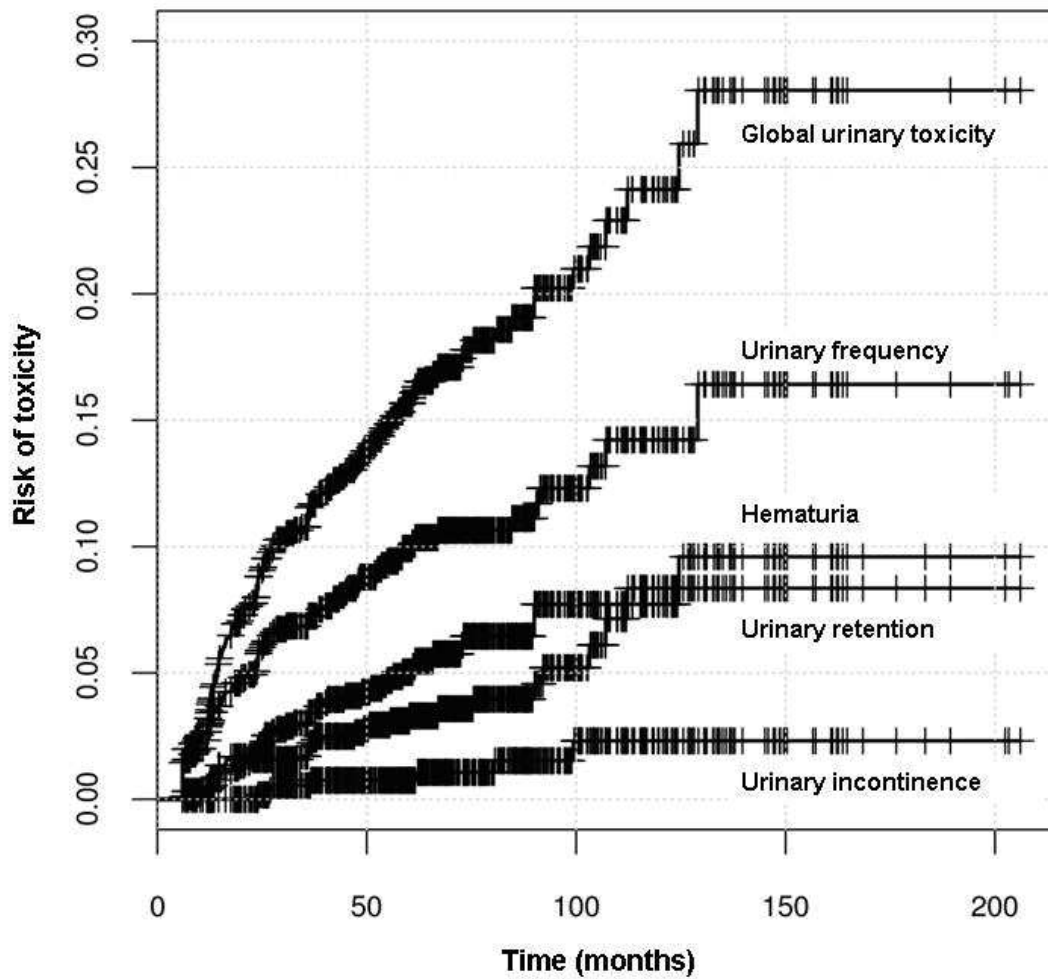
409

410

411

412 **Figure legends**

413

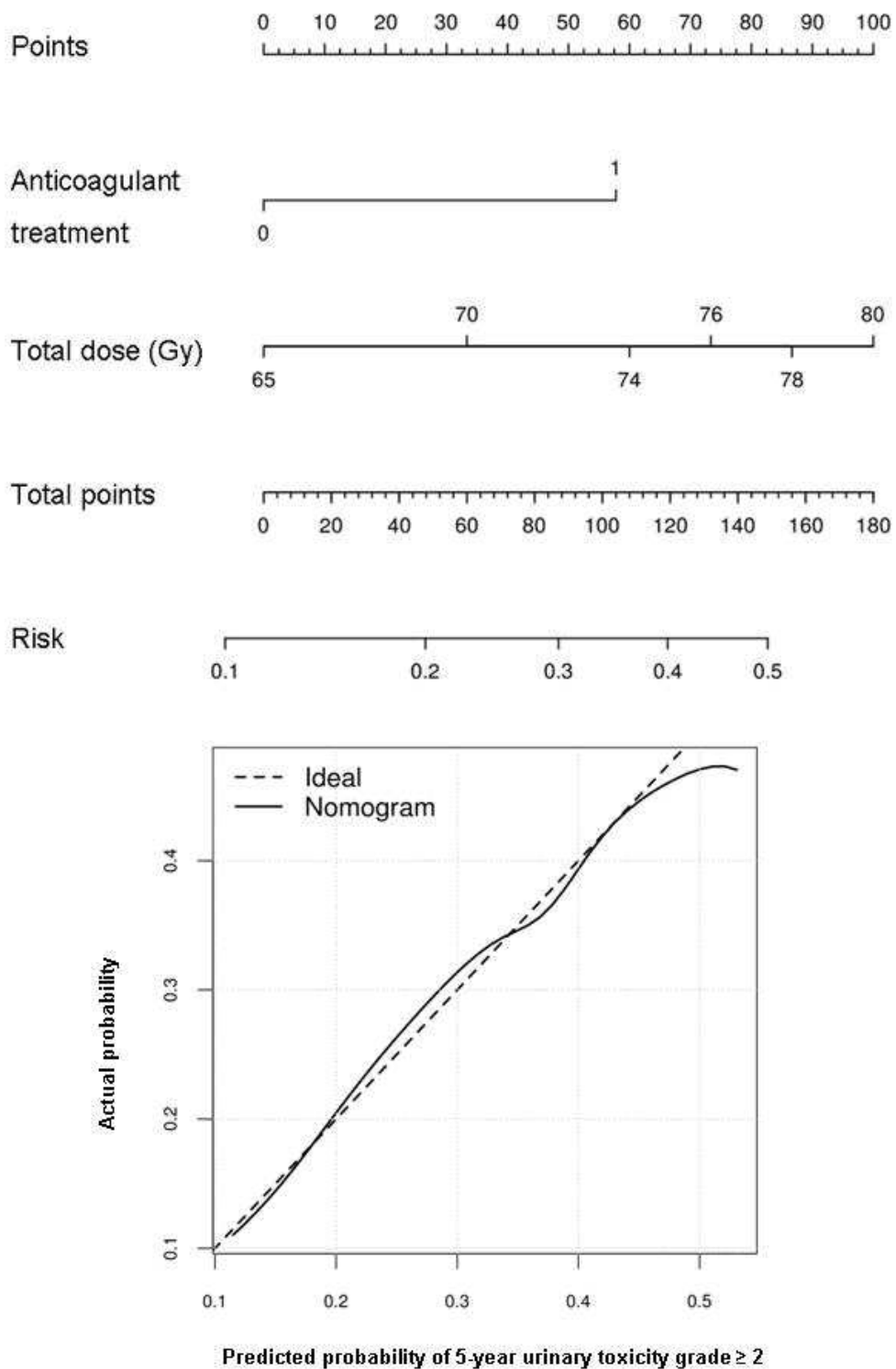


414

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

