

Striated muscle in radical prostatectomy specimens: a marker of apical dissection quality and an independent predictor of urinary continence after Endoscopic Extraperitoneal Radical Prostatectomy (EERPE)

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Abstract

Introduction:

To determine if the presence and amount of striated muscle on the apical sections of the cruciate sections of laparoscopic radical prostatectomy (LRP) specimens predicts early and long-term urinary continence outcomes.

Patients & Methods:

We conducted a retrospective review of our prospectively collected single surgeon LRP database. We identified patients based on their continence outcomes (continent [0 pads] or incontinent at 12 months), with an approximate even spread early continent and incontinent patients).

An uropathologist separate to the urology team was blinded to outcome and assessed each patients' apical cruciate sections (H&E stained) for the presence, percentage and maximal diameter of muscle and extraprostatic tissue on these sections.

Specifically 2 scoring systems were used: 1) semi-quantitative estimation of percentage of muscle on the apical cruciate sections (low <5% and high >5%) and percentage of total extraprostatic tissue on cruciate section (low <10% and high >10%).

Logistic regression and classification and regression tree analysis was performed to identify predictors of UI.

Results:

In total 80 patients were analysed, 38 were continent at 12 months and 42 were incontinent at 12 months follow-up. The percentage of extraprostatic tissue/muscle being an independent predictor of being wet at 12 months ($p = 0.002$) on multivariate regression along with age ($p = 0.04$).

Using percentage of extraprostatic tissue in cruciate section (high >10%) to predict UI at 12 months, it yielded 71% sensitivity, 82% specificity, 81% PPV, 72% NPV and 76% accuracy.

Conclusion

The use of simple additional reporting of muscle and extraprostatic tissue on the apical sections of RP specimens can help to better predict the likelihood of continence return.

Introduction:

The life altering functional consequences of undergoing RP include, but are not limited to, urinary incontinence (UI) and erectile dysfunction (ED). Rates of UI vary widely with reported rates between 4 – 31% for UI at 12 months follow-up after RP [1]. The modality used (LRP or RARP) appears to affect the rate of early continence after radical prostatectomy over and above surgeon experience although these observations come from retrospective studies [2]. These observations may be due to the RARP approach facilitating a more precise apical dissection. However, it appears that at 12 months follow-up the difference in incontinence rates between different modalities is far smaller [3], which may be explained by recovery of temporary nerve injury. The presence of UI is certainly a major concern for patients and has a major impact on quality of life after radical prostatectomy [4-6]. The lack of good predictors for identifying which patients will require surgical intervention to correct their UI leads to a longer period of observation that can add to this anxiety for patients, and the time for continence to improve.

The external urinary sphincter (rhabdosphincter) is thought to be critically important to continence after RP and the damage to this structure that can occur during apical dissection may lead to UI [7, 8]. It is possible that the presence and amount of striated muscle on the apical cruciate sections of the RP specimen may be a surrogate marker of the extent damage to the sphincter. There is very little data to date on whether the amount of rhabdosphincter present in the post-operative RP specimen correlates with long-term urinary incontinence [9].

The aim of this study was to determine if the presence and amount of striated muscle and extra-prostatic tissue on the apical sections of the cruciate sections of laparoscopic radical prostatectomy (LRP) specimens was related to the extent of UI and predicted whether recovery may be expected in the longer term.

Patients & Methods:

We conducted a retrospective review of our prospectively collected single surgeon LRP database (SAM). We have previously studied the outcomes of this group of patients (575 patients) and have published 5-year functional and oncological outcomes [10]. Our previous study demonstrated that the continence rate at 12 months was 88%. Further analysis demonstrated the early continence rate at 3 months was 35% [2]. For the current study we identified patients' based on their continence outcomes (continent [0 pads] or incontinent at 12 months), with a similar number of early continent and incontinent patients. This selection criteria was used in a case-controlled manner in order to assess whether the amount of striated muscle in apical cruciate sections was related to continence outcome (continent vs incontinent at 12 months). The benefit of this method was to ensure that there were sufficient numbers in each group to reduce the risk of introducing statistical error with uneven groups. However, we recognise that using this selection criteria may have resulted in groups that were not well matched with regard to other variables.

One of our uro-pathologists independently assessed the apical RP sections according to the scoring system below. This pathologist was blinded to outcome and assessed each patients' apical cruciate sections (H&E stained) for the presence, percentage and maximal diameter of muscle and extraprostatic tissue on these sections. Two scores were assigned: 1) semi-quantitative estimation of percentage of muscle on the apical cruciate sections (low <5% and high >5%) and percentage of total extraprostatic tissue on cruciate section (low <10% and high >10%). A measurement of the maximal dimension of muscle or extra prostatic tissue on the apical section was also noted. Our uro-pathologists process and report radical prostatectomy specimens as described in ISUP guidelines and do not use the cone method of

apical processing [11]. Figure 1a,b and c show images of the apical section of a LRP specimen with minimal extraprostatic tissue present, muscle present and extraprostatic tissue present respectively.

Patient age, PSA, pT stage, Gleason grade, surgeon experience, blood loss, operative time, salvage radiotherapy, presence or absence of nerve sparing and pad usage per day were included. Continence was defined as 0pads/day at a specific time point (within 3 months for early continence and at 12 months for long-term continence). Patients were also followed longer to determine if further surgery was required to achieve continence (Artificial Urinary Sphincter – AUS).

