Preoperative MRI-measured membranous urethral length as a predictor for urinary continence after prostate cancer surgery.

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Preface to the thesis

This thesis is article-based and includes an abstract, an acknowledgement statement, an introductory chapter, two articles, a discussion chapter, and an appendix. The first article is a systematic review with a meta-analysis on the association between magnetic resonance imaging measured pre-operative membranous urethral length and 12-month post-prostatectomy urinary continence. For this study, ethics board approval was not required. Dr. Rodney H. Breau, the supervisor of this thesis, helped to define a clinically meaningful objective for this work: how to better guide patients in their prostate cancer treatment choice based on their pre-operative risk of urinary incontinence. Dr. Cristina Negrean, the author of this thesis, reviewed the literature and verified that this question was not previously answered. Dr. Negrean established a protocol for a systematic review and registered it with PROSPERO. The literature search was conducted by a medical librarian. In collaboration with a second author, Dr. Negrean screened and selected articles for the review, determined the risk of bias in those articles, collected relevant data, and interpreted the results. Dr. Negrean wrote the manuscript, updated based on co-authors' and journal editor's suggestions and submitted for publication. Dr Breau and Dr McInnes, my supervisors, guided the research question and methods, provided support and feedback.

The second study is a validation cohort study, aiming to externally assess the performance of a prediction model for urinary continence recovery after prostatectomy. This model was identified from our systematic review and to our knowledge, had never been externally validated. Dr. Negrean wrote the protocol for the study and registered it with Open Science Framework. She prepared and submitted all the necessary documents for Ethics Board Approval from The Ottawa Hospital. After approval, she and five co-authors were trained by a

radiologist from The Ottawa Hospital to measure membranous urethral length on magnetic resonance images. After multiple rounds of training, the measurement technique was standardized with high interobserver agreement. Each author, including Dr. Negrean, measured approximately 200 membranous urethras from MRI. Dr. Negrean wrote the manuscript, updated it based on co-authors suggestions and then submitted it for publication. Dr Breau and Dr McInnes, my supervisors, guided the research question and methods, provided support and feedback.

Abstract

This thesis addresses prediction of post-prostatectomy urinary continence, which is of major importance to patients and clinicians. Urinary incontinence significantly impacts quality of life, and some patients may choose non-surgical treatments if their risk of post-surgery incontinence is unacceptably high. The membranous urethra is a small segment of the urethra surrounded by pelvic floor musculature. In theory, a longer membranous urethra on pre-operative imaging may signify a more robust sphincter complex and a lower probability of involuntary urinary leakage after surgery. In practice, data from several studies suggest MRI-measured membranous urethral length (MUL) is one of few predictors of post-prostatectomy continence. However, it is currently not clear how to use MUL when counseling patients since proposed prediction models have never been externally validated. To address this issue, we systematically reviewed the existing literature, and performed a meta-analysis, allowing us to conclude, with a moderate degree of confidence, that longer MUL is predictive of urinary continence after prostatectomy. We also observed that MUL measurement techniques vary between studies, posing a significant risk for miscalibration when applied to clinical practice. We then externally validated a published continence prediction model, by Jeong et al. We observed that the model has good calibration and discrimination when continence is defined as 0-1 incontinence pad/24h but does not perform well in predicting complete urinary continence (no incontinence pads needed). In conclusion, we now know the benefits and limits of a MUL prediction model that can be applied to our future patients.

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Introductory chapter

Prostate cancer is one of the leading causes of death worldwide with more than 300,000 deaths per year[1,2]. Patients with high-grade clinically localized (i.e. not metastatic) prostate cancer are faced with two main treatment options: radical prostatectomy (surgical) or radiation therapy (non-surgical)[3]. Both treatment approaches offer similar oncological outcomes, but the potential for adverse events differ[4]. Radiation therapy is less invasive than surgery but can lead to complications such as radiation cystitis, proctitis, erectile dysfunction, and secondary cancers[4]. On the other hand, radical prostatectomy is more invasive and can lead to erectile dysfunction and urinary incontinence[4]. Accurate prediction of treatment-related adverse effects is essential to help patients select the treatment that is most congruent with their values and preferences.

Among the most feared side effects of surgery is urinary incontinence. Generally, the risk of post-prostatectomy incontinence is stated to be between 1% and 40%[5], but even the terms "incontinence" and "continence" are not consistently defined. This broad range of outcome is likely confusing for patients as a 1% risk of urinary leakage may be acceptable, but a 40% is likely not. Urinary incontinence has a major impact on quality of life – independent of other outcomes, the mean quality of life score reported by severely incontinent patients was 30% compared to a mean quality of life score of 85% among continent patients[6]. The inability to accurately predict an individual's risk of incontinence is a major barrier to informed decision making.

Post-prostatectomy urinary continence is worst immediately post-surgery and often gradually improves, reaching a plateau at approximately 12 months[7,8], making 1-year post-prostatectomy continence the most clinically relevant time point to determine long-term urinary function. Incontinence beyond one year is unlikely to improve with conservative measures and

surgical interventions to improve continence can then be considered[7]. The factors most often associated with post-prostatectomy urinary continence are younger patient age and performance of neurovascular bundle sparing during surgery[9,10]. Recently, membranous urethral length (MUL), measured preoperatively by magnetic resonance imaging (MRI) has been suggested as an independent predictor for post-operative continence (Figure 1)[11]. The membranous urethra is a short segment of urethra (0.5 to 2.5cm) inferior to the prostate. As such, a longer MUL possibly serves as a proxy for a more robust urethral sphincter which also lies in this area[12].

The evidence evaluating MUL and post-surgery continence is mainly derived from retrospective cohort studies, some of which reported conflicting results[13,14]. Three systematic reviews on this topic have attempted to address the controversy. Since these reviews lack rigor, consistency, or clarity in methods, results, and outcome definitions, clear conclusions have not been drawn [9,11,12].

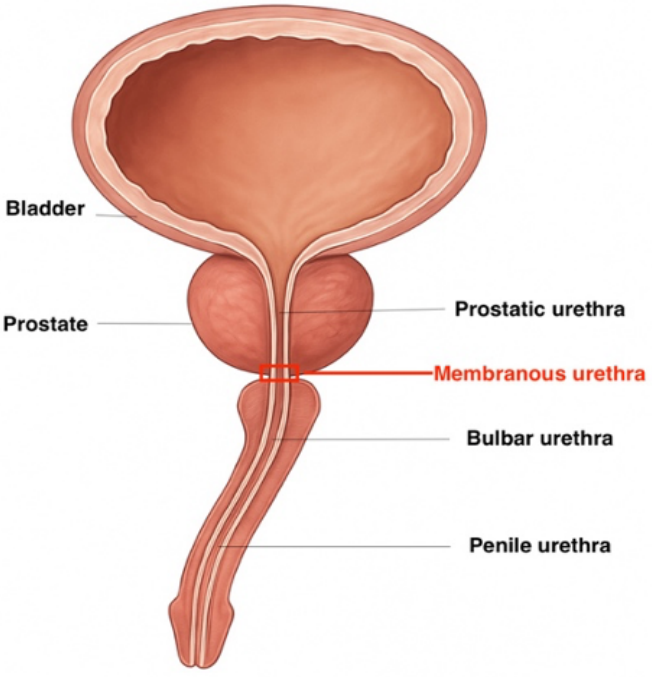

Figure 1. Anatomic depiction of the bladder, prostate and segments of urethra. The membranous urethra is represented in red.

Furthermore, the published systematic reviews are dated - one identified 6 studies that examined 12-month continence, but all 6 studies were published prior to 2015.

They predate the recent recommendations by the Canadian and American Urology Associations to adopt the routine use of pre-biopsy MRI of the prostate[15,16], and therefore lack data on routine preoperative MUL. The first objective of this thesis was to summarize our current understanding of the relationship between MUL and continence 12 months after prostatectomy, by performing a rigorous systematic review of the literature.

The second objective of my thesis was to determine if preoperative membranous urethral length, measured by MRI, could be used to narrow the estimate of continence following prostatectomy.

When advising patients on treatment options, physicians should avoid general risks and reference relevant patient-specific risk estimates, if possible. Ideally, prediction models should incorporate pre-operative patient factors that are independently associated with continence. Proposed models must then be externally "validated" to determine if the model performs well enough to be used in clinical practice. In our systematic review, we identified 4 proposed models to predict continence at 12 months after prostatectomy. To our knowledge, none of the urinary continence prediction models have been externally validated. The goal of the second article of this thesis was to externally validate the most promising published prediction model (based on methodologic rigor and highest internal discrimination).

In summary, the objectives of this thesis were to summarize the evidence evaluating the association between MRI-measured MUL and post-prostatectomy continence and to evaluate the performance of a proposed prediction model on a contemporary independent population of patients from our institution. The overall aim of this work is to improve pre-operative patient counseling through individualized estimation of post-operative adverse events.

Component articles chapter

Article 1:

Preoperative MRI membranous urethral length as a predictor of urinary continence after radical prostatectomy: a systematic review and meta-analysis

Preface

The objective of this systematic review was to summarize the available evidence of MRI measured membranous urethral length as a predictor for urinary continence and severe urinary incontinence at 12 months after prostatectomy. No Ethics Board Approval was necessary for this study. The paper is presented in the following format: abstract, introduction, material and methods, results, discussion, tables, figures and supplements. The contribution of each author is listed below:

- Dr Cristina Negrean – background literature review, writing the protocol and its registration with PROSPERO, article screening, data collection, results interpretation, manuscript writing, submission for publication.
- Ammar Alam - article screening, data collection, manuscript editing.
- Dr Duane Hickling – question refining, manuscript editing.
- Dr Humberto R. Vigil – question refining, manuscript editing.
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- Dr Ranjeeta Mallick – data analysis, manuscript editing.
- Rissa Shorr – literature search, manuscript editing.
- Dr Anathea S. Flaman – article screening, manuscript editing.

- Dr Matthew McInnes – question refining, manuscript editing.
- Dr Rodney H. Breau – question design and refining, results interpretation, oversight, manuscript editing.

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Competing interests

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ABSTRACT

Background and Objective: The evidence regarding membranous urethral length (MUL) and urinary continence after radical prostatectomy is inconsistent. The primary objective of this review was to evaluate the association between MUL and post-prostatectomy continence.

Methods: Multiple databases were searched up to August 31st, 2024. Studies evaluating the association between MRI-measured MUL and urinary continence at 12-months after prostatectomy were included. Published abstracts were excluded. The pooled association between longer MUL and continence was evaluated using meta-analysis with random-effects. Risk of bias was assessed using QUIPS. Certainty of evidence was determined using GRADE approach. PROSPERO protocol: CRD42023483229.

Key Findings and Limitations: Thirty studies (11,239 patients) were included. Risk of bias was low in most studies for measurement, confounding, and statistical analysis/reporting. Median MUL between studies ranged from 10.4 to 17.3 mm. Longer MUL (usually dichotomized at the median) was associated with greater probability of continence (15 studies, 4025 patients; pooled RR 1.30, 95%CI 1.18, 1.44; $p<0.0001$, $I^2=80\%$). After excluding high risk-of-bias studies, the association between longer MUL and continence remained significant (pooled RR 1.18, 95%CI 1.08, 1.29; $p=0.003$). The certainty of the association between MUL and continence was moderate. No publication bias was evident. The results are limited by high attrition bias.

Conclusion and Clinical implications: Longer preoperative MRI-measured MUL is associated with better urinary continence 12-months after radical prostatectomy, regardless of

continence definition and assessment method. MUL measurement techniques should be standardized and MUL should be incorporated in prognostic models.

What does this study add? This systematic review incorporates the latest evidence regarding the association between pre-operative MRI-measured membranous urethral length and post-prostatectomy urinary continence. These data allow us to be moderately confident that patients with longer pre-operative membranous urethral have lower risk of incontinence after prostatectomy. This review also highlights the need for validated measurements techniques and multi-factor models to optimize pre-operative patient counselling.

Patient Summary: Urinary incontinence after radical prostatectomy can significantly impact quality of life. We evaluated the association between pre-operative MRI-measured membranous urethra and the chance of urinary continence after surgery. Longer membranous urethra is associated with better chance of continence at 12 months after prostatectomy and should be used when counselling patients.

INTRODUCTION

Radical prostatectomy is one of the most common treatments for patients with localized prostate cancer[1]. An important outcome for patients after surgery is urinary continence[2]. The urinary function of most patients plateaus by 12-months after surgery and only a small percentage will gain additional urinary control after this period[3]. Pre-operative factors that have been associated with post-operative continence include: patient age, preoperative continence status, and pre-operative MRI-measured membranous urethral length (MUL)[4]. The most common intraoperative factor association with continence is peri-prostatic neurovascular bundle preservation [5,6].

The association between pre-operative MRI-measured MUL and post-operative continence has been recognized for many years[4,7,8], but clinical use of MUL remains low, perhaps due to poorly defined measurement techniques, poorly defined MUL thresholds, or uncertainty about how to apply the information in individual patients[9, 10]. Furthermore, the evidence consists mainly of single-center retrospective cross-sectional studies reporting a wide range of techniques and associations [4,8,10], which impedes the integration of MUL into clinical practice.

There have been 3 systematic reviews assessing MUL, among other MRI and tumor factors, predicting post-prostatectomy urinary outcomes[4,7,8]. A systematic review published in 2017 reported that longer MUL was associated with 12-months continence after prostatectomy (pooled OR 1.12, 95%CI 1.03-1.22; p=0.006)[7]. Other reviews suggest that MUL has the strongest and most consistent association with continence compared to other MRI characteristics,

such as prostate volume[8]. None of the systematic reviews considered urinary incontinence severity or certainty of evidence.

Since publication of previous reviews, there have been many new studies evaluating the association between MUL and continence. Therefore, a new systematic review is necessary to include contemporary studies that are likely less biased and more generalizable. Recent randomized trials support the use of MRI prior to prostate biopsy[11–13] and national guidelines have endorsed pre-biopsy MRI[14,15]. Therefore, it is expected that nearly every patient in tertiary care centers will have a pre-biopsy MRI available prior to radical prostatectomy. Since recent publications evaluating MRI MUL were not included in previous systematic reviews, the primary objective of this systematic review was to comprehensively describe the association between pre-operative MRI MUL and continence 12-months after radical prostatectomy. Our secondary outcome was to summarize the evidence evaluating the association between MUL and severe urinary incontinence.

METHODS

Conduct and reporting of this systematic review was in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 (PRISMA)[16], the Cochrane handbook[17] and Declaration of Helsinki. The study protocol was registered with PROSPERO (CRD42023483229). The secondary outcome was amended from mild and moderate incontinence to severe urinary incontinence because no studies specifically reported mild or moderate incontinence and only one study reported severe urinary incontinence.

