A novel tool to assess the risk of urinary incontinence after nerve-sparing radical prostatectomy


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What’s known on the subject? and What does the study add?

• Urinary incontinence is one of the most important morbidities after radical prostatectomy that has detrimental effect on the postoperative quality of life.

• The present study provides an accurate and dynamic multivariable risk stratification tool that predicts the postoperative urinary incontinence risk after radical prostatectomy based on patient-related as well as surgeon-related variables.

Objective

• To develop a multivariable risk classification tool to estimate postoperative urinary incontinence (UI) risk as UI represents one of the most disabling surgical sequelae after radical prostatectomy (RP).

Patients and Methods

• We evaluated 1311 patients treated with nerve-sparing RP between 2006 and 2010 at our institution.

• Regression tree analysis was used to stratify patients according to their postoperative UI risk. Kaplan–Meier curve estimates were used to assess the UI rate in the novel UI-risk groups. The discrimination of the novel tool was measured with the area under the curve method.

Results

• At 3, 6 and 12 months, the UI rates were 44%, 26% and 12%, respectively.

• Regression tree analysis stratified patients into high risk (International Index of Erectile Function – Erectile Function domain [IIEF-EF] = 1–10), intermediate risk (IIEF-EF > 10, age < 65 years and body mass index [BMI] ≥ 25 kg/m²) and very low risk (IIEF-EF > 10, age < 65 years and BMI < 25 kg/m²) groups.

• The 3-month UI rates in these groups were 37%, 43%, 45% and 48%, respectively. The 6-month UI rates were 19%, 23%, 29% and 34%, respectively. The 12-month UI rates were 7%, 13%, 14% and 15%, respectively (log-rank P < 0.001).

• The area under the curve was 71%, 70% and 68% at 3, 6 and 12 months, respectively.

Conclusions

• We developed the first risk classification tool that predicts patients at high risk of UI after RP. These consisted mainly of individuals who were impotent before RP, elderly and/or overweight.

• This tool can be used for patient counselling.

Keywords

prostatectomy/adverse effects, risk assessment, survival analysis, urinary incontinence/aetiology, treatment outcome

Introduction

Radical prostatectomy (RP) represents one of the most commonly used first-line treatment modalities in patients with prostate cancer (PCa), especially in men with clinically localized disease and a life expectancy of 10 years or more [1–3]. Most of these patients have favourable cancer control outcomes after surgery [2,4,5]. However, a considerable proportion of them may suffer from long-term surgical sequelae, such as urinary incontinence (UI) and sexual dysfunction [6–12]. These functional changes represent...
important determinants of postoperative quality of life [12–14]. While some patients might not be so bothered by the postoperative sexual impotence, the majority of patients would refer to UI as the most disabling morbidity after RP. Although several studies have assessed a series of risk factors associated with a higher UI rate after surgery [9,11,12,15,16], there is currently no preoperative tool that quantifies the postoperative UI risk according to patient and treating surgeon characteristics. Such preoperative individualized risk assessment is a key for accurate patient counselling, contributing to a properly balanced clinical decision-making process. To address this void, we develop and validate a novel preoperative risk classification tool aimed at estimating the postoperative UI risk in patients treated with nerve-sparing RP (NSRP).

Materials and Methods

Patient Population

The study included 1311 patients with PCa treated with NSRP between 2006 and 2010 at San Raffaele Hospital. Neurovascular bundle preservation was done whenever surgically feasible, regardless of preoperative erectile status. No patient in this cohort received neoadjuvant or adjuvant treatment for PCa. All subjects were continent before surgery.

Surgical procedures were performed by nine different surgeons. All NSRP specimens were examined by four dedicated genitourinary pathologists, using a standardized protocol [17]. All patients were extensively counselled about possible treatment options for PCa, including possible benefits and side effects of each approach. Thus, the decision to undergo RP followed patient and physician discussion about possible treatment options and expectations. All patients admitted to the hospital scheduled for RP were asked to join a prospective data collection protocol. For this aim, all patients signed an institutional review board approved informed consent form. All patients were informed that data would be used anonymously for the purpose of clinical research. On acceptance, preoperative clinical and functional data were prospectively collected for each participant. However, data analyses for the purpose of the present study were performed retrospectively.

