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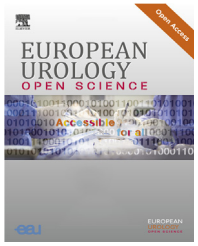

Prostate Cancer

Predicting Urinary Function Outcomes Following Low-dose-rate Brachytherapy for Prostate Cancer

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Abstract

Background and objective: Our aim was to develop a tool using readily available clinical parameters to predict the probability of poor urinary function following low-dose-rate brachytherapy (LDR-BT) for localized prostate cancer.
Methods: Data from the multicentre, prospective Swiss LDR-BT cohort were analyzed for men treated with LDR-BT. Inclusion criteria were minimum follow-up of 3 yr or postoperative treatment with transurethral resection of the prostate (TURP). A total of 914 men were analyzed, with complete data available for 607 men. Pre-interventional variables assessed were International Prostate Symptom Score (IPSS), prostate volume (PV), maximum urinary flow rate, prostate-specific antigen, postvoid residual urine volume, and age. The primary outcome was poor urinary function after LDR-BT, defined as an IPSS-Quality of Life score >3 (“mostly dissatisfied” or worse) at 3 yr or the occurrence of TURP during follow-up. Associations were evaluated using univariable and multivariable logistic regression. Receiver operating characteristic curve analysis was also performed.
Key findings and limitations: Poor urinary function outcomes were observed in 46 patients (5.0%). Significant predictors included pre-interventional IPSS (adjusted odds ratio [aOR] per point 1.18; $p < 0.001$) and PV (aOR per ml, 1.04; $p = 0.004$). Limitations of the study include potential selection bias and the absence of external validation.
Conclusions and clinical implications: Pre-interventional IPSS and PV were significant predictors of poor urinary function after LDR-BT for prostate cancer. A risk calculator based on these parameters was developed to assist individualized treatment

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planning. Further studies are needed to validate these findings before they can be applied in routine clinical practice.

Patient summary: We created a tool to predict the likelihood of urinary problems after a type of radiotherapy called brachytherapy for prostate cancer. The size of the prostate and urinary symptoms before treatment were associated with poor urinary function after treatment. This tool could help doctors and patients in making informed decisions about treatment for prostate cancer.

1. Introduction

Low-dose-rate brachytherapy (LDR-BT) is an effective and accepted standard of care for patients with localized prostate cancer. According to current international guidelines, LDR-BT alone is recommended as a treatment option for cT1b–2a tumors that meet specific criteria. These criteria include International Society of Urological Pathology (ISUP) grade group 1 (Gleason 3 + 3 = 6) with carcinoma involvement in ≤50% of the biopsy cores or ISUP grade group 2 (Gleason 3 + 4 = 7) with ≤33% positive cores. Further recommendations for patient selection outlined in international guidelines include a prostate-specific antigen (PSA) level of ≤10 ng/ml, prostate volume (PV) of ≤60 ml, and no severe micturition symptoms [1–3].

LDR-BT is a minimally invasive procedure and has oncological results comparable to those for radical prostatectomy (RP) and external beam radiation therapy (EBRT) in correctly selected patients [4]. In general, the side-effect profile of LDR-BT compares favorably to both RP and EBRT, with a lower risk of urinary and sexual side effects [5,6]. However, a small percentage of patients may experience poor functional outcomes after LDR-BT, such as issues with erectile function and/or urination [7,8]. Urinary dysfunction may present as urinary frequency, urgency, and difficulty in voiding [9]. Transient urinary symptoms typically improve over time [10], but persistent symptoms requiring transurethral resection of the prostate (TURP) can lead to permanent incontinence [11]. Previous research has identified the maximum urinary flow rate (Qmax) and prostate volume (PV) as predictors of postinterventional urinary retention after LDR-BT [12-14]. However, there is limited understanding of the variables associated with long-term morbidity after LDR-BT.