Information sources

Using Embase, MEDLINE and Cochrane, we included publications in English peer-reviewed journals (Search strategy in Supplement A). Additionally, the bibliographies of the articles were reviewed to retrieve additional eligible papers. The sources were last consulted on August 31st, 2024. We excluded data from unpublished papers, abstracts from conferences and non-peer reviewed articles.

Eligibility criteria

Articles were included from 1989, when multiparametric MRI of the prostate was first described in the literature[18]. Randomized trials and cohort studies were included if they assessed adult males (18 years of age or older) with localized prostate cancer (Tany, N0, M0) undergoing radical prostatectomy. Participants were required to have MUL assessed on preoperative MRI. All MRI protocols (including studies which provided few details of the MRI protocol) were eligible. At a minimum, studies needed to report continence outcomes 12-months after prostatectomy. All methods of continence assessment were included. Studies were excluded if they examined patients with history of previous pelvic radiotherapy, history of previous androgen deprivation therapy, prostatectomy for non-oncologic reasons, missing continence data at 12-months, and animal studies.

Selection process

Using Covidence, two authors (C.N. and A.A.) independently reviewed titles and abstracts of all the articles based on previously outlined selection criteria. Duplicates were removed. Any discrepancies were addressed through discussion. The retained articles were independently

reviewed for data extraction at the full-text level by the same authors. Disagreement between authors were resolved through discussion.

Data collection process

Authors abstracted data using a-priori specified data collection forms. A randomized half of studies were extracted by one author and verified by the second author. For the second half of studies, the authors switched roles. Authors of the included manuscripts were contacted via email for additional missing information.

Data items

Descriptive cohort information (age, ISUP grade group, clinical stage, prostatic specific antigen, type of surgery, nerve spare status), MUL (mean/median, range, methods for assessment including MRI sequence and plane, assessors' blinding, inter-observer agreement), sample size, definition of the continence outcome and analytic approach were collected. For the complete list of abstracted items, please refer to Supplement B. If information was missing or unclear, no assumptions were made.

The primary outcome of interest was 12-month post-operative continence (absence of urinary incontinence) and the secondary outcome was 12-month severe incontinence. In all cases, the outcomes were defined by the study authors. Due to heterogenous definitions of continence, no unified definition was possible, rather the study definition was used to define continence or

severe incontinence. The most common definition for continence was “0 pads or up to 1 safety pad in 24h”. The definition for severe urinary incontinence was “3 or more pads in 24h”.

Risk of bias assessment

Risk of bias assessment was performed in duplicate by two authors (C.N. and A.A.) independently using QUIPS (Quality In Prognosis Studies). To judge the bias for each domain, authors used a set of rules outlined in Supplement C. Any discrepancy was resolved through discussion.

Effect measures

The associations between MUL and urinary function in individual studies were documented using the effect measure reported by study authors. Unadjusted associations between MUL and continence were calculated if enough information was available in the manuscript.

Synthesis methods

Most studies presented MUL as a dichotomous variable (usually dichotomized at the median). For synthesis, we used dichotomous groupings from the original studies. MUL was used as a continuous variable in only three studies and insufficient information was available for meta-analysis. If a study provided the number of continent and incontinent patients in each MUL group, the unadjusted risk ratio (RR) for each study was calculated and pooled in a meta-analysis using a random-effects model. Risk ratio (i.e. relative risk) was used instead of odds ratios since risk ratios are more intuitive to patients and clinicians. Statistical heterogeneity was quantified using I^2. To assess for possible causes of heterogeneity, forest plots were ordered based on year

of publication, sample size, and risk of bias. Sensitivity analysis was performed removing high risk of bias studies. Statistical analysis was performed using Comprehensive Meta-Analysis - version 2.2.064.

Reporting bias assessment

Publication bias was assessed using visual inspection of the funnel plot and Egger's test.

Certainty of assessment

The confidence in the cumulative evidence was assessed using GRADE Guidelines 28 for prognostic factor studies by unanimous consensus among authors [19].

RESULTS

Study selection

After removing duplicates, the literature search yielded a total of 767 articles. Following title and abstract screening, 66 articles underwent full text screening, and 30 articles were included (Fig.1).

Study characteristics

The characteristics of the thirty included articles are listed in Table 1. Fifteen included enough information and were appropriate to be included in a meta-analysis. The studies were published between 2009 and 2024 and all were cohort studies. The most frequent country of origin was Korea (n=9) [5,20–27]. Sample size of studies ranged from 27 to 2,849 with a total of 11,239 patients.

Median patient age in studies ranged from 60 to 70 years old. Most patients had clinical stage 2 (range 17% to 87%) and ISUP grade group 2 prostate cancer (range 32% to 85%). The most frequently performed surgical approach was robotic assisted radical prostatectomy in 16 studies [5,20,22,25,28–39]. Neuro-vascular bundle spare during prostatectomy was inconsistently reported. Among those with complete reporting, bilateral nerve sparing was most frequently performed [5,21,22,34,38–43].

The mean MUL among studies ranged from 9.3 to 15.6 mm, median MUL ranged from 10.4 to 17.3 mm, while the individual participant MUL ranged from 5.0 to 34.3 mm. MUL was measured most frequently using a 3 Tesla MRI machine (in 11 studies) on T2 MRI sequence (in 19 studies) on sagittal or sagittal and coronal planes (in 18 studies). Assessors were not described in 15 studies. In manuscripts with available information, MUL was most often measured by radiologists (n=9). Assessors were blinded to continence status in 12 studies while no information on blinding was available in the remainder of included studies. Inter-observer agreement between assessors was reported in four studies using interclass correlation coefficient (0.62, 0.82) [35,43], kappa coefficient (0.76) [5] or correlation percentage (89%) [37]. No study reported specific definitions used for agreement/disagreement (i.e. within a prescribed distance).

Risk of bias in the studies

Risk of bias was low for most studies in the domains of outcome measurement, confounding and statistical analysis/reporting (Fig. 2). Prognostic factor measurement bias was low in 17 articles and high in 5 articles (Fig 2; Supplement E) [22–24,34,44]. Reasons for assigning high risk of bias included limited information on blinding, incomplete reporting of methods used to measure MUL, and absence of interobserver agreement assessment. Attrition bias was judged

high in more than half of the studies due to unreported loss to follow-up. Eleven manuscripts reported loss to follow-up ranging between 0.5% and 64.5% due to missing continence evaluation (n=6), unknown reasons (n=4) and unavailable MRI (n=1). No study used techniques to assesses for the potential impact of attrition on results. Lastly, participation bias was low in 14 articles, moderate in 13 (primarily because of unreported sampling frame), and high in three articles (mainly due to low participation rate for unknown reasons) [25,32,43].

Results of individual studies

Our primary outcome, urinary continence at 12-months after radical prostatectomy, was available in all 30 studies. Among them, 19 studies reported the odds of continence, ten studies reported the odds of incontinence [25,30–33,38,39,43–45] and one study reported both continence and incontinence outcomes. Severe urinary incontinence, was reported in one study[34]. Definitions of continence and incontinence varied significantly across the articles. The most frequent definition of continence was "0 pads or 1 safety pad in 24h" (11 studies) [21,22,24,25,29,31,33,41,43,45,46] followed by "0 pads/24h" (eight studies) [5,27,28,30,39,40,42,47]. Incontinence was most frequently defined as "any urine loss" (three studies) [36,44,45]. Both continence and incontinence were most frequently assessed using a validated questionnaire (19 studies) such as EPIC, ICIQ and modified IPSS (Supplement D).

MUL was presented as a dichotomous variable (usually at median MUL) in 27 studies and as a continuous variable in three studies. A longer MUL, as a dichotomous variable, was associated with higher probability of 12-month urinary continence. The association between MUL and continence was statistically significant in 19 of 27 studies (OR ranged between 0.96 and 13.6). Only two studies reported the difference in performance of post-operative continence

prediction models before and after addition of MUL. In both cases, area under the curve (AUC) increased with addition of MUL suggesting an improved performance (baseline AUC increased from 0.584 to 0.779[36] and from 0.589 to 0.674[40]). Three studies presented MUL as a continuous variable and reported that every additional millimeter of MUL significantly increased the odds of continence (OR per mm 1.20, 95% CI 1.06-1.37, p=0.005; OR per mm 1.20, 95%CI 1.07-1.35, p=0.002; and OR per mm 1.25, 95%CI 1.05-1.54, p=0.01; Table 1)[33,35,41]. In addition to MUL, other factors independently associated with continence were: age (13 studies [21–25,27,35,37,40,43,44,47,48]), BMI (5 studies [21,28,29,37,40]), levator muscle measurement (4 studies [32,36,38,40]), nerve spare (4 studies [22,24,30,45]), prostate volume (4 studies [22,24,28,45]) and surgery type (3 studies[22,22,27]).

The secondary outcomes of severe urinary incontinence was only reported by Clements et al.,[34] who found that longer MUL (dichotomous at 10 mm threshold) was associated with significantly lower odds of severe 12-month urinary incontinence (OR 0.42, 95%CI 0.21, 0.86; p=0.014).

Results of syntheses

Fifteen studies [5,21,26,28,32,36,38,39,41,43–47,49] contained enough information and were deemed appropriate to be included in the meta-analysis of MUL and continence (all reported MUL as a dichotomous variable). Fifteen studies were not eligible, as authors reported only adjusted OR (n=7[23,24,29–31,34,40]), the MUL was only reported as a continuous variable (n=2 [33,35]), there was not enough information to calculate associations (n=5[22,25,37,42,48]), or there was insufficient information to convert hazard ratios to risk ratios (n=1[27]). In all cases, risk ratios were calculated based on the raw numbers presented.

Studies included in the meta-analysis were published from 2009 to 2024 in Europe, Asia, and the United States and included a total of 4025 patients. Ten studies dichotomized at the median (range 10.3–17.3 mm)[5,26,32,36,39,41,44,46,49], four at the mean (range 10.4 - 14.3 mm)[21,28,43,45] and one study dichotomized at an optimized threshold based on receiver operating curve analysis (14.0 mm)[47]. Longer MUL was associated with statistically higher probability of 12-month urinary continence (unadjusted pooled risk ratio 1.30, 95%CI 1.18, 1.44; p<0.0001). The statistical heterogeneity calculated using I^2 was 80% (Figure 3).

Clinical heterogeneity was judged to be minimal based on comparable patient populations included in studies (age, tumor grade, tumor stage, etc; Table 1). To investigate potential sources of heterogeneity, we visually inspected the forest plot re-arranged by risk of bias (Figure 3), sample size, and year of publication (Supplement F). In a sensitivity analysis excluding high risk of bias studies[26,36,43], the pooled association between longer MUL and continence was similarly statistically significant (RR 1.18, 95% CI 1.08, 1.29; p=0.003; Supplement G). Sensitivity analysis excluding small studies (less than 150 patients) had a pooled RR of 1.32 (95% CI 1.17, 1.50; p <0.0001; Supplement G). A similar finding was observed for studies published in 2022 and later (pooled RR 1.43, 95%CI 1.02, 2.0; p=0.001; Supplement G).

Reporting bias

Reporting bias was assessed via visual inspection of the funnel plot (Fig. 4). It suggested low risk of publication bias (Egger's test intercept 1.22, p=0.22).

Certainty of evidence

Using a GRADE approach, our overall confidence in the body of evidence was moderate. The certainty was downgraded due to inconsistency between studies. (Supplement H).

DISCUSSION

MRI-measured pre-operative MUL may be one of the most important factors associated with post-radical prostatectomy urinary continence. As pre-biopsy MRI has become the standard of care, nearly every person with prostate cancer will have a prostate MRI that can be used for prediction of treatment outcomes. This systematic review and meta-analysis supports a clinically significant association between longer MUL and post-operative continence. Based on this summary of the evidence, we believe prediction models of post-prostatectomy incontinence should include MRI-measured MUL. The impact of these models on patient outcomes must then be externally validated and assessed using a measurement of clinical utility (e.g. decision curve analysis).

Previously published systematic reviews on this topic included fewer studies, which limited sensitivity analyses[7,8]. Also, as pre-operative use of MRI is likely becoming more common, the inclusion of the most contemporary studies may be less prone to selection bias (i.e. historic cohorts may have been biased toward patients with more advanced disease), and thus, more generalizable to contemporary patients [14,15]. Compared to other reviews, our literature search identified fourteen new studies, seven of which were published in 2022 or later. Among those seven articles, five presented significant associations between MUL and post-operative continence. Two studies did not observe a statistically significant association between MUL and continence, possibly due to low statistical power [28,31]. In summary, findings from our review

suggest that the association between longer MRI-measured MUL and better post-operative continence is present in contemporary patients receiving surgery. Sensitivity analyses eliminating high risk of bias studies and smaller studies show that the association is robust.

The severity of incontinence significantly affects patients' quality of life[2]. Therefore, we also reviewed the published associations between MUL and severe urinary incontinence. The lone study that reported on this outcome showed that longer preoperative MUL was associated with 58% lower odds of severe incontinence 12 months after prostatectomy [50].

Despite the association between MUL and post-operative continence, application to clinical practice has been limited, perhaps due to inconsistencies in measurement. We observed that the mean and median MUL ranged widely between studies, suggesting variability in measurement techniques. Indeed, correctly determining landmarks for MUL measurement especially at the proximal boundary can be challenging. Depending on the plane used (coronal vs sagittal vs both), results can vary significantly[10]. Evaluation of inter-observer agreement of MUL was sparsely reported. Recent efforts to standardize MUL measurement may improve inter- and intra-observer consistency, which could boost the external validity and clinical utility of prediction models that incorporate MUL[10, 28, 7].

While not the primary purpose of this systematic review, we identified four articles which incorporated MUL in a prognostic model - as a continuous variable in three models and as a dichotomous variable in one model[22,31,40,44]. Other factors included in these models were: age (four studies), nerve sparing status (two studies), previous trans-urethral resection of the prostate (one study), thickness of the urethra wall (one study), prostate volume (one study), surgical approach (one study), presence of PIRADS 3 or higher lesion at the apex (one study), body mass

index (one study) and American Society of Anesthesiologists score (one study). The discrimination of these models assessed by c-statistic ranged between 0.65 and 0.72. Internal validation was performed using bootstrap resamples[44], split-sample[22,40] or temporal validation[31]. To our knowledge, none of the models assessed clinical utility and none have been externally validated which precludes adoption into clinical practice.

Our findings are limited by the retrospective nature of the included studies, high attrition bias, variable MUL measurement technique, incomplete reporting, heterogeneous continence and incontinence definitions as well as its assessment methods. Nevertheless, not restricting our search to any of those elements allowed us to include a larger body of evidence and to highlight some literature gaps that could be addressed in future research.

