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Abstract

Objective: To analyze late urinary toxicity after prostate cancer radiotherapy (RT): symptom description and identification of patient characteristics or treatment parameters allowing for the generation of nomograms.

Methods: 965 patients underwent RT in seventeen French centers for localized prostate cancer. Median total dose was 70 Gy (range, 65-80 Gy), using different fractionations (2 or 2.5 Gy/day) and techniques. Late urinary toxicity and the corresponding symptoms (urinary frequency, incontinence, Dysuria/decreased stream and hematuria) were prospectively assessed in half of the patients using the LENTSOMA classification. Univariate and multivariate Cox regression models addressed patient or treatment-related predictors of late urinary toxicity (≥ grade 2). Nomograms were built up and their performance was assessed.

Results : The median follow-up was 61 months. The 5-year (≥grade 2) global urinary toxicity, urinary frequency, hematuria, dysuria and urinary incontinence rates were: 15%, 10%, 5%, 3% and 1%, respectively. The 5-year (≥ grade 3) urinary toxicity rate was 3%. The following parameters significantly increased the 5 year risk of global urinary toxicity (≥ 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 diabetes (RR=4). Hematuria was increased by anticoagulant treatment (RR=2.9). Dysuria was increased by the total dose (RR=1.1). Corresponding nomograms and their calibration plots were generated. Nomogram performance should be validated with external data.

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

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1. Introduction

Radical prostatectomy (RP) and radiotherapy (RT) are cornerstones of localized 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 adverse events. If the intensity of this toxicity after RT is relatively well-reported in the literature, the description of the symptoms corresponding to this toxicity is often 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 to generate urinary toxicity predictive tools (like nomograms), to guide the physician in deciding the treatment and to inform the patient, in this context of different therapeutic alternatives. To identify which radiation parameters increase toxicity is essential in understand how to decrease toxicity, in particular due to new highly-conformal radiotherapy techniques, such as Intensity Modulated Radiation Therapy (IMRT) and Image Guided Radiation Therapy (IGRT).

These new techniques allow for an increase of the dose in the prostate considering the strong dose-effect relationship for local control [2], while limiting the dose in the bladder and the rectum. Their part in decreasing urinary toxicity has not, however, 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]. Moreover, hypofractionated RT may be more efficient in eradicating prostate adenocarcinoma, but the impact of such modified fractionation on toxicity has not been well-established.

If nomograms have already been published to predict rectal bleeding and the risk of fecal incontinence [5, 6], to our knowledge no tools have as yet been developed to

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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.

2. Material and methods

2.1. Patient inclusion criteria

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

2.2. Patient and tumor characteristics

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

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Cancer staging system [9]. Patients were classified into the three prognostic risk groups defined by D'Amico [1]. Patient and tumor characteristics are presented in Table 1.

2.3. Treatment characteristics

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

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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 high risk cancer.

Details of treatment characteristics are presented in Table 1.

2.4. Follow up and toxicity grading

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

2.5. Statistical analysis

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The impact of the following parameters on late urinary toxicity (≥ grade 2) was tested 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.

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

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

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

3. Results

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

3.1. Late urinary toxicity: global quantification and symptom description

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

3.2. Nomograms to predict five-year late toxicity

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

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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)

4. Discussion

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

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fact that anticoagulation or antiplatelet agents increase the risk of late urinary toxicity 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 already associated with gross hematuria in the whole population and could be an independent risk factor of urinary complaints whatever a radiation is performed. Age and diabetes have been previously associated with urinary side effects after radical prostatectomy, especially urinary incontinence [14, 15]. Thus, their implications in urinary toxicity after RT should not be underestimated in treatment decision.

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 (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 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 higher doses [20]. More recently, the GETUG 06 randomized trial reported such an increase, when escalating the dose from 70 Gy to 80 Gy [7]. These differences can be explained by several reasons. The first one is the lack of follow-up. Indeed, the initial 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-up[16]. Secondly, studies might be different in terms of their treatment scheme (dose, target volume, technique), patient characteristics and grading scale. Finally, urinary toxicity might be more related to patient risk factors than dose parameters. The lack of correlation between dose distribution (dose-volume histogram) and urinary toxicity may also be due to the large bladder volume variation occurring at the planning stage and at the different

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

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 emphasize the interest of hypofractionated schedule in prostate cancer radiotherapy. IMRT and IGRT aim at increasing local control by allowing dose escalation, while reducing toxicity by sparing normal surrounding tissues. Compared to "standard" 3D 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 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 IGRT still do not allow for the preservation of this area. A recent non-randomized study of Zelefsky et al reported however that, with a median follow-up of 2.8 years and a high dose (86.4 Gy) delivered to the prostate by IMRT, patients treated with IGRT (using fiducials) experienced significantly less urinary toxicity than non-IGRT treated patients[25].