Current consensus suggests that patients with an International Prostate Symptom Score (IPSS) of ≤12 and Qmax of >15 ml/s are at the lowest risk of suffering from micturition symptoms after LDR-BT [1,13,15]. While LDR-BT is a proven and effective treatment option, adequate patient counseling and careful patient selection are crucial because of the potential significant morbidity associated with postinterventional urinary symptoms [11]. Patients at risk would benefit from TURP before undergoing LDR-BT [16] or a different treatment modality such as RP [17]. In this study we assessed a large prospective, multicentre cohort of patients treated with LDR-BT and analyzed the association between commonly available pre-interventional variables and the risk of long-term urinary symptoms after LDR-BT. We also developed a formula to estimate the risk of poor urinary function after LDR-BT for individual patients.

2. Patients and methods

2.1. Patient selection and ethics

This is an analysis of prospectively collected data from the Swiss LDR-BT registry, a national multicentre cohort that has continuously enrolled patients treated with LDR-BT in Switzerland since September 2004. All patients were treated with ^{125}I seeds using a prescribed dose of either 145 Gy or 160 Gy to the prostate. Approval was obtained from the local ethics committee (EKOS 22/111) and the registry is listed in the portal for clinical trials in Switzerland (SNCTP no. 886). Oncological outcomes, radiation doses, and risk factors were analyzed for data collected between September 2004 and June 2018 and reported separately by Viktorin-Baier et al [18]. Following seed implantation, functional and oncological follow-up evaluations were conducted at 6 wk, 6 mo, and 12 mo, and annually thereafter. In this study, we performed an in-depth assessment of urinary function outcomes for this cohort.

2.2. Study design

The literature lacks a clear definition of poor urinary function outcomes after LDR-BT for prostate cancer. Traditional metrics such as Qmax and the postvoid residual urine volume (PVR) do not necessarily reflect patients' subjective wellbeing [19]. Therefore, we defined a composite endpoint that includes subjective assessment and the need for surgical intervention. Poor urinary function after LDR-BT was defined as either an IPSS-Quality of Life (QoL) score >3 (where 4 = mostly dissatisfied, 5 = unhappy, and 6 = terrible) at the 3-yr mark or TURP at any time during follow-up. Patients from the Swiss LDR-BT cohort with baseline data and either an IPSS-QoL score at 3 yr or documented TURP during follow-up were included in the analysis for the primary endpoint.

2.3. Outcome measures

The primary endpoint of the study was the poor urinary function composite measure, defined as IPSS-QoL >3 at 3 yr or TURP at any time during follow-up. The following pre-interventional predictors were evaluated: age at inter-

vention, PV (ml), PSA (ng/ml), IPSS, Qmax (ml/s), and PVR (ml).

2.4. Statistical analysis

Statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) under macOS Catalina 10.15.7. The pROC v1.16.2 package was used for receiver operating characteristic (ROC) curve analysis. Univariable and multivariable logistic regression analyses were used to test the association of each predictor with the primary endpoint. Owing to highly skewed distributions, PSA and PVR were log(x + 1)-transformed. Regression coefficients and their confidence intervals (CIs) were converted to odds ratios (ORs) with 95% CIs for the increase in risk of a poor outcome for each unit increment in the value of the predictor. For log-transformed predictors, the OR refers to a unit increase on the log(x + 1) scale, that is, a 2.7-fold increase on the (x + 1) scale of the predictor.

For predictors that were significant in univariable models (IPSS and PV) and the multivariable model, the relationship between predictor values and the predicted risk of poor urinary function was plotted. ROC curve analysis was performed for individual predictors and for the probability of poor urinary function predicted by the multivariable logistic model. The area under the ROC curve (AUC) was calculated as an overall measure of discrimination, with CIs determined via bootstrapping. For predictors showing a significant association with outcome and for predictions from the multivariable model, optimal cutoffs were determined as the values that maximized the sum of sensitivity and specificity.

3. Results

3.1. Prediction of poor urinary function after LDR-BT

A total of 914 patients were included in the analysis. Poor urinary function after LDR-BT was observed in 46/914 patients (5.0%), of whom 23 had undergone TURP and 23 had IPSS-QoL >3 at 3 yr. Complete data were available for 607 patients, which were used to calculate the multivariable model. Median follow-up was 50.1 (range 36.1–97.5) mo. Pre-interventional patient characteristics are presented in Table 1. The group with poor urinary function after LDR-BT had significantly higher median IPSS at baseline (8 vs 5; $p < 0.001$) and larger median PV (38.7 vs 33.0 ml; $p = 0.002$; Table 1). The distribution of variables for both groups is illustrated in Figure 1.