416 **according to LENTSOMA classification**

417



418

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

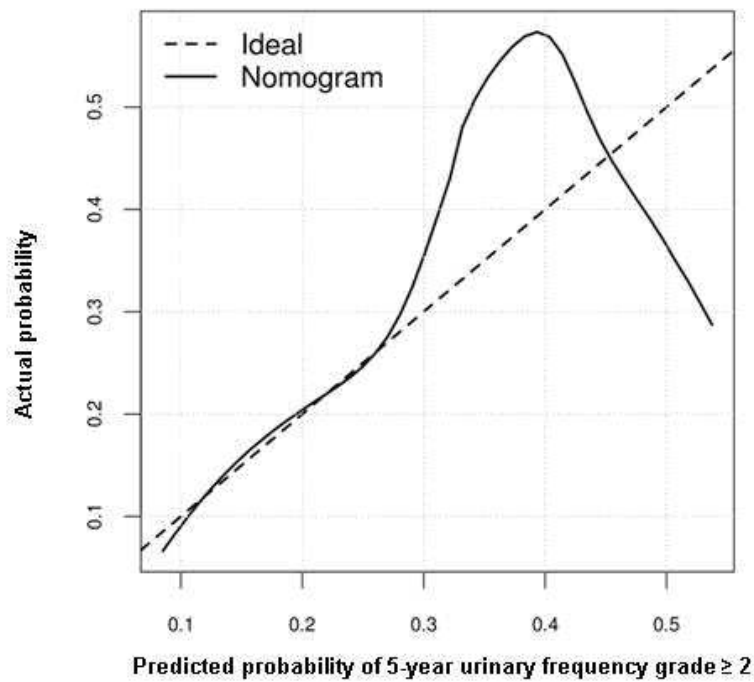