Variable Definitions and Patient Assessment

At baseline, patient-related variables consisted of age at surgery (years), comorbidity status evaluated using the Charlson Comorbidity Index (CCI), body mass index (BMI), serum PSA value (ng/mL), clinical stage, biopsy Gleason score, International Prostate Symptoms Score (IPSS), International Index of Erectile Function – Erectile Function domain (IIEF-EF) score, which was categorized according to Cappelleri et al. [18], and type of nerve sparing (unilateral vs bilateral). Similarly, for each patient, two surgeon-related variables were available: type of surgery (retropubic radical prostatectomy [RRP] vs. robot-assisted laparoscopic radical prostatectomy [RALP]), and procedure-specific surgical volume, defined as the count of procedures performed by the operating surgeon between the study start and the date of RRP or MIRP performed for each individual patient [19–21].

Patients were postoperatively assessed every 3 months for the first year and every 6 months thereafter. At each visit, all patients were asked to complete the International Consultation on Incontinence Modular Questionnaire – short form (ICIQ-SF) and the IIEF questionnaires. UI was defined as a postoperative ICIQ-SF questionnaire score ≥ 6 [22].

Statistical Analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians and ranges were reported for continuously coded variables. The chi-squared test and the t test were used to compare the statistical significance of differences in, respectively, proportions and means.

In the first step of our analyses, we used the regression tree for censored data that applies a standard and recursive algorithm to sequentially divide a group of patients into two subgroups, where the separation between the two class-specific survival curves in a pair is maximized [23]. The algorithm selects the optimal sequence of classifications, as defined by a hierarchy of prognostic factors and associated cut-points. All available patient-related covariates were included in the regression tree. Kaplan–Meier survival curves were used to estimate the UI rate in each subgroup at 3, 6 and 12 months after surgery. The results of these analyses are graphically represented. We used the time-dependent receiver operating characteristic curves for censored data as described by Heagerty et al. [24] to calculate the area under the curve of the regression tree.

In the second step of our analyses, we repeated the previous analyses after stratification according to surgeon-related variables, which consisted of type of surgery and the median number of procedure-specific surgical volume. Finally, in the third step of our analyses we used the multiplicative law of probability to calculate the conditional estimates of UI rate in our patients. This law states that the knowledge of the probability of an event A and event B occurring, and the probability of event A occurring, allows the calculation of the conditional
The probability of event B occurring, given that event A has occurred: \( P(B|A) = \frac{P(A \cap B)}{P(A)} \) [25,26].

All statistical analyses were performed using the R statistical package system (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided with a significance level set at <0.05.

**Results**

Patient characteristics are summarized in Table 1. Average age at surgery was 62.6 years (median 62.6, range 38.9–80.0). Average BMI was 26.0 kg/m² (median 25.6, range 17.3–42.0). The majority of patients had no comorbidity (76.0%), a preoperative IPSS score of 0–7 (51.0%) and an IIEF-EF score ≥ 22 (62.2%). Average PSA value was 7.4 ng/mL (median 6.0, range 1.2–54.3). Most patients had a clinical stage T1c (69.7%) and biopsy Gleason score of ≤6 (72.8%). Roughly half of patients received an RRP (56.8%) while the other half received an RALP (43.2%). Most patients received a bilateral nerve-sparing procedure (79.2%).

At 3, 6 and 12 months, the UI rates were 44%, 26% and 12%, respectively. The number of patients at risk was 702, 391 and 162 patients, respectively. The number of patients withdrawing within these intervals (lost to follow-up) was 26, 45 and 66 patients respectively.

All available patient-related covariates were included in the regression tree analysis. The regression tree analysis selected three variables to stratify patients according to their UI risk and estimated the cut-offs that maximized the separation in class-specific survival. These variables consisted of preoperative IIEF-EF (≤10 vs >10 score), age (<65 vs ≥65 years) and BMI (<25 vs ≥25 kg/m²). The stratification process resulted in four UI risk groups (Fig. 1): high (IIEF-EF = 1–10), intermediate (IIEF-EF > 10 and age ≥ 65 years), low (IIEF-EF > 10, age < 65 years and BMI ≥ 25 kg/m²) and very low UI risk (IIEF-EF > 10, age < 65 years and BMI < 25 kg/m²). The 3-month UI rates in these groups were 37%, 43%, 45% and 48%, respectively, the 6-month UI rates were 19%, 23%, 29% and 34%, respectively, and the 12-month UI rates were 7%, 13%, 14% and 15%, respectively. The observed differences in UI rate among these four groups were statistically significant (log-rank test \( P < 0.001 \)). The area under the curve of this risk classification was 71%, 70% and 68% at 3, 6 and 12 months, respectively.