ORs with 95% CIs for the risk of poor urinary outcome for each variable are shown in Table 2. Two variables were statistically significant: IPSS, with an OR of 1.13 (95% CI 1.07–1.20; $p < 0.001$) in the univariable model and an OR of 1.18 (95% CI 1.10–1.27; $p < 0.001$) in the multivariable model; and PV, with an OR of 1.04 (95% CI 1.02–1.07; $p = 0.001$) in the univariable model and an OR of 1.04 (95% CI 1.01–1.07; $p = 0.004$) in the multivariable model. Age, PSA, Qmax, and PVR did not reach statistical significance (Table 2).

3.2. Formula for calculating the risk score

The multivariable logistic model was used to calculate a risk score for predicting the probability of poor urinary function after LDR-BT. The risk calculator is provided as a separate Excel file in the Supplementary material.

$$\text{Risk score} = -5.55975 - 0.01897 \times \text{Age} + 0.16380 \times \text{IPSS} + 0.04255 \times \text{PV} + 0.04243 \times \text{Qmax} + 0.11157 \times \log(\text{PVR} + 1) + 0.10494 \times \log(\text{PSA} + 1)$$

$$\text{Predicted probability of poor functional urinary outcome} = \frac{e^{\text{risk score}}}{1 + e^{\text{risk score}}}$$

As shown in Figure 2, the predicted risk of a poor urinary outcome with higher IPSS (Fig. 2A), higher PV (Fig. 2B), and lower risk score (Fig.2C). The predicted risk was close to 0% for patients with a risk score below −4. It remained below 5% for patients with a risk score below −3 (61% of the patients) and exceeded 20% for patients with a risk score above −1.5 (5% of the patients). Nine patients (1.5%) had a risk score above −1; four of them had poor urinary function after LDR-BT, and this proportion (44%) was correctly predicted by the model (Fig. 2C).

ROC curve analysis revealed that PV and IPSS had the highest AUC values at 0.644 und 0.64, respectively, while all other predictors had AUC values of ∼0.5 (Supplementary Fig. 1A). The multivariable model had an AUC value of 0.743 (Supplementary Fig. 1B). Optimal cutoff values for PV and IPSS were calculated on a purely statistical basis (Table 3). The IPSS cutoff was 6.5 (95% CI 4.5–10.5), with sensitivity

Table 1 – Results for each predictor in the overall cohort and the groups stratified by urinary function outcome

Predictor	Sample [a] (n)	Median result (interquartile range)		
		Overall cohort	Poor urinary function outcome [b]	
			No	Yes
Age (yr)	914	64 (60–68)	64 (60–68)	64 (57–68)
IPSS	906	5 (2–8)	5 (2–8)	8 (4–11)
Prostate volume (ml)	889	33.1 (26.8–41.9)	33.0 (26.5–41.2)	38.7 (32.0–47.1)
Prostate-specific antigen (ng/ml)	913	5.5 (4.1–7.5)	5.5 (4.1–7.5)	6.5 (4.3–7.6)
Maximum flow rate (ml/s)	640	16.4 (12.0–22.3)	16.4 (12.0–22.2)	16.5 (11.8–23.4)
Postvoid residual volume (ml)	766	0.0 (0.0–23.0)	0.0 (0.0–22.8)	5.0 (0.0–37.8)

IPSS = International Prostate Symptom Score.
[a] Differences in sample size are because of missing data.
[b] Poor urinary function outcome defined as an IPSS Quality of Life score >3 at 3 yr or transurethral resection of the prostate at any time during follow-up.

