Preoperative Membranous Urethral Length Measurement and Continence Recovery Following Radical Prostatectomy: A Systematic Review and Meta-analysis

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Context: Membranous urethral length (MUL) measured prior to radical prostatectomy (RP) has been identified as a factor that is associated with the recovery of continence following surgery.

Objective: To undertake a systematic review and meta-analysis of all studies reporting the effect of MUL on the recovery of continence following RP.

Evidence acquisition: A comprehensive search of PubMed, EMBASE, and Scopus databases up to September 2015 was performed. Thirteen studies comprising one randomized controlled trial and 12 cohort studies were selected for inclusion.

Evidence synthesis: Four studies (1738 patients) that reported hazard ratio results. Every extra millimeter (mm) of MUL was associated with a faster return to continence (hazard ratio: 1.05; 95% confidence interval [CI]: 1.02–1.08, p < 0.001). Eleven studies (6993 patients) reported the OR (OR) for the return to continence at one or more postoperative time points. MUL had a significant positive effect on continence recovery at 3 mo (OR: 1.08, 95% CI: 1.03–1.14, p = 0.004), 6 mo (OR: 1.12, 95% CI: 1.09–1.15, p < 0.0001), and 12 mo (OR: 1.12, 95% CI: 1.03–1.22, p = 0.006) following surgery. After adjusting for repeated measurements over time and studies with overlapping data, all OR data combined indicated that every extra millimeter of MUL was associated with significantly greater odds for return to continence (OR: 1.09, 95% CI: 1.05–1.15, p < 0.001).

Conclusions: A greater preoperative MUL is significantly and positively associated with a return to continence in men following RP. Magnetic resonance imaging measurement of MUL is recommended prior to RP.

Patient summary: We examined the effect that the length of a section of the urethra (called the membranous urethra) had on the recovery of continence after radical prostatectomy surgery. Our results indicate that measuring the length of the membranous urethra via magnetic resonance imaging before surgery may be useful to predict a longer period of urinary incontinence after surgery, or to explain a delay in achieving continence after surgery.
1. Introduction

Radical prostatectomy (RP) is the mainstay surgical treatment for localized prostate cancer. The aim of such surgery is to achieve oncologic control while preserving urinary continence and erectile function [1]. In the majority of patients, urinary incontinence (UI) following RP is a predictable consequence. Despite improvements in surgical techniques, the incidence of UI remains high, especially during the early postoperative period and the time to achieve continence (continence recovery) after RP, is variable. The variability in the rates of UI following RP remains one of the most significant functional complications with the potential for a negative impact on quality of life [2–4].

The prevalence of postprostatectomy UI varies according to the definition applied [5]. Encouragingly, despite the lack of a common and consistent working definition of continence, postoperative UI typically resolves gradually with time, with reports of significant improvement occurring up to 2 yr following RP [2,6,7]. The mechanism for the time dependent recovery of UI is not clearly understood.

Various preoperative prognostic patient-related risk factors that affect continence recovery have been reported. The preoperative length of the membranous urethra (MUL) which is measured via T2-weighted magnetic resonance imaging (MRI) images (Fig. 1), is one patient-related anatomical factor that has been reported to affect continence recovery following RP. A comprehensive understanding of MUL is potentially of value to clinicians when counselling patients in clinical practice prior to surgery and when explaining a delay in continence recovery following surgery. Also, given the recent technical advances that have led to the wider application of MRI technologies for the diagnosis and staging of prostate cancer [8], clinicians also have increased accessibility to obtain measurements of MUL prior to RP.

2. Evidence acquisition

2.1. Objective

Our aim was to systematically review and meta-analyze studies reporting the prognostic value MUL measurements prior to RP for the recovery of continence.