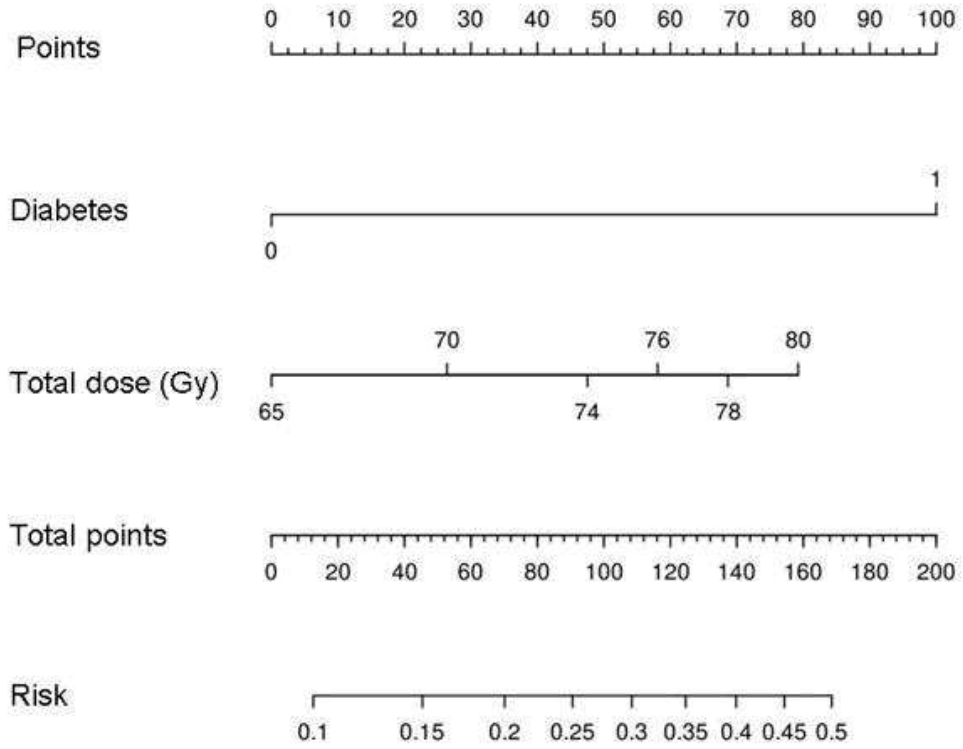
420 **calibration plot**

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

=

422 predicted probability versus the actual observed probability.