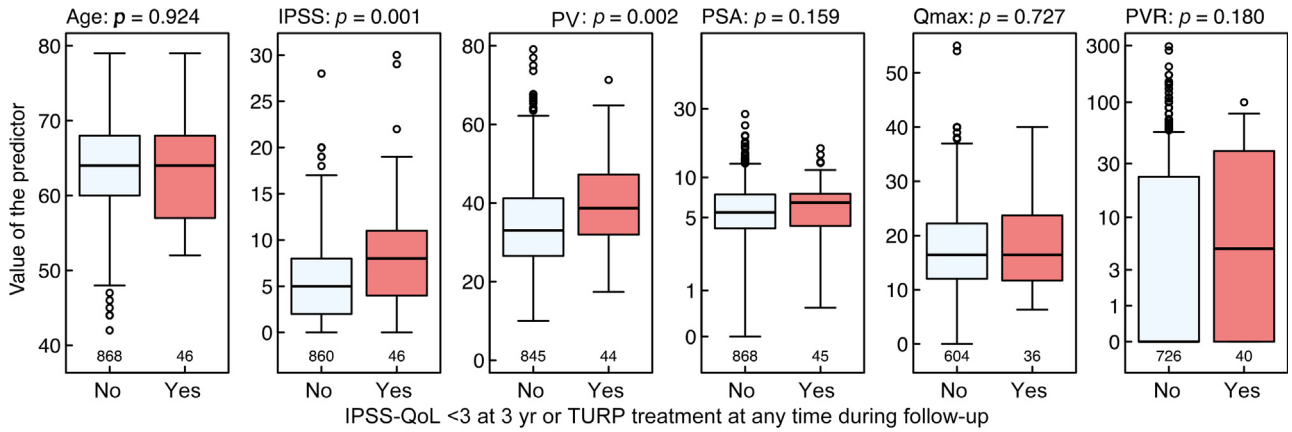

Fig. 1 – Distribution of values for the different predictors stratified by urinary function outcome. The *p* values are from Wilcoxon rank-sum tests. The number of patients with data available for the predictor is given below each box. IPSS = International Prostate Symptom Score; PV = prostate volume (ml), PSA = prostate-specific antigen (ng/ml); Qmax = maximum flow rate (ml/s); PVR = postvoid residual volume (ml); QoL =quality of life; TURP = transurethral resection of the prostate.

Table 2 – ORs with 95% CIs and *p* values from a Wald test for the association of each predictor with poor urinary function in univariable and multivariable models

Predictor	Univariable models			Multivariable model		
	n [a]	OR (95% CI)	*p* value	*n* [a]	OR (95% CI)	*p* value
Age	914	1.00 (0.96–1.05)	0.952	607	0.98 (0.93–1.04)	0.513
IPSS	906	1.13 (1.07–1.20)	<0.001	607	1.18 (1.10–1.27)	<0.001
Prostate volume	889	1.04 (1.02–1.07)	0.001	607	1.04 (1.01–1.07)	0.004
Prostate–specific antigen	913	1.42 (0.79–2.60)	0.255	607	1.11 (0.57–2.31)	0.77
Maximum flow rate	640	1.01 (0.97–1.05)	0.613	607	1.04 (0.99–1.09)	0.075
Postvoid residual volume	766	1.12 (0.93–1.34)	0.223	607	1.12 (0.91–1.38)	0.287

CI = confidence interval; IPSS = International Prostate Symptom Score; OR = odds ratio.
[a] Differences in sample size are because of missing data.

of 0.61 (95% CI 0.33–0.78) and specificity of 0.69 (95% CI 0.50–0.89). The PV cutoff was 34.7 ml (95% CI 30.7–42.0), with sensitivity of 0.75 (95% CI 0.48–0.93) and specificity of 0.56 (95% CI 0.38–0.77).

4. Discussion

We analyzed data from one of the largest prospective, multicentre cohorts collecting data for long-term functional and oncological outcomes in patients with prostate cancer treated with LDR-BT [18]. Elevated baseline IPSS and larger PV were significantly associated with poor urinary function after LDR-BT. Conversely, Qmax, PVR, age, and preoperative PSA did not show significant associations.