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

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

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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.

5. Conclusions

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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References

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

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

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

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

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

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

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

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

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

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

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

=

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

=

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

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

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

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412 **Figure legends**

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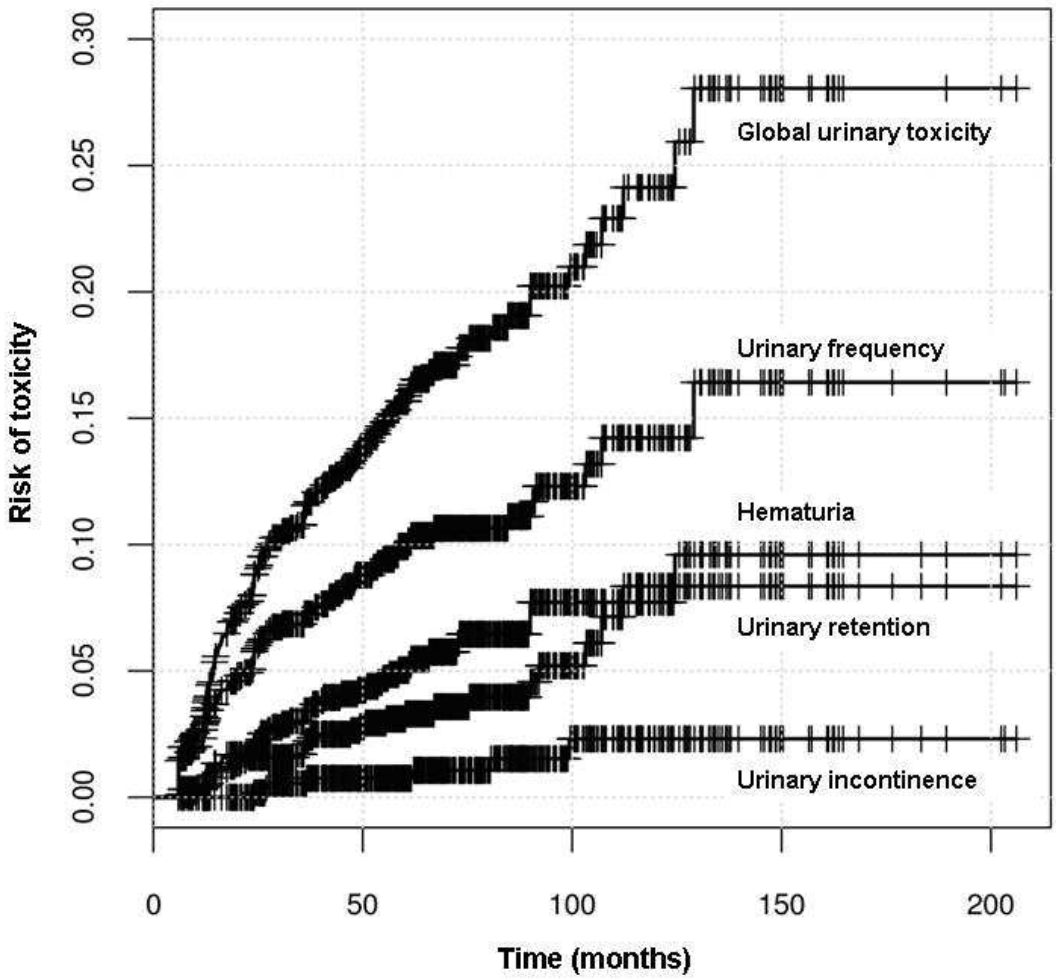

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415 **Figure1: Incidence of global and by symptoms late urinary toxicity (≥grade 2)**