423



424

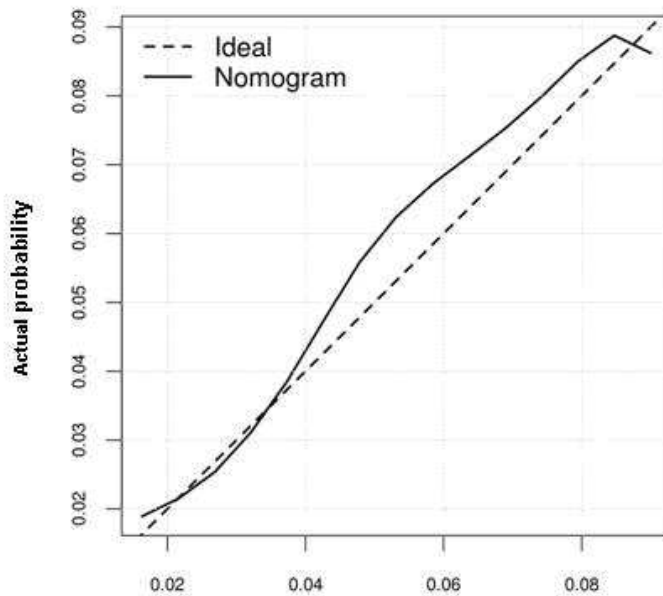
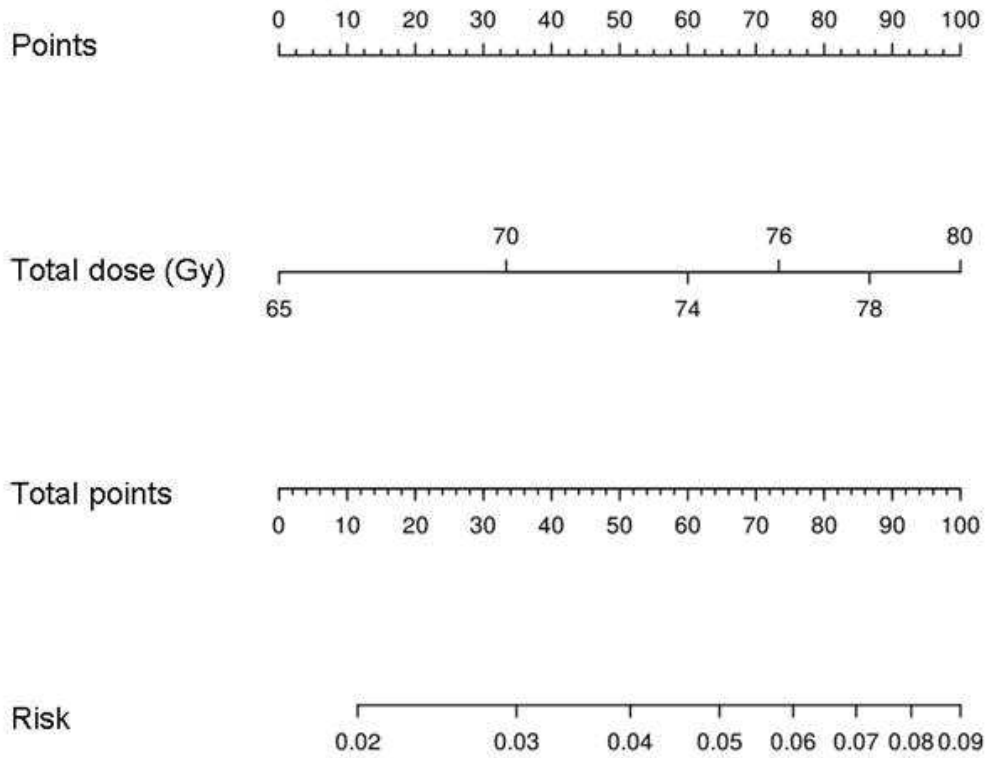
425 **Figure 3: Five-year risk of urinary frequency grade ≥ 2 : nomogram and**

=

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 ≥ 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%

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

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.