2.2. Search strategy

We adopted the Preferred Reporting Items for Systematic Reviews and Meta-analysis [PRISMA] guidelines for our systematic review [9]. The PubMed, EMBASE, and Scopus databases were searched for relevant articles from the inception of each database until September 22, 2015. The systematic searches were formulated and conducted with the guidance of two health sciences librarians from the University of New England, Australia. The PubMed search strategy included a free-text protocol using the combined terms “prostatectomy OR radical prostatectomy AND urinary incontinence AND urethral length OR urethral volume OR membranous urethra” across the title and abstract fields of the records.

Fig. 1 – T2-weighted (A) sagittal and (B) coronal magnetic resonance imagesa for the measurement of membranous urethral length (MUL).

a The image was not taken from the studies included in this systematic review and meta-analysis.

2.3. Study selection

After the removal of duplicates, two authors (SM and MP) screened all titles and abstracts independently to identify potentially relevant articles for eligibility. Full-text articles were obtained where there was insufficient information in the title or the abstract to determine eligibility. Reference lists were also manually searched to identify relevant articles not captured by the search strategies. Studies were included and excluded according to the criteria presented in Table 1. In all cases disagreements on eligibility were resolved by consensus.

2.4. Quality assessment

The methodological quality of each study was rated using the full version Downs and Black evaluation tool [10]. The tool consists of 27 questions across five sections: study quality (ten items), external validity (three items), internal validity bias (seven items), confounding selection bias (six items), and power of the study (one item) with an overall score out of a possible 30 points. The studies were...
between studies. While it was of interest to perform Egger bias tests, there were too few studies to allow this [13].

3. Evidence synthesis

3.1. Literature search

Figure 2 presents the PRISMA flow diagram for the study selection process. The searches retrieved 235 citations. After the removal of duplicates and a review of abstracts and full-text articles, 13 studies were eligible for inclusion in this systematic review and meta-analysis [14–26]. All corresponding authors were contacted via email to provide clarification and/or additional data where necessary. We received responses from eight authors [14,16,19,21–24,26]. Coakley et al [26] provided their data allowing for the calculation of required hazard ratios and ORs.

3.2. Quality assessment

The thirteen studies consisted of one intervention trial (randomized controlled trial) and twelve cohort studies (three prospective and nine retrospective) representing four different countries and seven different institutions. The ratings of the quality of the methods of the individual studies are presented in Table 2. Overall the scores were generally high with 11 out of the thirteen studies achieving 21 points or more. Studies typically lost points for internal validity and confounding and selection bias because of questions which were aimed at randomized and intervention trials. The two studies with lower scores had a poorer quality reporting of results.

3.3. Characteristics of the studies included

3.3.1. Patient and surgical characteristics

The patient and surgical characteristics are presented in Table 3. The mean age reported across all studies ranged from 58.0 yr to 66.1 yr (range, 37–85 yr). A total of 1738 patients (780 RRP, 937 RARP, and 21 LRP) were included in the four studies reporting the hazard ratio for the recovery of continence [20,22,24,26]. For the study reporting the OR of a return to continence at 1 mo, a total of 872 patients (416 RRP and 456 RARP) were included [18], for the studies at 3 mo 2517 patients (571 RRP,
235 records identified through databases and hand searching

85 duplicate records

150 unique records

52 records excluded: not related to the research question

98 records for full text review

24 studies: conference abstracts

9 studies: review articles

3 studies: non-English language

39 studies: no preoperative MRI MUL measurement results

4 studies: no reported odds ratio or hazard ratio results

4 studies: overlapping datasets

2 studies: operation other than radical prostatectomy

Fig. 2 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram presenting the outcome of the searches and selection of studies included in this review.

MRI = magnetic resonance imaging; MUL = membranous urethral length.

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3.4. MRI equipment and MUL measurement procedures

The MRI procedures are presented in Table 4. The MUL was measured either by urologists, radiologists, or both specialties via consensus who were blinded to the patient’s clinical data. MRI examinations were performed with the patient positioned in the supine position using 1.5T or 3T MRI units acquiring T2-weighted images which were used for MUL measurements. The use of an endorectal coil was used in four studies [16,19–21,25,26], not used in four studies [14,22,23,25], and not reported in five studies [15,17–20]. MUL was measured in either: (1) the coronal plane in six studies [16,19–21,25,26], (2) the sagittal plane in three studies [14,17,22], (3) the sagittal plane cross-referenced with the coronal plane in two studies [23,24], and (4) not reported in two studies [15,18].