416 **according to LENTSOMA classification**

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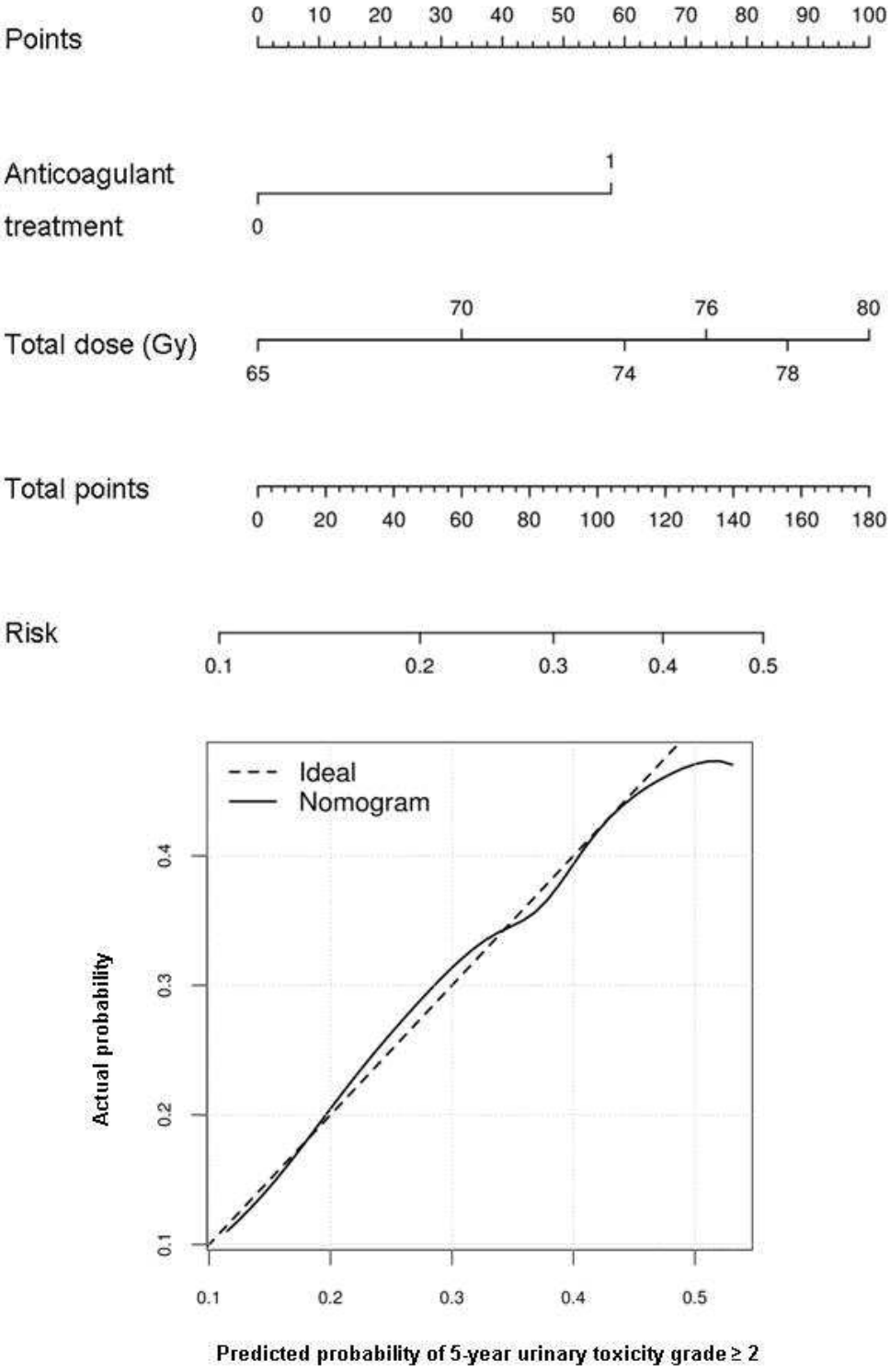

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419 **Figure 2: Five-year risk of global late urinary toxicity grade ≥ 2 : nomogram and**