CONCLUSION

There is moderate certainty that longer MUL is associated with higher probability of urinary continence at 12 months after radical prostatectomy. MUL measurement techniques should be standardized and MUL should be included in prostate MRI reports. Well-calibrated prediction models that incorporate MUL should be developed and externally validated in contemporary patients. Using this approach of accurate measurement and optimal clinical integration will allow for improved patient counseling on realistic continence expectations and treatment selection based on individual estimates of adverse treatment effects.

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TABLES

Table 1: Description of studies on membranous urethral length measured on MRI as a predictor for either continence or incontinence at 12 months after radical prostatectomy.

Study ID		Population							Exposure		Outcome
Author (year)	**Study design**	**Country**	**Sample size**	**Age (years)**	**Preoperative Gleason score**	**Type of surgery**	**Nerve sparing status**	**Follow-up (months)**	**Type of MRI machine, sequence, and plane**	**Membranous urethral length on MRI (mm)**	**Adjusted odds ratio for continence at 12 mo**
Clements (2022)	Cohort	USA	1430	Median 63.0 (Range 53-67)	6: 9.1% 7 (3+4): 53.0% 7 (4+3): 19.0 % 8: 12.0 % 9 or 10: 6.7 % unknown: 0.2%	Robotic (79%) LSC (19%) Open (2.7 %) Unknown (0%)	None: 8.6% Unilateral: 21% Bilateral: 71%	Unknown	Unknown	Short (<10): 13% Normal (>10): 87% Unknown: 9.2%	CONTINENCE: OR[1] 0.96 (p=0.2) Good function: OR[1] 1.01 (p=0.9) Social continence: OR[1] 1.30 (p=0.022) Severe INCONTINENCE OR[1] 0.62 (p <0.001)
Grivas (2017)	Cohort	Netherlands, Italy	439	Continent: Mean 62.4 (SD[2] 6.3) Incontinent: Mean 63.5 (SD[2] 6.1)	Continent: Mean 6.9 (SD[2] 0.8) Incontinent Mean 6.8 (SD[2] 0.9)	Robotic (100%)	Unknown	Mean 16 (Range 12-24)	3 Tesla, T2, coronal and sagittal	**MUL[5] sagittal:** Continent: Mean 12.9 (SD[2] 1.7) Incontinent: Mean 11.5 (SD[2] 1.5) **MUL[5] coronal:** Continent: Mean 12.9 (SD[2] 1.6) Incontinent: Mean 11.6 (SD[2] 1.6)	CONTINENCE: MUL[5] sagittal: OR[1]: 1.565 (95% CI: 1.362-1.798); p < 0.0001
Kim (2020)	Cohort	United Kingdom	190	Mean 62.0 (SD[2] 6.5)	6: 4 (2.3%) 7 (3+4): 116 (61.1%) 7 (4+3): 58 (30.7%) ≥ 8: 12 (6.3%)	Robotic (100%)	None: 40 (21%) Unilateral: 95 (50%) Bilateral: 55 (29%)	Median 21	3 Tesla, T2, coronal and sagittal	MUL[5] coronal: Mean 14.6 (SD[2] 3.0) MUL[5] sagittal: Mean 14.2 (SD[2] 2.7)	CONTINENCE: Adjusted not given Non adjusted HR[3] 1.425 (95%CI: 1.187-1.869), p=0.001
Kim (2019)	Cohort	Korea	529	Median 66.0 (IQR[4] 60-71) Mean 65.4 (SD[2] 7.4)	6: 154 (39.1%) 7: 263 (59.7%) ≥ 8: 112 (21.2%)	Robotic (100%)	None: 30 (5.7%) Unilateral: 214 (40.5%) Bilateral: 285 (53.9%)	Unknown	3 Tesla, unknown, sagittal	Mean 12.3 (SD[2] 11.7) Median 11.7 (IQR[4] 10.2-14.1)	CONTINENCE: OR[1] 0.993 (95% CI: 0.942-1.048), p 0.803
Ko (2020)	Cohort	Korea USA	580	Group 1: Mean 61.6 (SD[2] 7.51) Group 2: Mean 62.8 (SD[2] 7.45)	≤ 6: 132 (22.8%) 7: 360 (62.1%) ≥ 8: 84 (14.5%)	Robotic (100%)	Unknown	Unknown	3 Tesla, unknown, coronal, and sagittal	Mean 18.3	CONTINENCE MUL[5]>1.4cm OR[1]:11.255 (95%CI: 1.070-118.407), no p value
Lamberg (2022)	Cohort	USA	586	Mean 63.0 (SD[2] 7)	6: 129 (22%) 7: 321 (55%) 8: 58 (10%) 9: 76 (13%) 10: 3 (<1%) Unknown: 3 (<1%)	Robotic (100%)	None: 44 (7%) Unilateral: 46 (8%) Bilateral: 9 (2%) Unknown: 9 (2%)	Unknown	3 Tesla, unknown, coronal and sagittal	Continent: Mean 15.5 (SD[2] 3.7) Incontinent: Mean 13.4 (SD[2] 3.2)	CONTINENCE OR[1] 0.83 (95%CI: 0.73-0.94), p=0.005
Lim (2012)	Cohort	Korea	94	Mean 65.1 (SD[2] 5.82)	≤6: 52 (55.3%) 7: 30 (31.9%) ≥8: 12 (12.8%)	Open (100%)	None: 30 (31.9%) Unilateral: 25 (26.6%) Bilateral: 39 (41.5%)	Unknown	Unknown, T2, sagittal	Mean 10.40 (SD[2] 3.75)	CONTINENCE OR[1] 8.245 (95%CI: 1.830-37.149), p=0.006
Lin (2020)	Cohort	Australia	602	Mean 64.0 (SD[2] 6.63)	Unknown	Laparoscopic (100%)	None: 61 (27.5%) Bilateral: 85 (38.3%) Unilateral: 76 (34.2%)	Unknown	Unknown, unknown, coronal and mid-sagittal	Coronal: Mean 14.62 (SD[2] 3.61) Sagittal: Mean 14.64 (SD[2] 3.66)	CONTINENCE OR[1]: 1.22 (95CI: 1.06-1.46), p = 0.011

Study ID		Population							Exposure		Outcome
Author (year)	**Study design**	**Country**	**Sample size**	**Age (years)**	**Preoperative Gleason score**	**Type of surgery**	**Nerve sparing status**	**Follow-up (months)**	**Type of MRI machine, sequence, and plane**	**Membranous urethral length on MRI (mm)**	**Adjusted odds ratio for continence at 12 mo**
Matsushita (2015)	Cohort	USA Japan	2849	Median 60.0 (IQR[4]: 55-65)	≤6: 1487 (52%) 7: 1141 (40%) ≥8: 221 (8%)	Open: 1487 (52%) Laparoscopic: 931 (33%) Robotic: 431 (15%)	None: 272 (10%) Unilateral: 447 (15%) Bilateral: 2130 (75%)	Unknown	1.5 Tesla and 3 Tesla, T1 and T2, coronal, sagittal and transverse	Median 12 (IQR[4]: 10-15)	CONTINENCE OR[1] 1.14 (95%CI: 1.10-1.17), p <0.001
Nitta (2023)	Cohort	Japan	419	Mean 67.8 (Range 44-80)	6: 59 (14.1%) 7: 225 (53.7%) ≥8: 135 (32.2%)	Robotic (100%)	None: 278 (66.3%) Unilateral: 132 (31.5%) Bilateral: 9 (2.1%)	Unknown	Unknown	Mean 11.5 (Range: 4.6–21.2)	CONTINENCE: Adjusted not given Not adjusted: HR[3] 0.685 (95%CI: 0.630-2.355), p=0.188
Ohara (2022)	Cohort	Japan	300	Robotic: Mean 65.0 (Range: 60–69) Open: Mean 62.0 (Range: 57–65)	Unknown	Robotic and open	Bilateral: RARP 118 (59.6%) Bilateral: Open 73 (64.6%)	Unknown	3 Tesla, T2, coronal	Robotic: Median 14.27 (IQR[4]: 12.12–16.46) Open: Median 13.57 (IQR[4]: 11.12–16.03)	CONTINENCE MUL[5] <13.57 vs. ≧13.57 mm: Robotic: OR[1] 4.4, p = 0.01 Open: OR[1] 5.1, p = 0.01
Ota (2021)	Cohort	Japan	50	Retzius sparing robotic: Median 67.0 (IQR[4]: 63–70) Conventional robotic: Median 69.0 (IQR[4]: 66–72)	Unknown	Robotic (100%)	Unknown	Minimum 12	Unknown, unknown, sagittal	Retzius sparing robotic: Median 12.7 (IQR[4]: 11.2– 13.9) Conventional robotic: Median 11.3 (IQR[4]: 10.2– 12.8)	CONTINENCE OR[1]: 1.430 (95%CI: 0.773–2.650) p = 0.254
Yang (2020)	Cohort	China	150	Mean 69.0 (SD[2] 7.8)	6: 11 (7.3%) 7: 64 (42.7%) ≥8: 75 (50%)	Laparoscopic (100%)	None: 46 (30.7%) Unilateral: 6 (4.0%) Bilateral: 98 (65.3%)	Unknown	3 Tesla, unknown, coronal	Mean 13.8 (SD[2] 3.7)	CONTINENCE HR[3] 1.10 (95%CI: 1.04-1.16), p<0.001
Jeong (2012)	Cohort	Korea	708	Mean 68.5 (Range: 48-76)	Unknown	Open: 50 (68.5%) Laparoscopic:10 (13.7%) Robotic:13 (17.8%)	Unilateral or bilateral: 31 (42.5%)	Mean: 41.6 (range 25-79)	Unknown	Mean 12.5 (Range: 6.0–19.0)	CONTINENCE OR[1] 1.94 p=0.041
Jeong (2014)	Cohort	Korea	872	Mean 65.6 Median 67 (Range: 37-82)	Unknown	Open: 416 (47.7%) Robotic: 456 (52.3%)	None: 338 (38.8%) Unilateral: 95 (10.9%) Bilateral: 439 (50.3%)	Mean: 42.6 (range 12-102)	1.5 Tesla, unknown, unknown	Mean 12.8 Median 13.0 (Range: 5.0–23.0)	CONTINENCE OR[1]: 1.16 (95%CI: 1.07–1.25), p<0.001
Hikita (2020)	Cohort	Japan	119	Median 66.0 (IQR[4]: 48-76)	6: 21 (17.6%) 7: 50 (42.0%) ≥ 8: 48 (40.4)	Robotic (100%)	Bilateral or unilateral: 51 (42.9%)	Unknown	Unknown, T2, coronal	Median 12.1 (IQR[4]: 8.9-16.1)	INCONTINENCE: OR[1] 0.95 (95% CI: 0.85-1.10), p=0.039
Kitamura (2023)	Cohort	Japan	310	Median 67.0 (IQR[4]: 63-71)	Unknown	Robotic (100%)	None: 108 (35%) Unilateral: 101 (32.5%) Bilateral: 101 (32.5%)	Unknown	1.5 Tesla, T2, mid-sagittal	Median 10.4 (IQR[4]: 9.2-11.6)	INCONTINENCE: MUL[5] >10.3 mm: OR[1] 0.259 (p= 0.0676) MUL[5] >9.2 mm: OR[1] 0.467 (p=0.1506)
Sauer (2019)	Cohort	Germany	316	Median 65.0 (Range: 46–77)	Unknown	Open and robotic	None: 21 (7%) Unilateral: 65 (20%) Bilateral: 230 (73%)	Unknown	3 Tesla, T2, sagittal	Mean 10.5 (Range: 5.0–25.0)	INCONTINENCE OR[1]: 0.7 (95%CI: 0.56–0.89) p= 0.006
Son (2013)	Cohort	Korea	258	Mean 65.3 (SD[2] 6.4)	≤6: 45 (17.4%) 7 (3+4): 133 (51.6%) 7 (4+3): 45 (17.4%) ≥8: 35 (13.6%)	Open and robotic	Unilateral or bilateral: 124 (48.1%)	12	Unknown, T2, coronal	Mean 13.1 (SD[2] 2.4)	CONTINENCE HR[3]: 2.070 (95%CI: 1.089-3.935), p=0.026
Kohjmoto (2020)	Cohort	Japan	179	Median 67.0 (IQR[4]: 63-71)	≤6: 50 (27.9%) 7: 74 (41.3%) ≥8: 55 (30.7%)	Robotic and laparoscopic	Unilateral or bilateral: 80 (44.7%)	24	Unknown, T2, coronal	Median 17.3 (IQR[4]: 14.6-19.7)	CONTINENCE HR[3]: 1.04 (95%CI: 0.99-1.09), p=0.06
Fonseca (2024)	Cohort	Portugal	158	Median 60.0 (IQR[4]: 58-68)	GG 1: 13 (8%) GG 2: 95 (60%) GG 3: 44 (28%) GG 4: 5 (3%) GG 5: 1 (1%)	Robotic (100%)	None: 21 (14) Unilateral: 41 (27) Bilateral: 88 (59)	12	3 Tesla, T2, axial and sagittal cross-referenced with coronal	Median 15.1 (IQR[4]: 12.1-17.4)	INCONTINENCE OR[1]: 0.830 (95%CI: 0.706–0.975) p= 0.024