3.4.1. MUL measurements

The MUL measurement results are presented in Table 4. The mean MUL measurements reported across all studies range from 10.4 mm to 14.5 mm; however, individual measurements of MUL were as small as 5 mm and as large as 34.3 mm.

3.5. Definition of UI

All studies reported a definition of continence and the method of assessment used. Twelve out of the 13 studies reported similar methods for the assessment of postoperative UI via direct patient questioning and/or the use of questionnaires about the perceived degree of UI, the absence of involuntary leakage and/or the use of absorbent products including pads and/or drip collectors [14,16–26]. Eight studies used pad-free status or the use of a security liner [14,16,18,21–25], two studies defined continence as 0–1 pad use [19,20], and two studies used a patient report of complete continence [17,26]. There was only one study [15] that used a 24-h pad test to define continence with a strict definition applied (pad weight gain not exceeding a mean of 2 g/d for 3 consecutive d).

3.6. Outcomes

The outcome reported by each study (hazard of return to continence and/or odds of return to continence) is shown in Table 5. Most studies reported ORs at one or more time points with two studies providing both hazard ratios and ORs (via correspondence with Coakley et al) [26].

3.6.1. The risk of return to continence

Four studies [20,22,24,26] (1738 patients) reported the hazard ratio associated with MUL and the return to continence (Fig. 3). Each of the studies indicated that a
greater MUL was significantly associated with a faster return to continence. Overall, the combined hazard ratio indicated a significant positive effect of greater MUL (hazard ratio: 1.05; 95% confidence interval [CI]: 1.02–1.08, \( p < 0.001 \)). There was no evidence of heterogeneity between the studies (\( p = 0.1241 \)).

### 3.6.2. Return to continence at 1 mo

One study [18] (872 patients) reported the OR for the return to continence at 1 mo. This study found a significant positive effect of greater MUL on the odds of return to continence (OR: 1.16, 95% CI: 1.09–1.23, \( p < 0.001 \)).

### 3.6.3. Return to continence at 3 mo

Six studies [14,19,21,22,25,26] (2517 patients) reported ORs on return to continence at 3 mo (Fig. 4). All but one of the six studies found a significant positive effect of a greater MUL on the odds of return to continence. Figure 4 shows the results separated by whether or not the MUL was dichotomized. For each grouping and overall, a greater MUL is associated with significantly greater odds of return to continence by 3 mo (OR: 1.12, 95% CI: 1.09–1.15, \( p < 0.001 \)).

### 3.6.4. Return to continence at 6 mo

Three studies (3187 patients) reported the odds of return to continence at 6 mo [14,16,26] (Fig. 5). Two of these studies, both with smaller sample sizes [14,26], had 95% confidence intervals that included one (ie, it was not significant); however, point estimates consistently indicated a positive effect on return to continence with a greater MUL length. The third study [16] comprises a large cohort of patients and is highly significant. Overall, pooled results show a significant positive effect of a greater MUL on the odds of return to continence at 6 m (OR: 1.12, 95% CI: 1.09–1.15, \( p < 0.001 \)).
3.6.5. Return to continence at 12 mo
Six studies (4656 patients) reported a return to continence at 12 mo [15–18,23,26] (Fig. 6). The studies were presented by whether MUL was dichotomized for analysis. The point estimate for the odds of return to continence was large for the study in which MUL had been dichotomized [23]. The studies that have not have dichotomized MUL have smaller point estimates of the OR. Most (five out of six) of the studies [16–18,23,26] showed a significant positive effect of greater MUL on the odds of return to continence at 12 mo and the overall pooled OR indicated a significant positive relationship between MUL length and return to continence (OR: 1.12, 95%CI: 1.03–1.22, \( p = 0.006 \)).