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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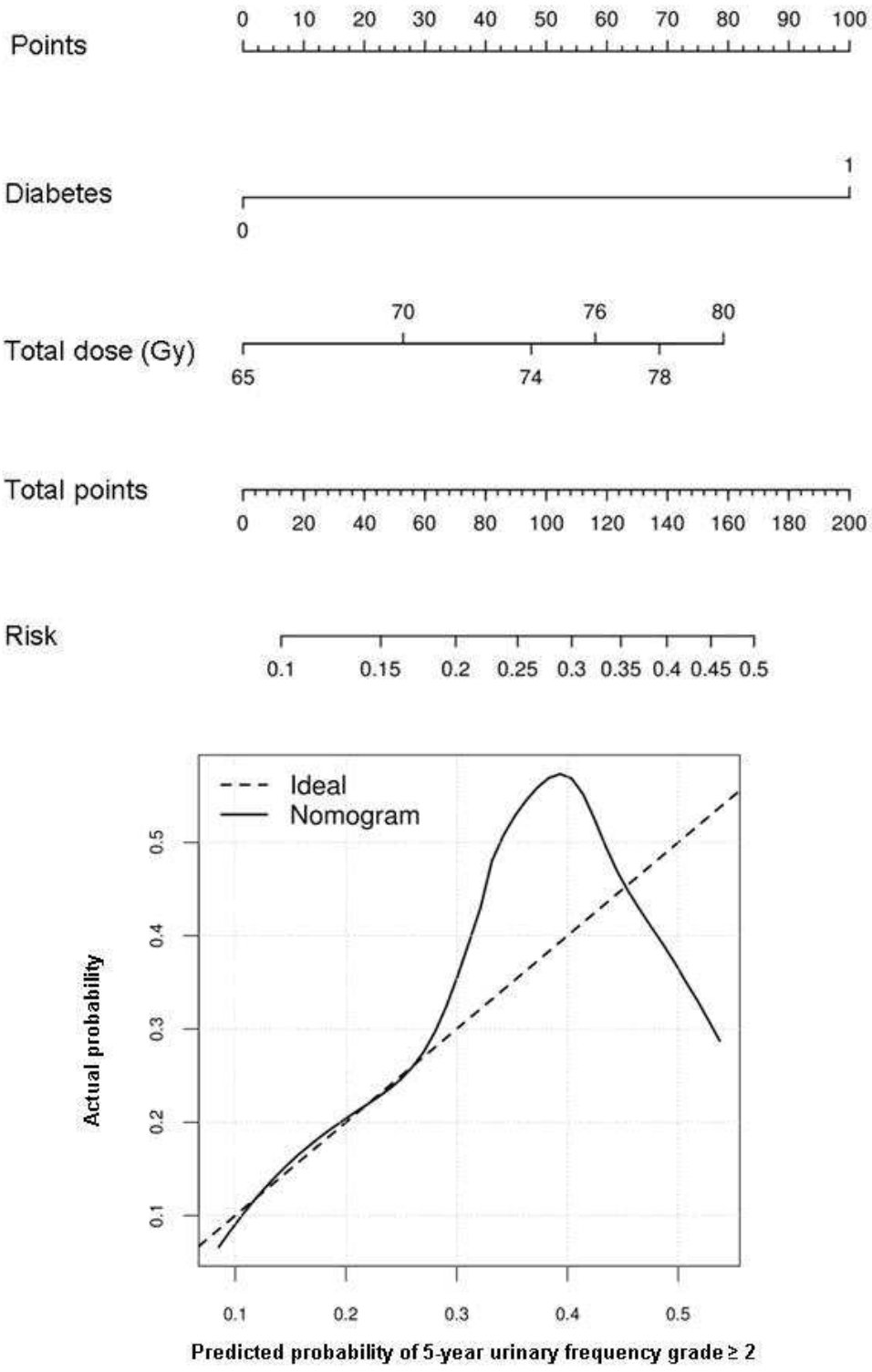

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425 **Figure 3: Five-year risk of urinary frequency grade ≥ 2: nomogram and**