Study ID		Population							Exposure		Outcome
Author (year)	**Study design**	**Country**	**Sample size**	**Age (years)**	**Preoperative Gleason score**	**Type of surgery**	**Nerve sparing status**	**Follow-up (months)**	**Type of MRI machine, sequence, and plane**	**Membranous urethral length on MRI (mm)**	**Adjusted odds ratio for continence at 12 mo**
Sadahira (2018)	Cohort	Japan	70	Continent: Median 65.0 (Range: 55-76) Incontinent: Median 70.0 (Range: 54-77)	≤6: Continent: 8 (22%); Incontinent:4 (12%) 7: Continent: 16 (43%); Incontinent: 15 (45%) ≥8: Continent: 13 (35%); Incontinent: 14 (43%)	Robotic (100%)	Unknown	Unknown	1.5 or 3 Tesla, T2, axial and sagittal	Continent: Median 12.1 (Range: 9.7-14.9) Incontinent: Median 10.3 (Range: 8.7-12.4)	INCONTINENCE OR[1]: 0.37 (95%CI: 0.20-0.68) p=0.002
Lee (2020)	Cohort	Korea	2301	2004-2006 ≤70 years: Mean 62.7 (SD[2] 6.3) >70 years: 72.8 (SD[2] 1.8) 2007-2009 ≤70 years: 63.1(SD[2] 5.7) >70 years: 73.4 (SD[2] 2.0) 2010-2012 ≤70 years: 63.6 (SD[2] 5.5) >70 years: 73.3 (SD[2] 2.0) 2013-2015 ≤70 years: 62.6 (SD.[2] 5.7) >70 years: 73.4 (SD[2] 2.0)	≤6: ≤70 years: 236 (10.3%) >70 years: 36 (1.6%) 7: ≤70 years: 1300 (56.5) >70 years: 484 (21.0) ≥8: ≤70 years: 155 (6.7) >70 years :80 (3.5)	Open and robotic	Unilateral or bilateral ≤70 years: 1233 (53.6%) >70 years: 342 (14.9%) Unknown 726 (31.5%)	Unknown	Unknown	2004-2006 ≤70 years: Mean 13.2 (SD[2] 2.4) >70 years: Mean 13.0 (SD[2] 2.2) 2007-2009 ≤70 years: Mean 13.0 (SD[2] 2.6) >70 years: Mean 12.7 (SD[2] 2.6) 2010-2012 ≤70 years: Mean 11.8 (SD[2] 3.1) >70 years: Mean 12.2 (SD[2] 2.9) 2013-2015 ≤70 years: Mean 11.5 (SD[2] 3.1) >70 years: Mean 11.4 (SD[2] 3.0)	CONTINENCE ≤70 years: OR[1] 1.08 (95%CI: 1.03–1.14), p=0.003 >70 years: OR[1] 1.118 (95%CI: 1.10-1.28) p <0.001
Tienza (2018)	Cohort	Spain	746	Mean 63.0 Median 63.0 (Range: 41-83)	≤6: 500 (70%) 7: 149 (21%) ≥8: 63 (9%)	Open and Laparoscopic	Unknown	Unknown	1.5 Tesla, T2 sagittal	Continent: Mean 14.5 (SD[2] 0.32) Incontinent: Mean 13.6 (SD[2] 0.29)	INCONTINENCE OR[1]: 0.173 (95%CI: 0.046–0.64) p= 0.009
Yamashita (2022)	Cohort	Japan	121	Median 69.0 (IQR[4]: 65-72)	≤6: 10 (8%) 7: 49 (40%) ≥8: 62 (51%)	Robotic (100%)	Unknown	Unknown	1.5 or 3 Tesla, T2, sagittal	Median 15.0 (IQR[4]: 12.0–17.5)	INCONTINENCE OR[1]:0.80 per 1mm (95%CI: 0.65–0.95) p=0.01
Tienza (2015)	Cohort	Spain	528	Mean 63.5 Median 63 (Range 41-83)	≤6: 339 (66.3 %) 7: 119 (23.3 %) ≥8: 53 (10.4 %)	Open and Laparoscopic	Unilateral or bilateral: 297 (54 %)	Unknown	1.5 Tesla, T2, sagittal	Mean 14.3 (Range: 6.7–34.3)	INCONTINENCE OR[1]: 0.134 (95%CI: 0.032–0.563) p= 0.006
Cho (2015)	Cohort	Korea	27	Mean 66.5 (SD[2] 6.0)	Mean 7.4 (SD[2] 0.8)	Open (100%)	Unknown	12	3 Tesla, T2, mid sagittal and coronal	Mean 13 (SD[2] 16)	CONTINENCE Adjusted not given Calculated unadjusted: OR[1] 1.5
Song (2017)	Cohort	Korea	186	Mean 64.5 (SD[2] 7.6) Median 65.0 (Range: 38.0–79.0)	≤6: 33 (17.7%) 7: 137 (73.7%) ≥8: 16 (8.6%)	Robotic (100%)	None or unilateral: 82 (44.1%) Bilateral: 104 (55.9%)	Unknown	Unknown, T2, coronal and sagittal	Mean 15.6 (SD[2] 2.7) Median 15.9 (Range: 7.2–22.9)	INCONTINENCE MUL[5] ≤13.5 mm: OR[1] 5.95 (95%CI: 1.85–19.21) p= 0.003 MUL[5] > 13.5 and ≤16mm: OR[1] 1.10 (95%CI: 0.28–4.28) p= 0.895 MUL[5] ≤16 vs. >16 mm: OR[1] 2.72 (95%CI: 0.97–7.64) p=0.057

Study ID		Population							Exposure		Outcome
Author (year)	**Study design**	**Country**	**Sample size**	**Age (years)**	**Preoperative Gleason score**	**Type of surgery**	**Nerve sparing status**	**Follow-up (months)**	**Type of MRI machine, sequence, and plane**	**Membranous urethral length on MRI (mm)**	**Adjusted odds ratio for continence at 12 mo**
Paparel (2009)	Cohort	USA	64	Median 61.0 (IQR[4]: 55-66)	≤6: 5 (8%) 7: 32 (50%) ≥8: 18 (28%)	Open: 57 (89%) Laparoscopic: 7 (11%)	None: 7 (10.9%) Unilateral: 15 (23.4%) Bilateral: 25 (39.1%) Unknown: 17 (26.6%)	At least 12	1.5 Tesla, T2, sagittal and coronal	Median 14 (IQR[4]: 11-15)	CONTINENCE HR[3]: 1.20 per 1mm (95%CI: 1.07-1.35), p=0.002
Schmid (2020)	Cohort	Switzerland	42	Continent: Mean 61.2 (SD[2] 8.8) Incontinent: Mean 65.3 (SD[2] 7.2) Excellent: Mean 60.0 (SD[2] 9.6) Poor: Mean 65.0 (SD 8.3)	G7: Continent: 16 (72.7%) Incontinent: 18 (90%) Excellent: 6 (60%) Poor: 10 (100%) GS 8–9: Continent: 6 (27.3%) Incontinent: 2 (10%) Excellent: 4 (30%) Poor: 0 (0%)	Robotic (100%)	None: Continent: 7 (31.8%); Incontinent: 7 (35%); Excellent: 2 (20%); Poor: 5 (50%) Unilateral: Continent: 7 (31.8%); Incontinent: 6 (30%); Excellent: 4 (40%); Poor: 2 (20%) Bilateral: Continent: 8 (36.4%) Incontinent: 7 (35%); Excellent: 4 (40%); Poor: 3 (30%)	Unknown	3 Tesla, T2, sagittal	Continent: Mean 14.5 Incontinent: Mean 9.3	INCONTINENCE Adjusted not given Unadjusted OR[1] 0.05 (95%CI: 0-0.29), p=0.034

[1] OR: odds ratio; [2] SD: standard deviation; [3] HR: hazard ratio; [4] IQR: interquartile range; [5] MUL: membranous urethral length.

FIGURES

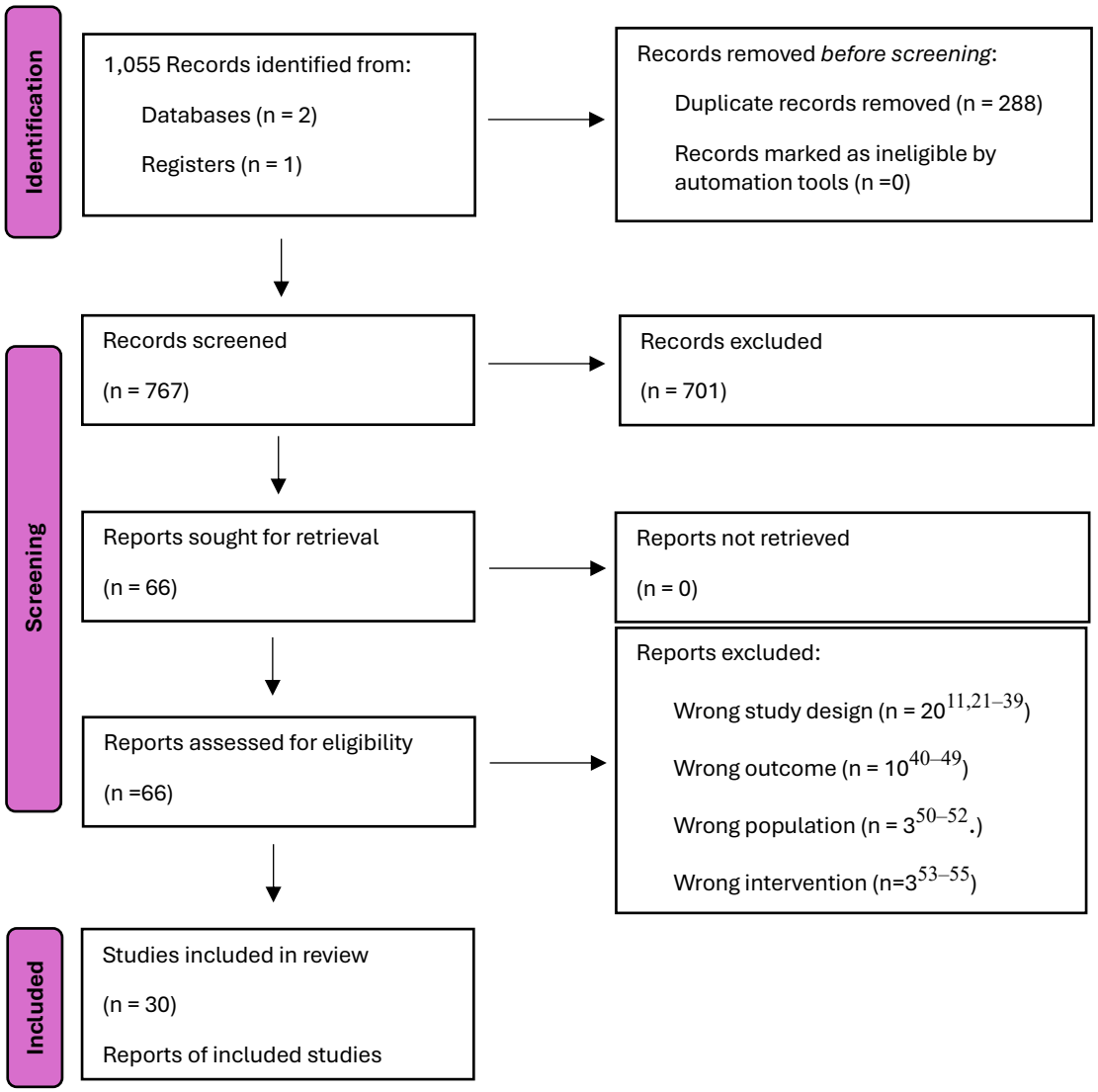


Figure 1: PRISMA flow diagram of the screened studies.

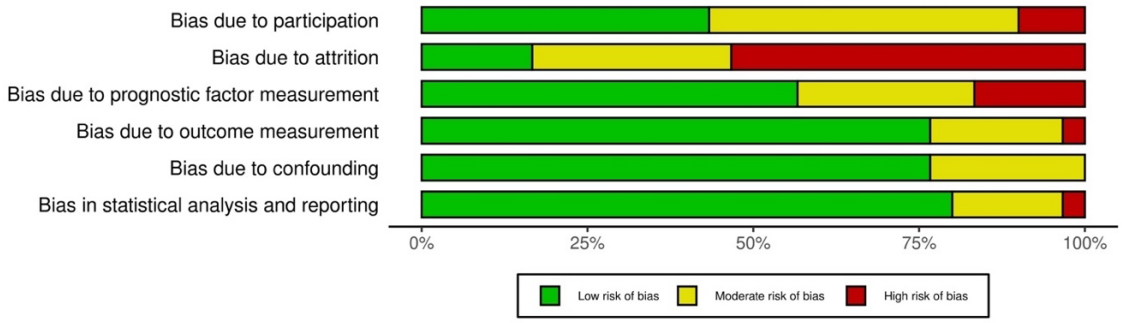


Figure 2. Risk of bias assessment of the 30 studies included.

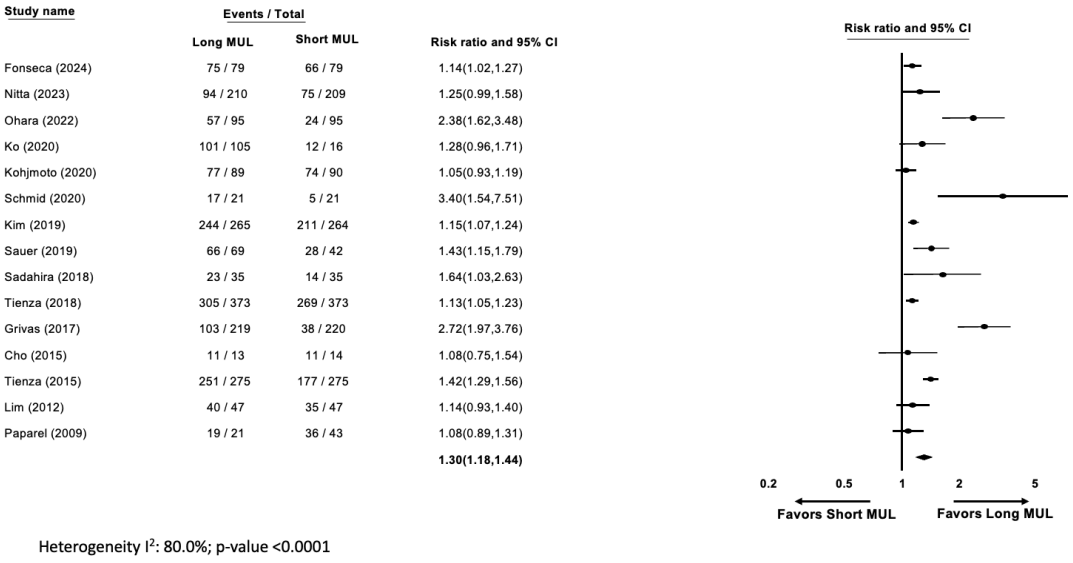


Figure 3: Unadjusted risk ratios with 95% confidence intervals of membranous urethral length (MUL), and probability of continence 12 months after radical prostatectomy. Studies were arranged based on risk of bias from lowest to highest.