Long-term data from 914 patients were used to create a patient-specific tool (Supplementary material) for estimating the risk of poor urinary function after LDR-BT. To the best of our knowledge, this is the first risk calculator developed for this purpose. The calculator uses six readily available patient parameters to calculate an individual's risk as a percentage. The risk calculator includes PSA, age, Qmax, and PVR, despite their lack of statistical significance, because of their clinical relevance and potential utility in future external validation. We believe that this tool will provide a genuine benefit for patients as there are discrepancies between major international guidelines regarding optimal cutoffs for key parameters such as IPSS, PV, and Qmax [1,2].

We defined a poor urinary function outcome as an IPSS-QoL score >3 at 3-yr follow-up or receipt of TURP at any time during follow-up. The 3-yr follow-up point was chosen to assess long-term effects, incorporating both objective surgical intervention and subjective IPSS-QoL scores. The IPSS questionnaire is a well-established tool for assessing urinary symptoms [7,20] and depression [21] after LDR-BT. We applied a strict cutoff of IPSS-QoL >3 for inclusion in the study, thereby including IPSS-QoL scores of 4 (mostly dissatisfied), 5 (unhappy), and 6 (terrible). We therefore believe that the definition we used adequately identifies patients with a poor urinary function outcome during long-term follow-up after LDR-BT. Prediction of acute toxicity following LDR-BT, such as acute urinary retention (AUR) and temporary catheterization, was beyond the scope of our study.

Ohashi et al [22] reported that up to 85% of patients developed urinary symptoms following LDR-BT, which generally improved over time. Transient worsening of several parameters during the first few months after LDR-BT with subsequent normalization over time was reported by Langley et al [23] and Iinuma et al [24]. A similar decrease in urinary function outcomes was seen in the Swiss LDR-BT