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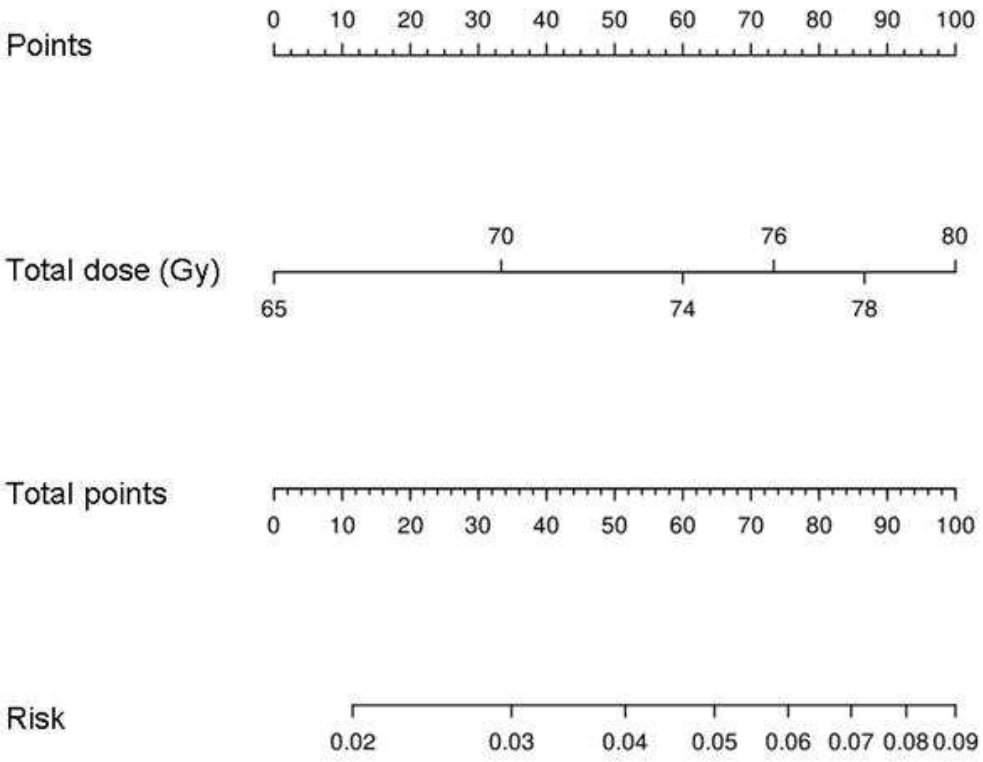
calibration plot

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



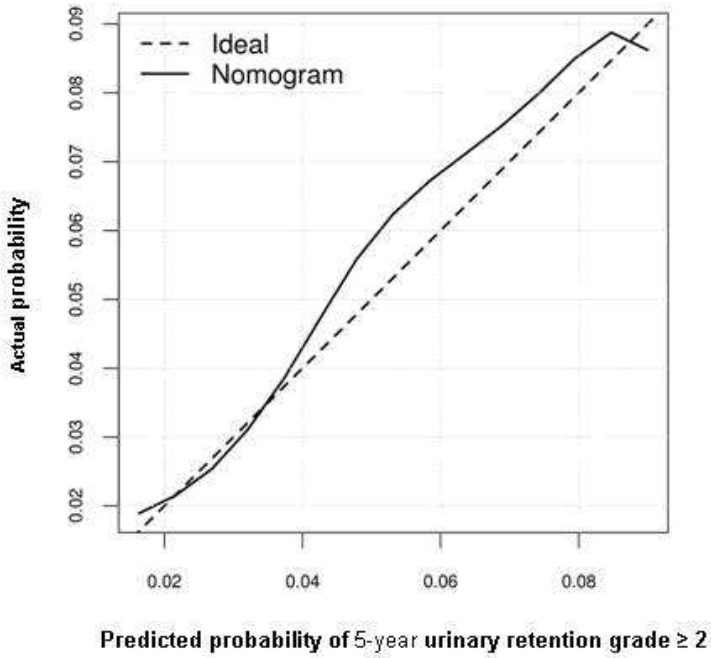


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Figure 4: Five-year risk of dysuria grade ≥ 2: nomogram and calibration plot

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

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

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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 transuretral 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		
Radiotherapy technique		
2D Technique		15%
« Standard » 3D Conformational (without IMRT)		66%
IMRT (without IGRT)		7%
IGRT (with IMRT)		12%
Prescribed dose and fractionation		
65 Gy	2.5Gy. 4/w	15%
70 Gy	2.5Gy. 4/w	16%
	2Gy. 5/w	28%
80Gy	2Gy. 5/w	41%
Target volume		
Prostate only		16%
Prostate + Seminal vesicles		75%
Prostate + Seminal vesicles + Pelvic lymph nodes		9%

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Dosimetric parameters		
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.

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Table 2: LENTSOMA grading scale (Urinary symptoms)

	grade I	grade II	grade III	grade IV
Subjective				
Dysuria Decreased stream	occasional and minimal occasionally weak	intermittent and tolerable intermittent	persistent and intense persistent but incomplete obstruction	refractory and excruciating 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 Decreased stream	occasional, nonnarcotic	regular nonnarcotic < 1/day self catheterization	regular narcotic dilatation or TUR, > 1/day self catheterization	surgical intervention 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.