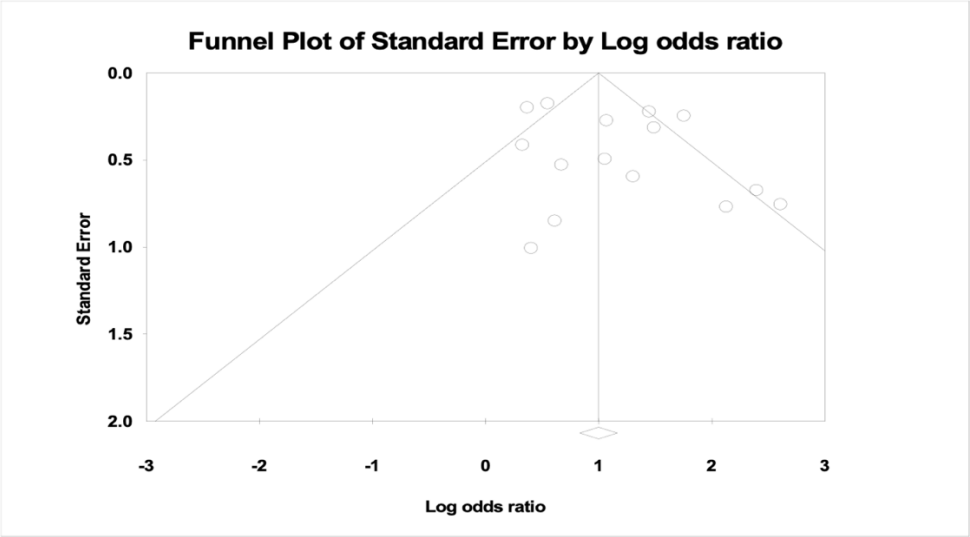


Figure 4. Funnel plot suggesting no publication bias in the articles regarding the association between membranous urethral length and continence at 12-months after radical prostatectomy.

SUPPLEMENT A

Search strategy

Articles were identified using the following search strategy

Ovid MEDLINE(R) ALL <1946 to November 10, 2023>

1 exp prostatectomy/ 36329

2 (prostatectom or RARP).tw,kf. 36659*

3 1 or 2 48643

4 Urinary Incontinence/ 24728

5 incontinen.tw,kf. 57997*

6 continence.tw,kf. 16394

7 Urinary Bladder, Overactive/ 5988

8 (overactiv adj3 (bladder or detrusor)).tw,kf. 10670*

9 voiding dysfunction.tw,kf. 2653

10 or/4-9 79434

11 3 and 10 6239

12 Magnetic Resonance Imaging/ 479023

13 (mpMRI or mri or magnetic resonan imag*).tw,kf. 497281*

14 fmri.tw,kf. 58047

15 mul.tw,kf. 32929

16 (urethra adj2 length*).tw,kf. 901*

17 Urethra/dg 2745

18 or/12-17 742238

19 11 and 18 423

20 exp animals/ not humans/ 5169565

21 19 not 20 421

22 limit 21 to yr="1989 -Current" 405

23 limit 22 to english language 353

Embase Classic+Embase <1947 to 2023 November 13>

1 exp prostatectomy/ 73821

2 (prostatectom or RARP).tw. 61603*

3 1 or 2 81249

4 exp urine incontinence/ or incontinence/ 106896

5 incontinen.tw. 94394*

6 continence/ 14490

7 continence.tw. 26198

8 overactive bladder/ or urinary dysfunction/ 22803

9 (overactiv adj3 (bladder or detrusor)).tw. 18690*

10 voiding dysfunction.tw. 4666

11 or/4-10 162036

12 3 and 11 12510

13 nuclear magnetic resonance imaging/ or functional magnetic resonance imaging/ or multiparametric magnetic resonance imaging/ 1113114

14 (mri or magnetic resonan imag* or fmri or mpMRI).tw. 769228*

15 urethral length/ 258

16 mul.tw. 102359

17 (urethra adj2 length*).tw. 1614*

18 or/13-17 1333602

19 12 and 18 1183

20 conference abstract.pt. 4951106

21 (exp animal/ or nonhuman/) not exp human/ 7978165

22 19 not (20 or 21) 722

23 limit 22 to yr="1989 -Current" 714

24 limit 23 to english language 660

EBM Reviews - Cochrane Central Register of Controlled Trials <October 2023>

1 exp prostatectomy/ 2562

2 (prostatectom or RARP).tw,kw. 4762*

3 1 or 2 5636

4 Urinary Incontinence/ 1947

5 incontinen.tw,kw. 11208*

6 continence.tw,kw. 2292

7 Urinary Bladder, Overactive/ 1044

8 (overactiv adj3 (bladder or detrusor)).tw,kw. 3431*

9 voiding dysfunction.tw,kw. 333

10 or/4-9 14140

11 3 and 10 1110

12 Magnetic Resonance Imaging/ 9611

13 (mri or magnetic resonan imag* or mpMRI).tw,kw. 39399*

14 fmri.tw,kw. 6332

15 mul.tw,kw. 2418

16 (urethra adj2 length*).tw,kw. 82*

17 Urethra/dg 1

18 or/12-17 45548

19 11 and 18 61

20 limit 19 to yr="1989 -Current" 61

21 conference proceeding.pt. 224708

22 20 not 21 36

Supplement B

Data items collected.

Source of data	• Title • First author • Year of publication • Study period • Study design • Duration of follow-up

Population	• Participants' inclusion, exclusion criteria and recruitment method
	• Patients' description
	  ○ Age
	  ○ Body mass index (BMI)
	  ○ Comorbidities (American Society of Anesthesiology index)
	  ○ Preoperative lower urinary tract symptoms (LUTS) captured by IPSS[1] or by EPIC[2] questionnaire
	  ○ Preoperative Prostate Specific Antigen (PSA)
	  ○ Preoperative Gleason score
	  ○ Preoperative clinical stage
	  ○ Preoperative prostate volume
	• Type of surgical approach
	  ○ Open
	  ○ Robotic
	  ○ Laparoscopic
	• Nerve spare status
	  ○ None
	  ○ Unilateral
	  ○ Bilateral

Primary predictor	• Preoperative MRI measured membranous urethral length (MUL[3]).
	  ○ MUL[3] (mean or median or range or standard deviation)
	  ○ Blinding of assessors
	  ○ Inter-observer agreement of measurements (if applicable)
	  ○ MRI sequence used for measurement
	  ○ MRI plane used for measurement (coronal, sagittal, or both)
	  ○ Type of MRI machine

Other comparator predictors	• Number and type of comparators used in each study will be extracted
Outcomes	• Definition of the outcomes. • Method used for outcome measurement. • Blinding to MUL[3] measurements when assessing continence (if applicable)
Sample size	• Sample size calculation (if applicable) • Number of participants
Missing data	• Number of participants with missing preoperative MRI-MUL[3] or continence assessment. • Number of loss to follow-up ○ How missing data was handled in the studies of interest
Analysis	• Statistical approach used Methods used for selection of prognostic factors for multivariable analysis.
Results	• Unadjusted and adjusted RR[4], OR[5], model coefficient and their associated confidence intervals. • Using raw data, risk ratios, hazard rations and model coefficient were converted to odds ratios, if possible.

[1] IPSS: International Prostate Symptom Score; [2] EPIC: Expanded Prostate Cancer Index Composite; [3] MUL: membranous urethral length; [4] RR: relative risk; [5] OR: odds ratio.

Supplement C

QUIPS tool – domain bias:

Participation:

- all information and all/consecutive patients = low risk
- partial information = moderate risk
- no information or very low participation rate= high risk

Attrition:

- all information = low risk
- partial information = moderate risk
- no information = high risk

Prognostic:

- all information, definition yes and blinding yes =low risk
- definition/blinding yes and partial information = moderate risk
- no definition and no blinding = high risk

Outcome:

- all information = low risk
- definition yes, but not validated = moderate risk
- no definition = high risk

Confounding:

- all information = low risk
- just reporting but no adjustment for age/nerve = moderate risk
- no reporting for age/nerve sparing and suboptimal Table 1= high risk

Statistical analysis and reporting:

- all information = low risk
- enough data or clear model inclusion = moderate risk
- no data and no model = high risk

Supplement D

Table 2: Definitions and assessment methods of continence and incontinence at 12-months after radical prostatectomy.

Author (year)	Definition of incontinence	Definition of continence	Assessment method
Clements (2022)	Severe: ≥3 pads/day	• Continence: 0 pads/day • Social continence: ≤1 pad/day	Questionnaires
Grivas (2017)	• Incontinence: Any involuntary urine loss • Mild: 1-5 points ICIQ-SF[1] • Moderate: 6-12 points ICIQ-SF[1] • Severe: 13-18 points ICIQ-SF[1]	ICIQ-SF[1] question 4a (When does urine leak?): "never"	ICIQ-SF[1] Questionnaire
Hikita (2020)	-	0 pads/day	Assessed by physician
Kim (2020)	-	<2 g of urine leak/24h on pad weight	• Self-reported pad usage • 24h pad-weight test if self-reported pad
Kim (2019)	-	0 pads/day for 3 days AND an absence of urine leakage on EPIC[2] questionnaire	• 3-day voiding diary • Number of pads/day • Pad weight test • EPIC[2] questionnaire
Kitamura (2023)	-	0 pads/day or safety-pad only	EPIC[2] questionnaire
Ko (2020)	-	0 pads/day	Self-reported pad usage
Lamberg (2022)	-	Unknown	EPIC-26 survey
Lim (2012)	-	• Continence: 0 pads/day or safety-pad only • Social: leaking only during heavy activity	Physicians' direct questioning the patients
Lin (2020)	-	100/100 in EPIC[2]-26 Urinary Continence domain	EPIC[2]-26 survey
Matsushita (2015)	-	0 pads/day	5-point scale
Nitta (2023)	-	0 pads/day	EPIC[2] questionnaire
Ohara (2022)	-	EPIC[2] question 1 (Over the past 4 weeks, how often have you leaked urine?): "Rarely or never"	EPIC[2] questionnaire
Ota (2021)	Incontinent volume to pads/total urine volume	0 pads/day or safety-pad only	IPSS[3] questionnaire
Sadahira (2018)	-	Unknown	EPIC[2] questionnaire
Sauer (2019)	≥1 wet heavy pad per day	0 pads/day or maximum 1 safety-pad/day	Self-administrated questionnaire
Schmid (2020)	• Incontinence: ICIQ[4]-score: ≥6 points • Mild: 0-5 points ICIQ[4] • Moderate: 6-10 points ICIQ[4] • Severe: ≥11 points ICIQ[4]	ICIQ[4]-score: 0-5	ICIQ[4] questionnaire
Song (2017)	-	0 pads/day or safety-pad only	5-point scale
Tienza (2018)	Any involuntary leakage of urine	-	ICIQ-SF[1] questionnaire
Yamashita (2022)	-	0 pads/day or safety-pad only	EPIC[2] questionnaire
Yang (2020)	-	0 pads/day	Self-reported pad usage
Jeong (2012)	-	0 pads/day or safety-pad only	Number of pads
Jeong (2014)	-	0 pads/day or safety-pad only	Self-reported pad usage
Tienza (2015)	Any involuntary leakage of urine	-	• ICIQ-SF[1] questionnaire • Number of pads
Lee (2020)	-	0 pads/day or safety-pad only	Assessed by physician and interview
Cho (2015)	-	Unknown	Modified IPSS[3] questionnaire
Paparel (2009)	-	0 pads/day or safety-pad only	Self-reported pad usage
Son (2013)	-	0 pads/day	EPIC[2] questionnaire
Kohjmoto (2020)	-	0 pads/day or safety-pad only	EPIC[2] questionnaire
Fonseca (2024)	-	0 pads/day	EPIC[2] questionnaire

[1] ICIQ-SF: International Consultation on Incontinence Questionnaire short form; [2] EPIC : Expanded Prostate Cancer Index Composite; [3] IPSS : International Prostate Symptom Score; [4] ICIQ: International Consultation on Incontinence Questionnaire.

Supplement E

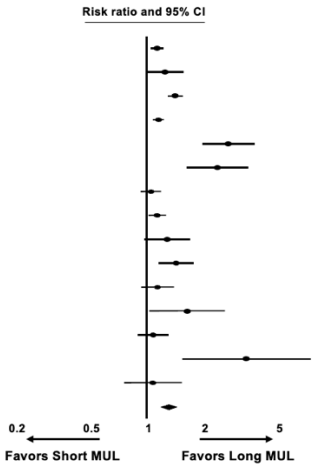
Risk of bias assessment for each study

Supplement F

Forest plot re-arranged according to sample size (panel 1) and year of publication (panel 2).

1) Sample size

Study name	Events / Total		Risk ratio and 95% CI
	Long MUL	Short MUL	
Tienza (2018)	305 / 373	269 / 373	1.13(1.05,1.23)
Nitta (2023)	94 / 210	75 / 209	1.25(0.99,1.58)
Tienza (2015)	251 / 275	177 / 275	1.42(1.29,1.56)
Kim (2019)	244 / 265	211 / 264	1.15(1.07,1.24)
Grivas (2017)	103 / 219	38 / 220	2.72(1.97,3.76)
Ohara (2022)	57 / 95	24 / 95	2.38(1.62,3.48)
Kohjmoto (2020)	77 / 89	74 / 90	1.05(0.93,1.19)
Fonseca (2024)	75 / 79	66 / 79	1.14(1.02,1.27)
Ko (2020)	101 / 105	12 / 16	1.28(0.96,1.71)
Sauer (2019)	66 / 69	28 / 42	1.43(1.15,1.79)
Lim (2012)	40 / 47	35 / 47	1.14(0.93,1.40)
Sadahira (2018)	23 / 35	14 / 35	1.64(1.03,2.63)
Paparel (2009)	19 / 21	36 / 43	1.08(0.89,1.31)
Schmid (2020)	17 / 21	5 / 21	3.40(1.54,7.51)
Cho (2015)	11 / 13	11 / 14	1.08(0.75,1.54)
			1.30(1.18,1.88)



Heterogeneity I^2: 80.0%; p-value <0.0001

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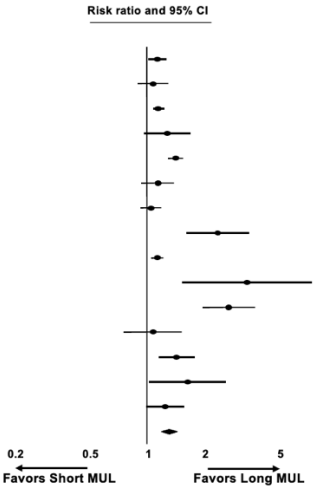
2) Year of publication

Study name	Events / Total		Risk ratio and 95% CI
	Long MUL	Short MUL	
Fonseca (2024)	75 / 79	66 / 79	1.14(1.02,1.27)
Paparel (2009)	19 / 21	36 / 43	1.08(0.89,1.31)
Kim (2019)	244 / 265	211 / 264	1.15(1.07,1.24)
Ko (2020)	101 / 105	12 / 16	1.28(0.96,1.71)
Tienza (2015)	251 / 275	177 / 275	1.42(1.29,1.56)
Lim (2012)	40 / 47	35 / 47	1.14(0.93,1.40)
Kohjmoto (2020)	77 / 89	74 / 90	1.05(0.93,1.19)
Ohara (2022)	57 / 95	24 / 95	2.38(1.62,3.48)
Tienza (2018)	305 / 373	269 / 373	1.13(1.05,1.23)
Schmid (2020)	17 / 21	5 / 21	3.40(1.54,7.51)
Grivas (2017)	103 / 219	38 / 220	2.72(1.97,3.76)
Cho (2015)	11 / 13	11 / 14	1.08(0.75,1.54)
Sauer (2019)	66 / 69	28 / 42	1.43(1.15,1.79)
Sadahira (2022)	23 / 35	14 / 35	1.64(1.03,2.63)
Nitta (2023)	94 / 210	75 / 209	1.25(0.99,1.58)
			1.30(1.18,1.44)



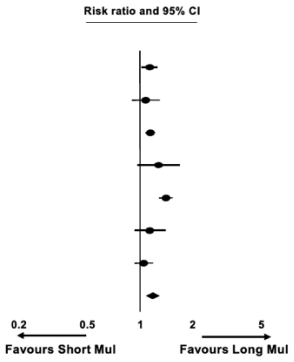
Heterogeneity I^2: 80.0%; p-value <0.0001

Supplement G

Sensitivity analyses removing high risk of bias studies (panel 1), small sample size studies (panel 2) and publications prior to 2022 (panel 3).