Similar trends of UI rate in relation to risk classification were observed when patients were classified according to surgery type (Fig. 2A) and procedure-specific surgical volume (Fig. 2B,C).

In patients who were still incontinent 3 months after surgery, the subsequent 3-month UI rates were 51%, 54%, 65% and 71% in patients with very low, low, intermediate and high UI risk, respectively. In patients who were still incontinent 6 months after surgery, the subsequent 6-month UI rates were 34%, 54%, 45% and 47%, respectively (Fig. 3).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 62.6, Median 62.6, Range 38.9–80.0</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>0 996 (76.0), 1 274 (20.9), ≥2 41 (3.1)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>Mean 26.0, Median 25.6, Range 17.3–42.0</td>
</tr>
<tr>
<td>Preoperative IPSS</td>
<td>0–7 (none to mild) 668 (51.0), 8–19 (moderate) 497 (37.9), ≥20 (severe) 146 (11.1)</td>
</tr>
<tr>
<td>Preoperative IIEF-EF</td>
<td>1–10 (severe ED) 291 (22.2), 11–17 (moderate ED) 109 (8.3), 18–21 (mild to moderate ED) 95 (7.2), 22–25 (mild ED) 281 (21.4), ≥26 (no ED) 535 (40.8)</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>Mean 7.4, Median 6.0, Range 1.2–54.3</td>
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<tr>
<td>Clinical stage</td>
<td>T1c 914 (69.7), T2 or higher 397 (30.3)</td>
</tr>
<tr>
<td>Biopsy Gleason score</td>
<td>2–6 955 (72.8), 7 306 (23.3), 8–10 50 (3.8)</td>
</tr>
<tr>
<td>Surgery type</td>
<td>RRP 746 (56.9), RALP 565 (43.1)</td>
</tr>
<tr>
<td>Nerve-sparing type</td>
<td>Unilateral 273 (20.8), Bilateral 1038 (79.2)</td>
</tr>
<tr>
<td>Surgical volume for RRP patients</td>
<td>Mean 103.2, Median 59.5, Range 1.0–350.0</td>
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<tr>
<td>Surgical volume for RALP patients</td>
<td>Mean 85.0, Median 79.0, Range 1.0–222.0</td>
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*Calculated considering patients treated with RRP only. †Calculated considering patients treated with RALP only. ED, erectile dysfunction.
UI is one of the most disabling surgical sequelae after RP, affecting up to 30% of contemporary patients at long term [7–9,11,12,15,16]. Previous studies have identified several risk factors associated with a higher postoperative UI risk [9,11,12,15,16]. However, to date there is no multivariable tool that predicts the postoperative UI rate based on preoperative clinical characteristics. This is crucial, since preoperative individualized predictions of UI would allow for accurate patient counselling aimed at delivering realistic expectations based on baseline patient status. This would in turn optimize patient satisfaction and contribute to maintaining a satisfactory quality of life after surgery. Based on these considerations, we developed and validated a novel preoperative risk classification tool aimed at predicting the risk of UI in patients treated with NSRP.

For the entire cohort, the 3-, 6- and 12-month UI rates were 44%, 26% and 12%, respectively. Regression tree analysis classified patients according to their preoperative characteristics and based on their postoperative UI risk. This process resulted in four UI risk groups, namely high (IIEF-EF = 1–10), intermediate (IIEF-EF > 10 and age ≥ 65 years), low (IIEF-EF > 10, age < 65 years and BMI ≥ 25 kg/m²) and very low (IIEF-EF > 10, age < 65 years and BMI < 25 kg/m²) UI risk. The UI rate across these groups was statistically significantly different.

3-month urinary incontinence rate (%)
- Very low: 37.0%
- Low: 43.2%
- Intermediate: 44.9%
- High: 47.7%

6-month urinary incontinence rate (%)
- Very low: 19.0%
- Low: 23.4%
- Intermediate: 29.1%
- High: 33.8%

12-month urinary incontinence rate (%)
- Very low: 6.5%
- Low: 12.7%
- Intermediate: 13.6%
- High: 15.3%

We opted to stratify our results according to surgeon-related variables (namely type of surgery and procedure-specific surgical volume) rather than including these variables in the risk classification tool. This was because not all centres and/or surgeons can offer both types of surgery (RRP and RALP) and the level of surgical expertise might vary from one centre to another. Such stratification may foster the immediate implication of the novel UI risk tool in clinical practice.