3.7. Subgroup analyses
Subgroup analysis was completed to determine whether the heterogeneity between studies could be related to: (1) continence definition, (2) surgical approach, or (3) the MRI method used to measure MUL. The number of studies reporting the MUL related odds for the return to continence at 3 mo (\( n = 6 \)) [14,19,21,22,25,26] and 12 mo (\( n = 6 \)) [15–18,23,26] permitted the meta-analyses by subgroupings within each of these three factors of interest. For continence definition (pad free, 0–1 pad, 24-h pad test, or no complaint of incontinence) the results are mixed and the MUL odds of return to continence at 3 mo or 12 mo is not related to continence definition (Supplementary Figs. 1 and 2). Studies grouped by surgical approach (RRP, RARP, LRP, or a combination of surgical approaches) are also inconclusive with no difference between these subgroups for the MUL odds of return to continence at 3 mo and 12 mo (Supplementary Figs. 3 and 4). For the MRI method used to measure MUL (coronal, sagittal, or coronal cross-referenced with sagittal [combination]), the results are also variable and more studies are needed to determine conclusively if the odds of return to continence at 3 mo and 12 mo is related to the MRI method used to measure MUL (Supplementary Figs. 5 and 6).
3.7.1. Multivariate meta-regression

All of the OR data were combined into a multivariate model using a random intercept to adjust for repeated measures by various studies and to control for studies with overlapping data [18,19] and a random slope over time. Overall for every extra millimeter of MUL the estimated odds of continence recovery is increased by between 5% and 15% (OR: 1.09, 95% CI: 1.05–1.15, \( p < 0.001 \)). When this result is re-expressed for every extra 10 mm of MUL, the odds of continence recovery is increased by between 53% and 405% (OR: 2.37, 95% CI: 1.63–4.05). The only significant modifier of the MUL related odds of return to continence was the MRI method.
used to measure MUL (p = 0.028; Table 6). There was one study [23] that reported the odds of return to continence using the sagittal MRI image alone (p = 0.009). There was no evidence of a difference in effect between the sagittal and coronal MRI methods for MUL measurement (p = 0.693). Given that only one study [23] used the sagittal plane cross-referenced with the coronal plane method, the significant difference between this study and the others should be interpreted with caution.

4. Conclusions

To our knowledge, this is the first systematic review and meta-analysis that has investigated preoperative MUL as a prognostic risk factor for overall continence recovery and recovery at 1 mo, 3 mo, 6 mo, and 12 mo specifically. The key finding is that a greater preoperative MUL has a significant positive effect on overall time to continence recovery (pooling the hazard ratios) and continence recovery (pooling the ORs) at 3 mo, 6 mo, and 12 mo following RP. The analyses undertaken represents a small but significant positive effect of an extra centimeter in preoperative MUL on return to continence (ie, OR: 1.09, 95% CI: 1.05–1.15 from the multivariate model). Given the anatomical variation in the MUL measurements that have been reported (as small as 5 mm and as large as 34.3 mm), this OR result is re-expressed as the OR for an extra 10 mm in preoperative MUL on the return to continence we obtained an OR of 2.37 with 95% CI: 1.63–4.05. This clearly indicates that with an extra centimeter of MUL the odds of return to continence are more than 200% more likely than for a man with a shorter MUL.

This finding is important because the variability of the reported UI outcomes has been identified as a major concern for patients and an important point of discussion that clinicians have with patients preoperatively and postoperatively. The variability in UI outcomes following prostatectomy includes both the overall continence recovery and the time-to-achieve continence. The uncertainty associated with the trajectory of the time course of recovery and the eventual outcome can potentially influence the decision to proceed with surgical management and can have a significant impact on the quality of life and psychosocial wellbeing following surgery [2–4]. The economic burden of postprostatectomy UI, including the cost of lost work productivity and associated management costs has also been reported [27–29]. Identifying patient-related factors including preoperative MUL is potentially important when counselling patients prior to and following surgery, in particular when setting expectations about the likely time course for the recovery of continence, and when discussing any delays in the recovery of continence. This systematic review supports the inclusion of preoperative MUL in these patient-centered discussions. This systematic review also supports MUL as a variable used in the development of predictive models for continence recovery after RP [16].