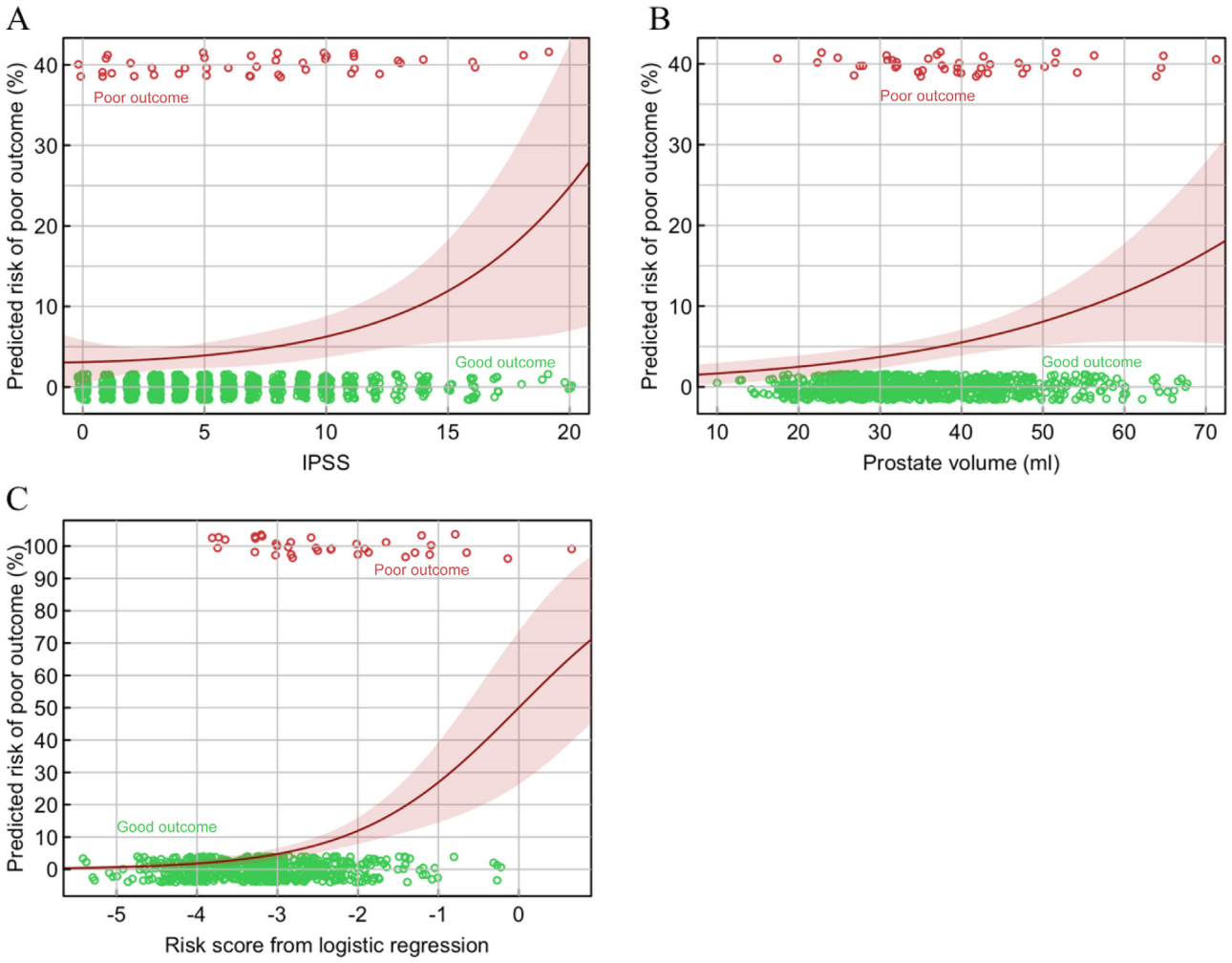

Fig. 2 – Risk of poor urinary function outcome (IPSS Quality of Life >3 at 3 yr or transurethral resection of the prostate at any time during follow-up) predicted by (A) IPSS, (B) prostate volume, and (C) the risk score calculated from the multivariable model. The red line indicates the predicted risk and the shaded areas represent 95% confidence intervals for the predicted risk at a given point on the *x*-axis. The distribution of individual predictor values associated with good and poor urinary function outcomes is shown by green and red points, respectively. IPSS = International Prostate Symptom Score.

Table 3 – Receiver operating characteristic curve results for significant predictors and the multivariable model

	AUC (95% CI)	Optimal cutoff (95% CI)	Sensitivity [a] (95% CI)	Specificity [a] (95% CI)	PPV [a] (95% CI)
IPSS	0.64 (0.55–0.73)	6.5 (4.5–10.5)	0.61 (0.33–0.78)	0.69 (0.50–0.89)	0.10 (0.07–0.17)
PV (ml)	0.64 (0.56–0.71)	34.7 (30.7–42.0)	0.75 (0.48–0.93)	0.56 (0.38–0.77)	0.08 (0.06–0.11)
Model	0.74 (0.66–0.82)	4.6% (2.2–11.9%)	0.80 (0.43–1.00)	0.63 (0.31–0.93)	0.12 (0.08–0.31)

AUC = area under curve; CI = confidence interval; IPSS = International Prostate Symptom Score; PV = prostate volume; PPV = positive predictive value.
[a] At the optimal cutoff.

cohort, with the greatest deterioration in Qmax and IPSS observed 1–3 mo after LDR-BT [18] and a gradual improvement thereafter. According to our definition, 95% of patients in the Swiss cohort did not have a poor long-term urinary function outcome.

Numerous studies have shown a correlation between high IPSS and greater toxicity after LDR-BT [12,13,25,26]. Therefore, all international guidelines recommend assessment of IPSS before treatment [1–3]. Urinary toxicity rates were acceptable for patients with pretreatment IPSS <20, as reported by Terk et al [27] and Gutman et al [28]. The American Brachytherapy Society (ABS) recommends discussing elevated IPSS with patients to determine its accuracy, as conditions such as diabetes or diuretic use can cause higher IPSS unrelated to prostate issues. Thus, the ABS defines IPSS >20 as a relative contraindication for LDR-BT [2]. According to the European Association of Urology (EAU) guidelines, LDR-BT can be offered to patients with good urinary function, defined as IPSS <12 and Qmax >15 ml/s [1]. Our study supports the use of IPSS and demon-

strates that it can be used to predict poor long-term urinary function outcomes, consistent with the literature on short-term toxicity.