When patients were stratified according to surgery type (Fig. 2A), substantially higher UI rates were observed in RRP patients in comparison with RALP patients, regardless of the UI risk group and/or the examined time endpoint. This might be related to the patient selection process and/or a difference in the postoperative morbidity rate between the two examined procedures. Regardless of the underlying cause, it is noteworthy that the correlation between UI risk classification and the actually observed UI rate holds true for both surgery types. Similar findings were observed when patients were further stratified according to procedure-specific surgical volume (Fig. 2B,C). Intuitively, being operated on by a high volume surgeon was associated with a more favourable UI rate than being operated on by a low volume surgeon. However, the correlation between UI risk classification and the actually observed UI rate holds true regardless of surgical volume.
Fig. 2 A novel UI risk classification tool based on the data of 1311 patients treated with NSRP between 2006 and 2010 at a single institution. Results were stratified according to surgery type (A), the median surgical volume in patients treated with RRP (B) and the median surgical volume in patients treated with RALP (C).

**Risk group:** Very low Low Intermediate High

**Retro-pubic radical prostatectomy**

<table>
<thead>
<tr>
<th></th>
<th>Very low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tbody>
<tr>
<td>3-month urinary incontinence rate (%)</td>
<td>46.2%</td>
<td>51.4%</td>
<td>52.7%</td>
<td>54.9%</td>
</tr>
<tr>
<td>6-month urinary incontinence rate (%)</td>
<td>48.1%</td>
<td>30.3%</td>
<td>32.8%</td>
<td>36.5%</td>
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<tr>
<td>12-month urinary incontinence rate (%)</td>
<td>8.8%</td>
<td>14.0%</td>
<td>14.9%</td>
<td>17.2%</td>
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**Robotic-assisted laparoscopic radical prostatectomy**

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<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tbody>
<tr>
<td>3-month urinary incontinence rate (%)</td>
<td>30.3%</td>
<td>31.3%</td>
<td>37.3%</td>
<td>43.9%</td>
</tr>
<tr>
<td>6-month urinary incontinence rate (%)</td>
<td>11.4%</td>
<td>13.5%</td>
<td>24.6%</td>
<td>37.7%</td>
</tr>
<tr>
<td>12-month urinary incontinence rate (%)</td>
<td>4.6%</td>
<td>5.9%</td>
<td>11.8%</td>
<td>24.7%</td>
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**B**

**Risk group:** Very low Low Intermediate High

**Retro-pubic radical prostatectomy – Low surgical volume (≤ 59 cases)**

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<tr>
<td>3-month urinary incontinence rate (%)</td>
<td>52.6%</td>
<td>53.7%</td>
<td>55.4%</td>
<td>55.4%</td>
</tr>
<tr>
<td>6-month urinary incontinence rate (%)</td>
<td>33.7%</td>
<td>35.6%</td>
<td>36.5%</td>
<td>37.2%</td>
</tr>
<tr>
<td>12-month urinary incontinence rate (%)</td>
<td>14.2%</td>
<td>18.4%</td>
<td>17.8%</td>
<td>18.2%</td>
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**Retro-pubic radical prostatectomy – High surgical volume (> 59 cases)**

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<th>Very low</th>
<th>Low</th>
<th>Intermediate</th>
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<tbody>
<tr>
<td>3-month urinary incontinence rate (%)</td>
<td>40.3%</td>
<td>48.7%</td>
<td>50.0%</td>
<td>54.3%</td>
</tr>
<tr>
<td>6-month urinary incontinence rate (%)</td>
<td>22.6%</td>
<td>24.7%</td>
<td>27.4%</td>
<td>36.1%</td>
</tr>
<tr>
<td>12-month urinary incontinence rate (%)</td>
<td>3.5%</td>
<td>9.5%</td>
<td>11.9%</td>
<td>16.4%</td>
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</table>
Recently, we demonstrated the impact of the postoperative elapsed period, defined as the postoperative period in which the patient did not recover urinary continence, on the subsequent UI rate [26]. Intuitively, the longer the postoperative elapsed period without urinary continence recovery, the higher is the subsequent UI risk. The UI rate estimations of our novel tool were adjusted for this factor (Fig. 3). For example, at baseline (immediately after surgery), the 6-month UI rate was 19%, 23%, 29% and 34% in patients with respectively very low, low, intermediate and high UI risk. However, for patients who did not recover their urinary continence during the first three postoperative months, the subsequent 3-month UI rates (a total of 6 months after surgery) increased to respectively 51%, 54%, 65% and 71%. These ‘time-adjusted’ conditional estimates provide more dynamic and realistic results, which might be helpful in informing the patients about their real UI risk in the postoperative period.