1) Removing high risk of bias

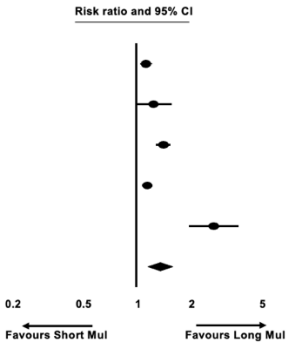
Study name	Events / Total		
	Long MUL	Short MUL	Risk ratio and 95% CI
Fonseca (2024)	75 / 79	66 / 79	1.14(1.02,1.27)
Paparel (2009)	19 / 21	36 / 43	1.08(0.89,1.31)
Kim (2019)	244 / 265	211 / 264	1.15(1.07,1.24)
Ko (2020)	101 / 105	12 / 16	1.28(0.96,1.71)
Tienza (2015)	251 / 275	177 / 275	1.42(1.29,1.56)
Lim (2012)	40 / 47	35 / 47	1.14(0.93,1.40)
Kohjmoto (2020)	77 / 89	74 / 90	1.05(0.93,1.19)
			1.18(1.08,1.29)



Heterogeneity I^2: 69.3%; p-value 0.003

2) Removing small sample size

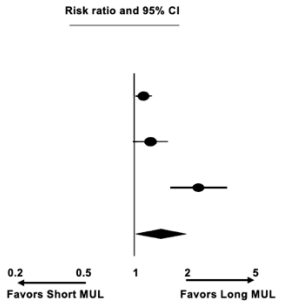
Study name	Events / Total		
	Long MUL	Short MUL	Risk ratio and 95% CI
Tienza (2018)	305 / 373	269 / 373	1.13(1.05,1.23)
Nitta (2023)	94 / 210	75 / 209	1.25(0.99,1.58)
Tienza (2015)	251 / 275	177 / 275	1.42(1.29,1.56)
Kim (2019)	244 / 265	211 / 264	1.15(1.07,1.24)
Grivas (2017)	103 / 219	38 / 220	2.72(1.97,3.76)
			1.36(1.16,1.60)



Heterogeneity I^2: 89.9%; p-value <0.0001

3) Removing publications prior to 2022

Study name	Events / Total		Risk ratio and 95% CI
	Long MUL	Short MUL	
Fonseca (2024)	75 / 79	66 / 79	1.14(1.02,1.27)
Nitta (2023)	94 / 210	75 / 209	1.25(0.99,1.58)
Ohara (2022)	57 / 95	24 / 95	2.38(1.62,3.48)
			1.43(1.02,2.00)



Heterogeneity I^2: 84.9%; p-value 0.001

Supplement H

Summarizing GRADE evidence for the ten studies included in the meta-analysis.

	Comments	Grading
Risk of bias	- All studies are cohort studies. - Risk of bias is low in two studies, moderate in five studies and high in three studies. High risk of bias studies have been removed in a sensitivity analysis and results remained statistically significant. - The odds ratios in the original manuscripts were adjusted for age and/or nerve sparing status in all studies.	**0**
Inconsistency	- Five studies show statistically non-significant effect. Three studies show much larger effect which seem to pool the overall results towards significance. = serious concerns	**(-1)**
Indirectness	- No concerns. The target population was similar in all studies.	**0**
Imprecision	- No concerns. All the odds ratios are above 1 with a significant margin except for three studies – likely not concerning.	**0**
Publication bias	- Possibly present, but the impact is likely minimal and not statistically significant based on Egger's test.	**0**
Dose-effect	- Not applicable.	**0**
Large effect size	- None (Odds ratio range from 1.05 to 3.40).	**0**
Effect plausibility/residual confounding	- None.	**0**

Summarizing GRADE evidence for the studies included in the meta-analysis.

Study	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Dose-effect	Large effect size	Effect plausibility/ residual confounding
Paparel (2009)	Low, cohort, adjusted for age **0**	Statistically non-significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a small margin, but likely not concerning **0**	None **0**	None **0**	None **0**	None **0**
Lim (2012)	Moderate to high, cohort, adjusted for age **0**	Statistically non-significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Cho (2015)	High, cohort, adjusted for age, removed for sensitivity analysis and same results **0**	Statistically non-significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a small margin, but likely not concerning **0**	None **0**	None **0**	None **0**	None **0**
Grivas (2017)	High, cohort, adjusted for age, removed for sensitivity analysis and same results **0**	Very large effect size, statistically significant results. Serious concerns **-1**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Kim (2019)	Low to moderate, cohort, adjusted for age and nerve sparing **0**	Statistically significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Sauer (2019)	High, cohort, adjusted for age and nerve sparing, removed for sensitivity analysis and same results **0**	Statistically significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	Possibly, approximately 100 patients with a significantly positive OR but likely not concerning **0**	None **0**	None **0**	None **0**
Ko (2020)	Low to moderate, cohort, adjusted for age and nerve sparing **0**	Statistically non-significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Kohjmoto (2020)	Moderate to high, cohort, adjusted for age and nerve sparing **0**	Statistically non-significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a small margin, but likely not concerning **0**	None **0**	None **0**	None **0**	None **0**
Ohara (2022)	Moderate to high, cohort, adjusted for nerve sparing **0**	Very large effect size, statistically significant results. Serious concerns **-1**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Fonseca (2024)	Low, cohort, adjusted for age **0**	Statistically significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Tienza (2015)	Low to moderate, cohort, adjusted for age **0**	Statistically significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**

Tienza (2018)	Moderate, cohort, adjusted for age **0**	Statistically significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Nitta (2023)	Moderate to high, cohort, adjusted for age and nerve sparing **0**	Statistically non-significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Sadahira (2018)	High, cohort, adjusted for age **0**	Statistically significant results **0**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	None **0**	None **0**	None **0**	None **0**
Schmid (2020)	Moderate to high, cohort, adjusted for age and nerve sparing **0**	Very large effect size, statistically significant results. Serious concerns **-1**	No concerns, same target population **0**	OR[1] above 1, by a considerable margin **0**	Possibly, 42 patients with a significantly positive OR but likely not concerning **0**	None **0**	None **0**	None **0**

[1] OR: odds ratio.

Article 2:

Post-prostatectomy urinary continence prediction: External validation of a model incorporating MRI derived membranous urethral length

Preface

The objective of this study was to externally validate the prediction model for urinary continence at 12 months after prostatectomy. The Ottawa Hospital Ethics Board Approval was obtained for this study. The paper is presented in the following format: abstract, introduction, material and methods, results, discussion, tables, figures and supplements. The contribution of each author is listed below:

- Dr Cristina Negrean – background literature review, writing the protocol and its registration with Open Science Framework, membranous urethral measurement, data collection, results interpretation, manuscript writing, submitting for publication.
- Ammar Alam – membranous urethral measurement, data collection, manuscript editing.
- Nathan Biniam – membranous urethral measurement, data collection, manuscript editing.
- Dr Emmanuel Salinas Miranda – membranous urethral measurement, data collection, manuscript editing.

- Dr Adam Birosh – membranous urethral measurement, data collection, manuscript editing.
- Dr Duane Hickling – question refining, manuscript editing.
- Dr Humberto R. Vigil – question refining, manuscript editing.
- Dr Luke T. Lavallée – question refining, manuscript editing.
- Dr Ranjeeta Mallick – data analysis, manuscript editing.
- Dr Matthew McInnes – question refining, manuscript editing.
- Dr Nicola Schieda – membranous urethral measurement training, question refining, manuscript editing.
- Dr Rodney H. Breau – question designing and refining, membranous urethral measurement training, results interpretation, oversight, manuscript editing.

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Competing interests

None of the authors has any competing interests.

ABSTRACT

Purpose

MRI membranous urethral length is associated with post-prostatectomy continence. Nevertheless, it is not routinely used for patient counseling because predictive models do not include membranous urethral length or have not been externally validated. The objective of this study was to assess the performance of a membranous urethral length-informed continence model on an external cohort.

Methods

The Jeong et al. model was applied to a prospective cohort of patients with a pre-prostatectomy MRI and validated assessment of post-operative continence between 2015 and 2023. Membranous urethral length was retrospectively measured by two reviewers. The model included: age, nerve spare plan, prostate volume, surgical approach, and membranous urethral length. Definitions of continence were: 0 pads/24hours and 0-1 pad/24 hours. Model performance was assessed using c-statistics, calibration curves, and decision curve analyses.

Results

Among 500 patients, median membranous urethral length was 11.0 mm (IQR 8.1, 14.0). One-year post-prostatectomy continence (defined as 0 pads/24h) occurred in 312 (62%) patients. The c-statistic was 0.64. The calibration was poor. The decision curve analysis showed no advantage of using the model. Continence defined as 0-1 pad/24h was achieved in 450 (90.0%) patients.

The c-statistic was 0.69 and the calibration was excellent. Decision curves showed an advantage of using the model over a range of clinically relevant risk thresholds.

Conclusion

The predication model proposed by Jeong et al. incorporating MRI derived membranous urethral length, is well calibrated and provides net-benefit for predicting continence as 0-1 pad/24 hours. However, it was not useful for predicting 0 pad use.

INTRODUCTION

Patients with prostate cancer must carefully weigh the potential benefits and harms of radical prostatectomy prior to selecting this treatment. The reported probability of post-prostatectomy urinary continence ranges widely, from 60% to 99%, depending on baseline factors and definitions of "continence"[1]. Those who develop urinary incontinence may experience reduced quality of life, increased psychological distress, and social withdrawal [2–4]. As such, predicting urine control after prostatectomy is important for patients and physicians.

One year following surgery is likely the most relevant time to assess urinary continence, as minimal improvement in urinary function is expected beyond 1 year and surgical interventions are usually offered to patients whose incontinence persists beyond 1 year[5,6]. Among published cohorts, consistent factors associated with 1-year post-prostatectomy continence include younger patient age, neurovascular bundle sparing during surgery[7,8] and longer membranous urethral length (MUL)[9,10]. Increased membranous urethral length may indicate a more robust external urethral sphincter complex, and in this way, may contribute to urinary continence[9].

While MUL has potential utility in predicting post-operative continence, its clinical use has been limited due to few patients having pre-operative prostate MRI available, lack of validated prognostic models[10], and inconsistencies in MUL measurement technique. In a recent systematic review, the median MUL reported between studies ranged broadly, from 10.4 mm to 17.3 mm, probably reflecting differences in measurement technique rather than true differences in MUL between populations [11].

To date, four models incorporating MUL have been published aiming to predict 1-year post-prostatectomy continence[11]. The nomogram proposed by Jeong et al., seems to have the most promise for clinical use because it has the highest internal discrimination (c-statistics 0.72) and includes factors consistently associated with post-prostatectomy urine control. To our knowledge, none of those models have been externally validated, so the accuracy in other populations is not known[11,12]. Given the observed variability between studies in MUL measurement technique, and since prediction models often perform worse in an external cohort compared to the development cohort, external validation is necessary to establish if a proposed model can be used in clinical practice [13]. The primary objective of this study was to assess the performance of the Jeong et al. model at predicting 1-year post-prostatectomy continence in an independent contemporary cohort of patients.

MATERIALS AND METHODS

Study design and settings

This study was conducted at The Ottawa Hospital (Ontario, Canada), a tertiary care hospital. The Ottawa Hospital provides health care to approximately 1.3 million people from Champlain Local Health Integration Network[14]. Eight urologists perform radical prostatectomy and their patient pool represents approximately 80% of all prostate cancer patients treated in the Champlain Local Health Integration Network [14]. Since 2015, all radical prostatectomy patients at The Ottawa Hospital are included in a quality improvement program where patient reported urinary function is assessed prior to, and one year following surgery, using a validated questionnaire (Expanded Prostate cancer Index Composite; EPIC), as part of standard care[14]. Ethical board approval was obtained from The Ottawa Hospital prior to study commencement (20240054-01H).

Participants

Adult males (18 years of age or older) with localized prostate cancer undergoing radical prostatectomy (open, robotic, or laparoscopic) between January 2015 and June 2023, with a pre-treatment MRI were eligible. Participants with follow-up less than 1-year or incomplete MRI (precluding accurate MUL measurement) were excluded.

Prediction variables

Patient and tumor characteristics including age, body mass index (BMI), preoperative prostate specific antigen (PSA) serum concentration, tumour stage, Gleason grade group, neurovascular bundle sparing status (unilateral, bilateral or no nerve spare) and surgical approach (open, laparoscopic, or robotic) were prospectively collected by a trained abstractor. Prostate volumes were recorded from MRI reports, where volume is derived from a standard ellipsoid formula (length*width*height/2).

Membranous urethral length measurement

MUL was not measured prospectively and therefore was not used for patient counseling. For the purposes of this study, MUL was retrospectively measured on T2-weighted (T2W) sagittal plane turbo-spin-echo images using a previously published approach[10]. Details of the full MRI protocol are provided in the supplementary materials. First, the T2W hyperintense urethra was identified on sagittal images. The margins of the membranous urethra were proximal penile bulb in the

sagittal plane and the prostate apex (delineated using axial slices T2W and fat-suppressed T2W images where prostate tissue is no longer visible). The distance between prostate apex and bulb was measured with a straight line along the urethra in the sagittal plane (Figure 1). The assessors included: a urology fellow, radiology fellow, a urologist, and medical students - all were trained by a dedicated prostate MRI radiologist with 13 years of post-fellowship training in prostate MRI. All measurements were performed in duplicate, and assessors were blinded to post-operative continence status. Each assessor measured their 100 assigned MULs and 100 MULs assigned to another assessor. Agreement in MUL measurement was defined as within 3mm of each other (which represents approximately one MRI slice thickness). If a difference of less than 3mm was observed, the average MUL was used. If the discrepancy was >3mm, these cases were reviewed by an independent third assessor and consensus length was used as the MUL in the analysis.