The literature does not set an absolute upper PV limit for LDR-BT eligibility [29]. Larger PVs pose technical challenges but can yield acceptable toxicity and cancer control results [30,31]. Several studies demonstrated that PV was predictive of postimplant urinary retention or greater urinary morbidity after LDR-BT [12,13,32]. The ABS guidelines identify PV >60 ml as a relative contraindication [2], while the EAU guidelines do not specifically mention PV for patient selection [1]. Our data demonstrate the predictive impact of PV on poor long-term urinary function outcomes, with an optimal cutoff of 34.7 ml (95% CI 30.7–42). This value should be interpreted with caution owing to the relatively low AUC of 0.64. Achieving adequate dose distribution in larger prostates is difficult, making PV a critical factor in patient selection for LDR-BT. It should be noted that the IPSS and PV cutoffs were derived via statistical modeling for our data set and are not intended as strict clinical thresholds. These values are most informative when used together in the multivariable model and in the appropriate clinical context.

Williams et al [14] found that Qmax was the most important predictor of AUR and Martens et al [13] showed that patients requiring catheterization after LDR-BT had higher baseline IPSS and lower Qmax. According to the EAU guidelines, patients with the best outcomes after LDR-BT monotherapy have good urinary function, defined as IPSS <12 and Qmax >15 ml/s [1]. The ABS recommended caution and appropriate patient consent when Qmax is <10 ml/s and PVR is >100 ml, but these factors alone do not preclude LDR-BT as a treatment option [2]. In our study, Qmax was not a significant predictor of poor urinary function after LDR-BT. Reasons for the difference may be the differing definitions of the primary endpoint (short-term vs long-term) and the low number of patients with a poor urinary function outcome in our study. Furthermore, the median Qmax of 16.4 ml/s in our cohort probably reflects appropriate patient selection in line with current guideline recommendations. This relatively high Qmax may have obscured its potential predictive significance in our analysis.

Study limitations include the relatively small number of patients with a poor urinary function outcome (46/914, 5.0%), reflecting adequate patient selection and the low incidence of long-term urinary symptoms after LDR-BT. Despite good sensitivity and specificity, the positive predictive value of our tool is constrained by the low absolute number of patients in our cohort who experienced adverse events (Table 3). A further potential limitation is the lack of inclusion of other relevant parameters, such as the morphological configuration of the prostate (intravesical prostatic protrusion) and relevant medical history (α_1-blocker use or previous TURP). Further research using independent data sets may help in refining and externally validating our risk calculator.

Our risk calculator allows individual prediction of poor urinary function after LDR-BT, for which IPSS and PV are significant predictors. Poor urinary function has a significant impact on QoL and is therefore an important factor in treatment decisions [17]. The choice of treatment option for localized prostate cancer is determined not only by oncological outcomes but also by a variety of factors, including functional outcomes [33], and has a significant impact on patient QoL [34]. The risk calculator offers clinicians valuable additional information by identifying patients at higher risk of poor urinary function after LDR-BT, guiding discussions and supporting shared decision-making based on each patient's individual risk profile.

5. Conclusions

Our study shows that it is possible to predict the probability of poor urinary function after LDR-BT. IPSS and PV are significant predictors of poor urinary function outcomes. Our risk calculator can be used to calculate the risk of poor urinary function outcomes after LDR-BT and help patients in choosing the optimal therapy.

Author contributions: Manolis Pratsinis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pratsinis, Müllhaupt, Engeler, Rüedi.
Acquisition of data: Rüedi, Pratsinis, Schmid, Putora, Plasswilm, Schwab, Burkhardt, Thoeni, Hochreiter, Prikler, Suter, Stucki, Müntener, Blick, Schiefer, Müllhaupt, Engeler.
Analysis and interpretation of data: Müllhaupt, Engeler.
Drafting of the manuscript: Rüedi, Pratsinis.
Critical revision of the manuscript for important intellectual content: Pratsinis, Schmid, Putora, Güsewell, Plasswilm, Schwab, Burkhardt, Thoeni, Hochreiter, Prikler, Suter, Stucki, Müntener, Blick, Schiefer, Müllhaupt, Engeler.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.11.004.

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