Our findings corroborate previous reports. For example, Loeb et al. [9], Sacco et al. [11] and Stanford et al. [12] documented the role of increasing age as a predictor of a higher postoperative UI rate. Similarly, two recent reports [15,16] that focused on RALP patients showed that age, sexual potency and BMI were independent predictors of the postoperative UI risk. However, none of the previous reports provided a multivariable risk classification tool aimed at prediction of the postoperative UI risk. The present paper addresses this void and provides an accurate UI risk classification tool that can be applied to patients treated with the traditional RRP as well as to patients treated with RALP. Moreover, the estimates provided account for surgical volume as well as elapsed postoperative UI period. This tool might be useful to accurately inform each patient about his postoperative UI risk, thus improving the quality of patient counselling. In our cohort, the risk of long-term UI was the lowest in younger, non-overweight patients with favourable preoperative IIEF-EF values. In consequence, it appears that these individuals may suffer the least from surgical sequelae of RRP such as UI. Similar results have also been obtained when sexual dysfunction was considered as the endpoint [6]. That being said, it may be argued that these individuals represent the optimal candidates for this treatment modality.

Despite these strengths, our study is not without limitations. First, because of the observational nature of our cohort, our findings must be interpreted within the context of the limitations applicable to observational data. Second, we adjusted our analyses for all available covariates. However, other unobserved confounders might have
contributed to the observed results. For example, data collection in our cohort was initiated at the time of patient admission to the hospital. Prior to this, all patients were extensively counselled about possible treatment options for PCa, including possible benefits and side effects of each approach. Thus, the decision to undergo RP followed patient and physician discussion about possible treatment options and expectations according to the clinical and oncological profile of each individual patient. However, in our prospectively filled database of surgically treated patients, it was not possible to retrieve functional and quality of life data of patients treated with other forms of therapy for PCa. Therefore, differences in subjective and objective impacts of different forms of therapeutic approaches could not be assessed in our study. It may be argued that some individuals included in our cohort, especially older and/or more overweight subjects, could have benefited from other treatment options potentially associated with more favourable functional outcomes. This limitation is shared with virtually all previous reports that addressed a similar endpoint [9,11,12,15,16].

Moreover, only a minority of the cases in our cohort had an extremely high BMI value (BMI > 30 kg/m²: 8.8%). Fourth, our novel model was based on the 'best' predictors of UI in a selected cohort of patients who did not suffer from preoperative UI. This may have contributed to the exclusion of preoperative IPSS score as a predictor of UI, which may seem counterintuitive. Finally, our cohort represents data from a single institution. It remains to be tested whether our findings are applicable to other cohorts. Therefore, a multicentric or a population-based validation of our model is warranted to confirm our results.

In conclusion, we developed and validated the first multivariable risk classification tool based on preoperative patient data that allows an accurate estimation of the postoperative UI rate in patients treated with NSRP. It appears that impotent men before RP as well as elderly and/or overweight patients are those harbouring the
highest risk of UI after RP. This tool may significantly help in improving patient counselling as well as in optimizing patients’ expectations about their functional status after surgery.

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Conflict of Interest

None declared.

References

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Abbreviations: RP, radical prostatectomy; PCa, prostate cancer; UI, urinary incontinence; NSRP, nerve-sparing RP; CCI, Charlson Comorbidity Index; BMI, body mass index; IPSS, International Prostate Symptoms Score; IIEF-EF, International Index of Erectile Function – Erectile Function domain; RRP, retropubic RP; RALP, robotic-assisted laparoscopic radical prostatectomy; ICIQ-SF, International Consultation on Incontinence Modular Questionnaire – short form.