Chosen continence prediction model

A recent systematic review identified four published prognostic models[11]. The Jeong et al. nomogram was chosen for this validation since it incorporated factors consistently associated with continence (age, MUL, and nerve-spare status), and had the best internal discrimination[11]. In addition to age, neurovascular bundle (NVB) sparing status, and MUL, the model included prostate volume and surgical approach. The authors of the Jeong et al. model defined continence as 0 to "1 security pad" per day. Specific parameters in the model were:

Logit(probability of continence) = 4.2 + [ln(0.93) × **Age (years)]** + [ln(1.16) × **Membranous Urethral Length (in mm)]** + ln(0.99) × **Prostate Volume (in cc)]** + [ln(1.52) × **Surgical**

Approach (1 if robotic, 0 if not)] + [ln(1.6) × **Planned Unilateral Nerve Spare** (1 if planned, 0 if not)] + [ln(1.84) × **Planned Bilateral Nerve Spare** (1 if planned, 0 if not)]

Outcome

The outcome of interest was post-prostatectomy urinary continence. Since the definition of continence in the Jeong model (up to 1 security pad per day) was not exactly as stated in the EPIC questionnaire[15], the model performance was assessed against 2 definitions of "continence" based on the EPIC questionnaire: 0 pads/24hrs and 0 to 1 pad/24hrs (more similar to the Jeong definition). For this study, the assessment of continence captured closest to 12 months post-surgery, with the allowable range for assessment between 10-14 months.

Study size

The estimated sample size necessary to assess a model with a c-statistic of 0.7 and a continence rate of 80% was approximately 500 patients. The sample size was calculated across different standard errors for c-statistics, calibration slopes, and calibration-in-the-large using the Pavlou et al. approach[16]. The consecutive patient list from 2015 to 2023 was randomly rearranged and the first five hundred patients with all necessary model parameters (including a preoperative MRI of the prostate adequate for MUL measurements) and a 12-month self-reported continence assessment was used.

Statistical analysis methods

Descriptive statistics of the validation cohort were summarized using mean/SD or median/IQR, as appropriate. Categorical variables were presented using frequency and proportions. After a training period to learn the MUL measurement technique, the inter-observer agreement for MRI MUL measurements between readers was calculated using the intraclass correlation coefficient. Model performance for each of the urinary continence definitions at 12 months after prostatectomy was assessed using c-statistics, calibration slopes, calibration plots (with LOESS smoothing) of predicted versus observed probability of continence, and decision curve analysis. In this example, for decision curve analysis, urinary continence risk thresholds were assigned based on what patients might use for choosing, or excluding, surgery. While this threshold will vary from patient to patient, it was assumed that few patients would choose surgery if their probability of continence was less than 70% and that most patients would accept a probability of continence above 95%, so the range of risk thresholds for clinical use of a prediction model to be between 70% and 95%. Analysis was performed using SAS (9.4).

RESULTS

During the study period, 1380 patients had an MRI prior to radical prostatectomy at our institution. A random sample of 500 patients with complete data comprised the validation cohort (Figure 2). Baseline characteristics are presented in Table 1. Participants' mean age at the time of prostatectomy was 64.2±SD 6.8 years. Most patients had Grade Group (GG) 2 prostate cancer (n=247, 53.1%) and underwent a robotic assisted surgical approach (n=458, 91.6%). On pre-operative MRI, the median prostate volume was 39.0 ml (IQR 29.0, 52.5) and median MUL was 11.0 mm (IQR 8.1, 14.0). The intraclass coefficient for MUL measurement was 0.91 (95%CI 0.90, 0.93).

Model performance of urinary continence (0 pads/24 hours)

One-year post-prostatectomy continence was achieved in 312 patients (62.4%) using a 0-pad definition. The calibration curve is presented in Figure 3a. The calibration slope was 0.58. The C-statistic was 0.64. On decision curve analysis, the model showed no benefit within a range of clinically relevant risk thresholds compared to assuming all patients would be continent or assuming no patients would be continent (Figure 4a).

Model Performance of urinary continence (0 to 1 pad/24 hours)

One-year post-prostatectomy continence was achieved in 450 patients (90.0%) using 0 to 1 pad per 24-hour definition. The calibration curve of predicted versus observed continence is presented in Fig.3b. The calibration slope was 0.72. The C-statistic was 0.69. On decision curve analysis, there was net clinical benefit across a portion of clinically relevant risk thresholds compared to assuming all patients would be continent or assuming no patients would be continent (Figure 4b).

DISCUSSION

The purpose of this study was to externally validate the Jeong et al. nomogram, the most promising post-prostatectomy continence prediction model that incorporated MUL[11,12]. When this model was applied to our patient cohort, it was well calibrated, if urinary continence was defined as 0 to 1 pad per 24 hours. However, if the more stringent definition of 0 pads was used, the model was less well calibrated and had no clear net clinical benefit across a range of meaningful risk thresholds.

In an external validation, the calibration of the model is examined primarily by visual inspection of the calibration plot[17]. In this study, the predicted continence prior to surgery (for groups of patients with similar baseline characteristics) was almost exactly aligned with the patient-reported continence 1-year after surgery. However, it should be noted that this excellent calibration was only observed when continence was defined as 0 to 1 pad/24hours. If continence was defined as 0 pads, the Jeong model overestimated 1-year continence for many patients.

We assessed if there were differences in baseline characteristics that might explain the miscalibration observed when using 0 pads as a continence definition. The baseline characteristics were similar for age, BMI, PSA, Gleason score, prostate volume, and MUL. The only notable differences between cohorts were in the use of robotic assisted surgery (92% in validation cohort vs. 52% in development cohort) and nerve sparing (no nerve spare in 24% in the validation cohort vs. 39% in the development cohort).

In addition to calibration, discrimination may be an important component of model accuracy. Discrimination, quantified using a c-statistic, represents the proportion of patients where the model assigned a higher probability of continence to a patient who achieves continence 1-year after surgery compared to a patient who does not achieve continence. Discrimination in our cohort was poor to moderate. Poor discrimination might be due to the narrow range of continence risk, or the inclusion of factors that are not consistently associated with continence. (eg. prostate volume and surgical approach)[7,18,19]. Perhaps remodeling excluding prostate volume and surgical approach may achieve better discrimination, or similar discrimination with a more parsimonious model.

While MUL is an invaluable factor predicting continence, it is rarely used in patient decision aids and counseling, probably due to poor measurement reliability[10,20]. Indeed, the apex

of the prostate can be ambiguous as the infra-prostatic periurethral tissue has similar MRI intensity to the prostate apex. Likewise, the penile bulb can be difficult to identify due to the double contoured anatomy, and the urethra can be angulated, suggesting a shorter length[10]. More recently, several authors have described key landmarks to standardize MUL measurements and increase interobserver agreement[10,20]. Using these recommendations, and with expert teaching, we observed high inter-rater reliability across radiologists and non-radiologists.

To our knowledge, this is the first study to externally validate a prediction model for 1-year post-prostatectomy continence. It is a comprehensive analysis in a large cohort of patients, nevertheless, some limitations are worthy of discussion. One discrepancy between our validation cohort and the development cohort, was the definition of continence. As per the options in the EPIC questionnaire, we defined continence as either 0-1 pads/24h or 0 pads/24h. Continence in the Jeong et al. model was "up to 1 "security" pad". The proportion of patients in our cohort who selected 0-1 pad/24 hours that would characterize the pad as a "security pad" is unknown. Regardless, we found that the model was valid to predict continence in our population if continence was defined as 0 to 1 pad/24hours. This nuance is likely important when counseling patients. Another limitation is the external validity of MUL measurements. Interobserver agreement in MUL measurements can be as low as 62%[11]. Therefore, if other groups use the Jeong et al. model to predict continence, we strongly recommend following the measurement technique employed in our validation. Lastly, some of our patients were excluded because their MRI did not capture images necessary for MUL assessment and some patients did not complete validated functional questionnaires. There may be systematic differences in these patients compared to those included in this validation.

Based on this study, the Jeong et al. model will be used in our clinical practice as a component of an informed decision to define appropriate post-operative expectations. Based on decision curve analysis, it seems that this model provides a net-benefit for a portion of clinically meaningful risk thresholds. However, we also conclude that more work is required to better predict complete continence and severity of incontinence. Machine learning algorithms may improve prognostication, but small studies using artificial intelligence methods have not been shown to perform better than traditional analytic methods[21–24].

Lastly, while one might be tempted to use this model to exclude patients from surgery if they have a low probability of post-operative continence, it is important to consider that some prognostic factors (e.g. short MUL or older age) may also be associated with increased risk of urinary bother after non-surgical treatments, such as focal therapy or radiation therapy. Unfortunately, to our knowledge, studies on the associations between age and MUL on these outcomes have not been conducted. Further research defining risks of common adverse events across different treatments will improve individualized patient counseling to help them select treatments with good oncologic outcomes and the lowest risk of adverse events.

CONCLUSION

In conclusion, the Jeong et al. prognostic model that incorporates MUL, age, nerve spare status, prostate volume, and surgical approach is well calibrated to predict the use of 0 to 1 incontinence pad/24hrs in a contemporary cohort of patients for self-reported 1-year urinary continence using a validated questionnaire. This model is useful to help counsel patients on treatment expectations following radical prostatectomy. Further work, to improve the prediction

of outcomes following all prostate cancer treatments, will allow patients to choose their best treatment option.

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TABLES

Table 1: Baseline characteristics of validation cohort.

Characteristics		Validation Cohort Characteristics (N=500)
Age* (years)		64.2 (SD 6.8)
BMI* (kg/m^2)		27.9 (SD 4.2)
Pre-operative PSA (ng/mL)**		7.2 (IQR 4.9, 11.6)
Prostate volume on MRI (ml)**		39.0 (IQR 29.0, 52.5)
MUL on MRI* (mm)		11.1 (SD 4.4)
Planned nerve sparing (%)		
	Bilateral sparing	251 (50.2)
	Unilateral sparing	131 (26.2)
	None	118 (23.6)
Surgical approach (%)		
	Open	42 (8.4)
	Robotic	458 (91.6)
Pathological Grade Group (%)		
	1	16 (3.4)
	2	247 (53.1)
	3	122 (26.2)
	4	11 (2.2)
	5	69 (13.8)

** Mean; ** Median*

BMI= body mass index, PSA= prostate specific antigen, MUL= membranous urethral length, SD= standard deviation, MRI = magnetic resonance imaging.

FIGURES

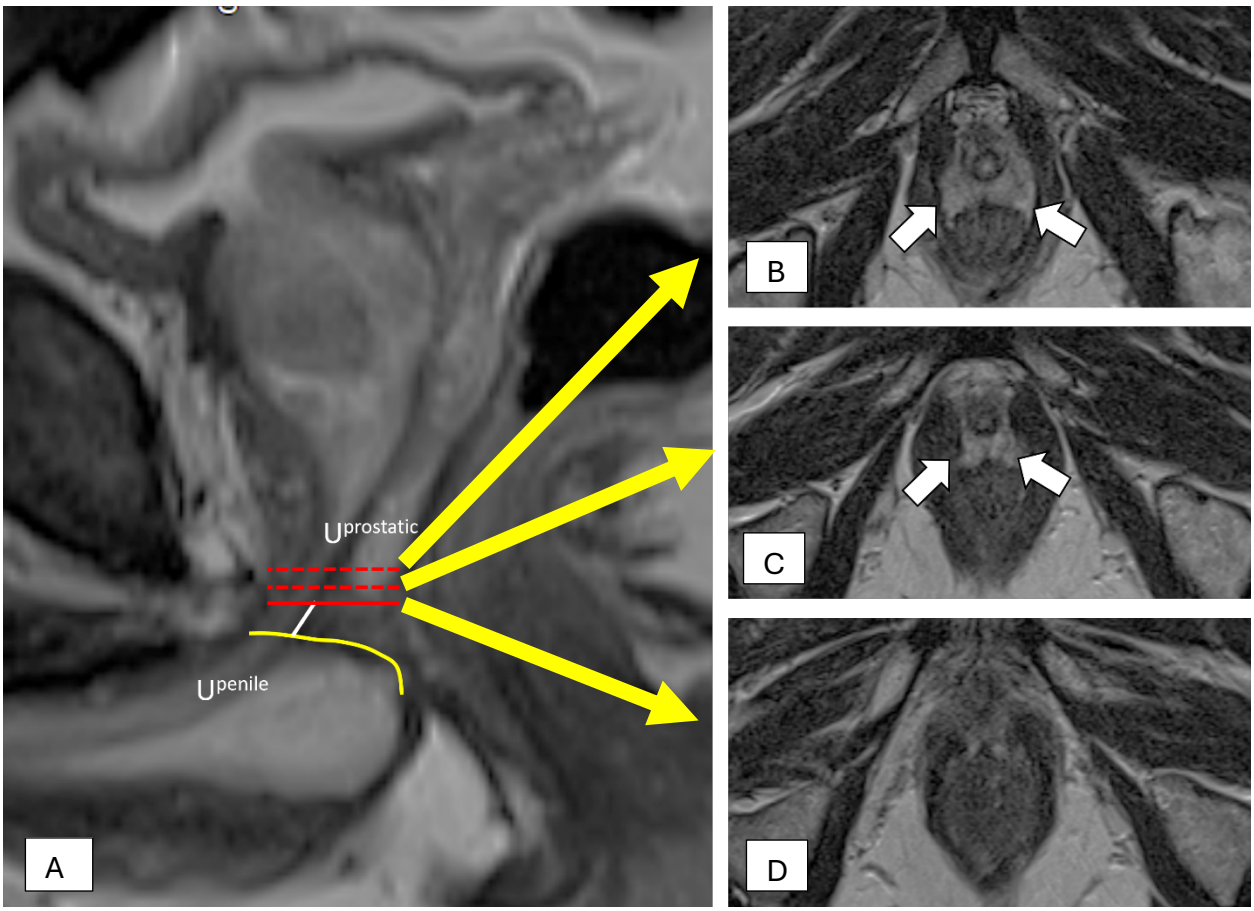


Figure 1. Landmarks used for MUL measurement on MRI.

Image A: White line is the MUL measured from solid red line (where prostate apex ends) to yellow line (where penile bulb starts). Dashed red lines show visible prostate apex. U is urethra.

Images B and C: White arrows indicate presence of prostate apex seen on axial plane.