The comparison of studies reporting UI outcomes is also difficult due to the lack of a standardized definition of UI, inconsistent methods of assessment, and variable time points selected for patient follow-up. In our systematic review and meta-analysis we were able to pool 12 studies that used similar, clinically accessible, and frequently used approaches to continence definition and assessment and one study that used 24-h pad testing. We were also able to group studies according to identical time points for follow-up patient assessments. The use of patient-reported pad use and subjective reports of UI for continence definition and assessment following RP has, however, been questioned by some authors [3,32] and supported by others [7,30,31,33]. The approach used to define and assess UI after RP surgery in this systematic review, however, remains clinically accessible and widely used. There was only one study that used and reported 24-h pad test data with a strict and rarely clinically applied definition [15].

Our multivariate analysis indicates that follow-up time is not an important predictor of return to continence after adjusting for MUL; however, individual patient data analysis would help to better indicate the time course of recovery. Prostate removal by all surgical methods (RARP, RRP, and LRP) results in a change to the structure and function of the components of the urinary sphincter complex which are inherently related to the structure and function of the membranous urethra. The membranous urethra contains smooth muscle fibers along its entire length and is also surrounded by the rhabdosphincter (striated urethral sphincter) [33–35]. The rhabdosphincter is separated from the membranous urethra by a thin sheath of connective tissue and forms a muscular coat in an omega shaped loop around the membranous urethra [33–35]. The combined and coordinated functionality of the intact smooth muscle fibers and the rhabdosphincter has an important role in continence, contributing to maintaining and increasing urethral closure pressures [34,36]. Postoperative urethral sphincter insufficiency has been reported to affect continence outcomes following RP [33,34,36,37]. An increased length of MUL, which includes a greater amount of smooth muscle fibers and rhabdosphincter, potentially increases the length of the urethral pressure profile. Preoperative and postoperative conditioning of the
rhabdosphincter may also be optimized with a greater membranous urethral length incorporating a greater volume of muscle for training, further improving postoperative continence outcomes [38].

The importance of MUL has also been identified with modifications to and development of surgical techniques designed to improve continence outcomes after RP [39–41]. Many of these developments and modifications have centered on the preservation of the MUL and improved periurethral suspension for the protection and maintenance of the native continence system. A longer preoperative MUL may maximize the potential of these modifications to preserve the integrity and optimal functioning of the continence mechanism that is associated with the MUL. The preservation of MUL may, however, be limited by disease-related factors in order to achieve oncologic control.

The accessibility to acquire preoperative MUL measurements in clinical practice is greater with the wider application of preoperative MRI technologies for the diagnosis and staging of prostate cancer [8]. Standard multi-parametric MRI prostate imaging also includes the routine capturing of T2-weighted coronal and sagittal images. These T2-weighted images provide clinicians with the opportunity to obtain preoperative measurements of MUL as an inclusion to standard multi-parametric MRI radiological reporting procedures. Traditionally preoperative prostate MRI imaging has been undertaken using a 1.5T and 3-Tesla to 3T scanner and an endorectal coil. The application of a higher field strength (3-Tesla) and subsequent higher spatial resolution has resulted in a reduction in the use of endorectal coils, further increasing the accessibility of preoperative MRI scanning in clinical practice.

Despite a comprehensive search strategy and a rigorous approach to the study selection, the omission of relevant studies may have been possible. The inclusion of only English language manuscripts may also have excluded some relevant studies. The conclusions and recommendations contained within this review are based upon the synthesis and evaluation of twelve studies that have relied on patients reporting the degree of UI and pad usage for the assessment of postoperative UI and one study that used a 24-h pad test. In conclusion, the preoperative measurement of MUL via MRI is recommended prior to RP to predict the recovery of UI after surgery or to explain a delay in achieving continence after surgery.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.euro.2016.06.023.

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