Image D: Indicates the beginning of MUL (prostate apex not visible).

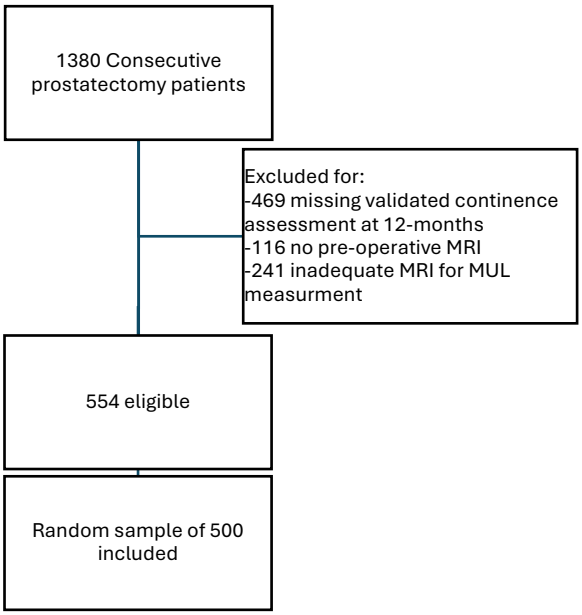
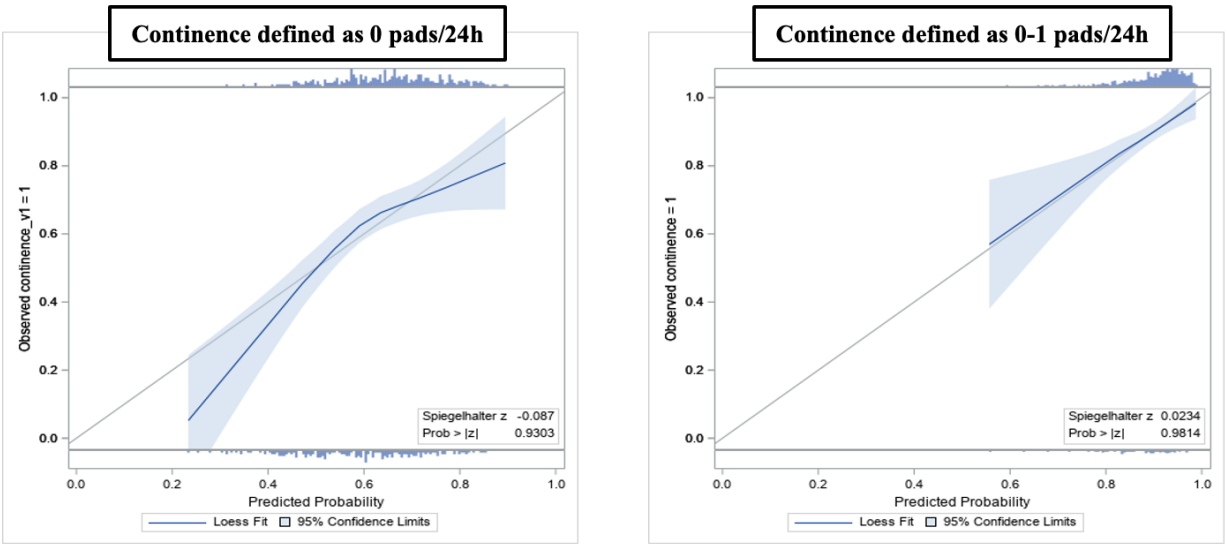
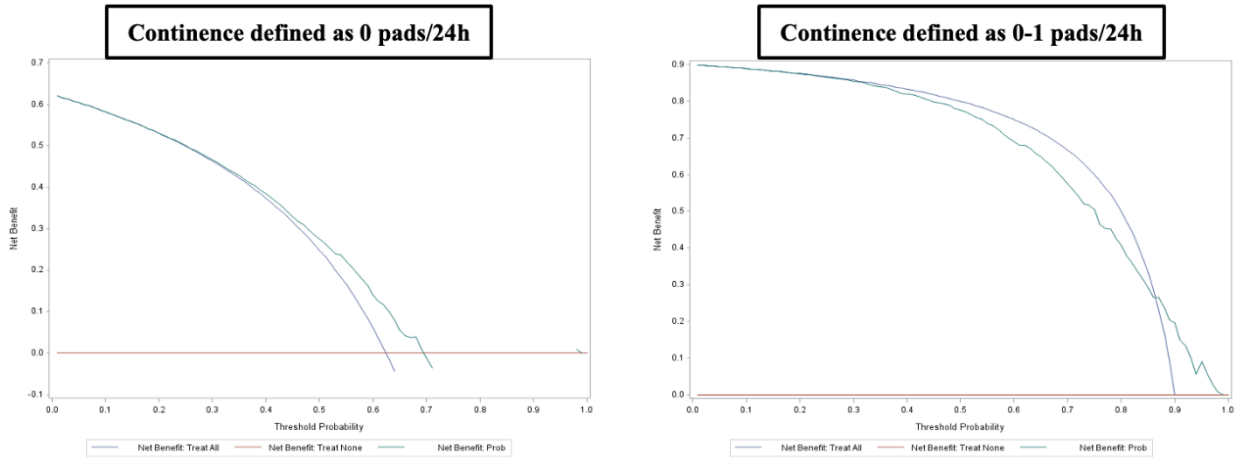


Figure 2. Flow of participants through the study.



A B

Figure 3. Calibration curves and 95%CI of expected versus observed probability of continence using two definitions of continence (panel A: 0 pads/24h; panel B: 0 to 1 pad/24h)



A B

Figure 4. Decision curve analysis showing the net benefit of using the Jeong et al. post-prostatectomy continence prediction model over "treating all" or "treating none" approach. The clinically meaningful range of risk thresholds was estimated to be 70% to 95%. Panel A: Continence defined as 0 pads/24h. Panel B: Continence defined as 0-1 pad/24h

Discussion chapter

The key outcomes of radical prostatectomy are oncological control and treatment-related adverse events/function. The most important cancer-related outcomes include biochemical recurrence, development of metastasis, and cancer-related death[17–19]; while the most common and serious functional side-effects are erectile dysfunction and urinary incontinence[20].

Urinary incontinence is a significant issue: following prostatectomy, people with incontinence may experience depression, anxiety, increased financial burden, and may require adjunctive anti-incontinence surgeries[21,22]. A recent study with a 6-year follow-up indicated that decision regret after prostatectomy was approximately 15% and patients with incontinence tended to be less satisfied with their treatment[23]. Poor pre-operative understanding of the risk of urinary incontinence is associated with negative patient perception of their received treatment[24]. Conversely, patients who play a more active role in treatment selection experience less regret following surgery, probably due to awareness of potential side effects[23,25]. Informed patients may feel more empowered to manage arising consequences. Therefore, accurate preoperative counseling is paramount, so patients have realistic expectations of cancer cure, erectile function, and urinary continence.

However, accurate prediction of post-prostatectomy continence is inexact, because continence is a complex physiologic process. Continence relies on the balance between the bladder and urethral pressures during the urinary storage phase[26]. The urethral closing pressure is created largely by the internal and external sphincters, located at the junction between the bladder and prostate and between the prostate and pelvic floor, respectively. The pelvic floor muscles (the puborectalis, ileococcygeal and pubococcygeal muscles) also contribute to urethral pressures, but likely to a lesser degree than the sphincter complexes. Indeed, urethral coaptation

can be achieved by voluntary contraction of the pelvic floor muscles but those muscles usually need training[28].

During radical prostatectomy, the internal sphincter is resected, so after surgery, patients rely mainly on their external sphincter for urethral pressure and thus for urinary control[27]. The external sphincter is a striated, horseshoe-shaped muscle that lies between the prostatic apex and the penile bulb and is under voluntary control. It is innervated by branches of pudendal nerve, which are in close proximity with the apex of the prostate[27,28].

While we do not fully understand why longer pre-operative MUL is associated with continence, we suggest several plausible hypotheses. The external sphincter surrounds the membranous urethra. Therefore, a longer membranous urethra on MRI may be an indirect sign of a larger external sphincter muscle complex. Another hypothesis is that a longer MUL offers more surface to be compressed by the external sphincter [27]. Lastly, sensation in the membranous urethral mucosa may play an important role in activation of the spinal urinary guarding reflex (i.e. subconscious contraction of the external sphincter) [29,30]. If urine is felt in the membranous urethra, a subconscious reflex contraction of the external sphincter is triggered through the hypogastric nervous plexus to prevent urinary leakage[26,30].

While accurate prediction models for cancer outcomes have been developed and externally validated, the same is not true for functional outcomes and this thesis focuses on improving post-operative continence prediction[31]. The association between MRI-measured MUL and post-operative continence had been reported by several investigators for many years but, to our knowledge, MUL is rarely used to counsel patients. We conducted a systematic review of

the literature and found, with moderate certainty, that longer preoperative MRI measured MUL is predictive of urinary continence at 12 months after radical prostatectomy.

While MUL seems to be a major factor for estimating post-prostatectomy continence, some issues have led to its underuse in clinical practice. First, radiologists and clinicians must be trained to accurately and consistently measure MUL; second, physicians must understand how to incorporate MUL with other prognostic factors, such as patient age and intraoperative autonomic neurovascular preservation.

Determination of the measurement limits of the membranous urethra can be ambiguous and learning how to consistently and accurately measure the membranous urethra is a challenge[32]. We experienced significant measurement disagreements between assessors, even after an initial training session from a fellowship-trained expert radiologist specialized in prostate MRI. However, after 3 iterations of reviewing 10 MRIs each, we reached excellent agreement between readers. Tools to educate clinicians on how to measure MUL will likely be essential for knowledge translation and practice integration.

In addition to challenges in accurate MUL assessment, clinical use is likely limited by lack of knowledge on how to incorporate MUL with other prognostic factors[11] (i.e. age and neurovascular bundle preservation[5,9]). A recent study examining 3D reconstructions of pelvic floor anatomy revealed that the puborectalis muscle was atrophied in older, compared to younger patients. Interestingly, patients with urinary incontinence after prostatectomy showed the same degree of puborectalis muscle atrophy, regardless of age[33]. Therefore, age may indicate pelvic floor atrophy (and correspondingly shorter MUL) for some, but not necessarily all patients. Additionally, detrusor overactivity or bladder spasms can present more frequently in the older

population[34]. The prevalence of moderate to severe lower urinary tract symptoms increases with age, reaching 40% in those ≥ 75 years[34,35]. Among those symptoms, urgency and frequency was reported in 20% of men and urge urinary incontinence was documented in up to 9% of men[36]. Hence, younger patients with less urgency/urge incontinence and higher urethral pressure due to well-developed pelvic floor musculature likely have a higher chance of continence after prostatectomy. In addition to MUL and age, the preservation of the neurovascular bundles during surgery is also independently associated with post-operative continence[37]. The reason for this association is unclear, since the autonomic nerves located near the prostate do not innervate the external sphincter. The most plausible explanation is that peri-prostatic tissue preservation maintains the peri-urethral structures including branches of pudendal nerve providing better urethral support for external sphincter function.

Urinary continence encompasses many processes. A prediction model incorporating all of these variables will likely be superior to a model that considers a single variable. Prediction models can inform patients of the chance of post-prostatectomy urinary continence and can guide them in their decision making. Our systematic review identified four models that predict urinary continence one year after prostatectomy [38–41]. Among them, the Jeong et al. model had the best internal discrimination. They reported an area under the receiver-operating curve of 0.72 in the development cohort and 0.71 in a slip-sample cohort. However, none of the models have been externally validated. Before implementing a prognostic model in decision-making, external validation is necessary, mainly because models often perform worse in a new cohort of patients[42].

To externally validate the Jeong et al. model, we enrolled a cohort of 500 patients. Interestingly, despite our concerns for selection bias in the development cohort, we observed

remarkably similar patient characteristics between the development and validation cohorts, including patient age, tumour stage, tumour grade and median MUL. One noteworthy discrepancy between the two cohorts was how continence was defined. In Jeong et al. continence was described as "0 to 1 security pad per day" but did not detail how "security pad" is defined. In our patient population at The Ottawa Hospital, the EPIC questionnaire was used to assess continence status at 12-months after prostatectomy. The EPIC questionnaire does not capture the use of "security pads", so we defined a patient "continent" if they selected "0 pads" or an alternative definition of "up to 1 pad per 24h", and assessed the performance of the model with both continence definitions[43]. We found that the model performs well when continence in our cohort was defined as "0 to 1 pad/24h", but with the more conservative definition of "0 pads/24h", the model was poorly calibrated and likely had no net clinical benefit compared to assuming all patients would be incontinent or all patients would be continent (as depicted in the decision curves).

A potential limitation of the Jeong et al. model is the inclusion of factors (prostate volume and surgical approach) that have not been consistently associated with post-operative continence.[9,11,44]. It is possible that inclusion of non-informative variables could limit the performance of the prediction model.

In summary, our best available prediction model of continence does not accurately predict complete continence, and further work is needed to better understand mechanisms that cause continence and how to use these factors for risk prediction. Despite this, some patients may view mild incontinence (i.e. 1 pad/day) as an acceptable outcome. Based on our work we have begun using the Jeong et al. model to counsel patients on their probability of continence (defined as 0 to 1 pad/24hours).

Following the work in this thesis, we plan to continue research to maximize clinical impact. Using knowledge translation strategies, we will develop education tools on how to consistently measure MUL from pre-operative MRI and develop online continence calculators that clinicians can use to help counsel patients. We also aim to develop or improve on existing continence prediction models using a stricter definition of continence (0 pads).

We plan to follow a similar process of systematic review, external validation, and prediction model development for other adverse events following surgery (e.g. erectile dysfunction) and other prostate cancer treatments (e.g. prostate radiation). Ideally, the most accurate models will be incorporated into a patient decision aid, where benefits and harms of various treatment options will be generated for individual patients to help inform treatment decisions.

In conclusion, our work should compel surgeons and radiologists to learn how to consistently measure MUL and to use MUL and prediction models when counseling patients on their probability of continence after surgery. We anticipate that more accurate patient counseling will lead to more appropriate post-operative expectations and less treatment regret.

Approvals

1. “Preoperative MRI membranous urethral length as a predictor of urinary continence after radical prostatectomy: a systematic review and meta-analysis” protocol was registered with PROSPERO (CRD42023483229).

2. Ethical board approval was obtained from The Ottawa Hospital prior to “Post-Prostatectomy Urinary Continence Prediction: External validation of a model incorporating MRI derived Membranous Urethral Length” study commencement (20240054-01H).

3. Anatomic representation of the membranous urethral (Figure 1 in Introductory chapter) was generated using artificial intelligence: ChatGPT website.

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