Patient details and demographics were entered into a Microsoft Excel (Seattle, USA). Continuous variables between both groups were compared using the Mann-Whitney U test and categorical variables using the Pearson Chi-squared test. Regression analysis was performed to identify whether patient variables, surgical outcomes or histological variables predicted outcome. Those factors that were found to be significant on uni-variate analyses were included in multivariate regression analysis. Statistical analysis was performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0 Amok, NY: IBM Corp) and statistical significance was set at < 0.05 . Classification and regression tree analysis (CART) and RandomForest (RF) were performed to identify predictors of UI and was performed using Salford Systems (San Diego, USA).

Results:

In total 80 patients were identified and included in the study. This was the largest number of patients that we could assess using this surgeon's cohort as there was a low rate of incontinent patients in the series. 42 patients who were incontinent at 12 months post LRP were included in our study and compared to 38 who were continent. Patient pre, peri- and

post-operative characteristics are shown in Table 1. There was no statistically significant difference in Age, pathological T stage, Blood loss, Gleason score, apical positive surgical margin rate, pelvic lymph node dissection, nerve sparing procedure or surgeon case experience. Despite our best attempts to match these patients there was a significantly higher mean PSA and mean operative time in the incontinent group compared to the continent group of patients ($p = 0.03$ and 0.04 respectively), however, there was no significant difference in mean prostate weights ($p = 0.7$).

Logistic regression analysis was performed in order to identify which variables listed in Table 1 were predictors of being incontinent at 12 months. Univariate analysis showed that increasing age (0.04), higher PSA (0.04), lack of nerve sparing (0.008), higher percentage of extra-prostatic tissue in the cruciate section (<0.0001) as well as a higher percentage of muscle in the cruciate section (<0.0001) were all significant. These were combined into a multivariate regression model which showed that increased age ($p = 0.04$) and the higher percentage of muscle in the cruciate section were independent predictors of incontinence at 12 months ($p = 0.002$).

Area under the curve analysis (ROC) was then performed comparing the significant univariate variables for prediction of incontinence at 12 months. This demonstrated that a higher percentage of muscle in the cruciate section had the highest ROC of any of the other variables tested (ROC = 0.76) Figure 2. We performed Classification and Regression Tree analysis (CART) (Salford Systems, San Diego, USA) using percentage of extra-prostatic tissue in cruciate section (high = $>10\%$) to predict UI at 12 months, it yielded 71% sensitivity, 82% specificity on testing of the model.

CART analysis was also used to create a model of all the variables assessed in this study to predict early continence. The most accurate model created was a three node model using

the percentage of extra-prostatic tissue in the cruciate section, PSA and nerve sparing (Figure 3). This model demonstrated a ROC of 0.86 (Sensitivity 86%, Specificity 70%) on testing of the model for the prediction of early continence (Figure 4).

Discussion:

Urinary Incontinence (UI) is a source of significant anxiety and regret for patients during the post-operative period [5, 6]. This study examined the value of quantifying the amount of rhabdosphincter present on the apical cruciate sections of the LRP specimens to predict continence outcomes and has identified that increasing muscle on the apical sections (OR = 8.04) and age (OR = 4.27) were independent predictors of UI at long term follow-up ($p = 0.002$ & 0.04 respectively). Age and nerve sparing procedure have previously been shown by our group to be important factors in predicting a slower return of continence after LRP [12]. Furthermore the ROC for prediction of long term UI was 0.76 for increased muscle of the apical section which was significantly higher than the other standard risk factors such as age, prostate weight or nerve sparing procedure [1]. We also identified and internally validated with high accuracy a novel model incorporating the percentage of extraprostatic tissue, PSA and presence of nerve sparing procedure for predicting early continence (ROC 0.86).

This study presents a novel method of assessing the presence and extent of muscle and extraprostatic tissue on the apical sections of RP specimens and relating these to outcomes including both urinary incontinence (long-term) and early continence. A previous study assessed the relationship of striated muscle on apical sections of the prostate to functional outcome and suggested a correlation with urinary incontinence. However in that study the cone method of apical assessment was used. This is not recommended by ISUP [11] as it can affect assessment of apical positive margin rates. Furthermore we have assessed this parameter for both UI and early continence (EC) in LRP rather than predominantly open RP. We have also simplified the scoring system to a low or high classification rather than having

three different categories. We believe such an approach is more easily generalizable and reproducible by other pathologists. Lastly, our study included patients who had either early continence or long term severe incontinence (>3pads/day), which enabled more accurate assessment of these markers to predict outcome.

We recognise that our study has weaknesses that include utilising a prospectively collated database with retrospective validation. However, the blinding of the pathologist to the continence outcomes of the patients whose specimens were examined ensured the reliability of these assessments and validity of the final findings. Furthermore, in a larger cohort of patients, we have provided validation of the findings reported by Skeldon et al [9]. The statistical differences in mean operative time and PSA levels in our patient groups mean that the groups are not matched for these parameters, however, the fact that other important parameters such as pT stage, nerve sparing, surgeon case experience, age and mean prostate weight were similar helps to offset these differences.

The external urinary sphincter (EUS), which extends from the apex of the prostate to the proximal bulbar urethra is horseshoe shaped and contains striated and smooth muscle [7, 8, 13], has been recognised for its importance for urinary continence after RP. Others believe it is composed exclusively of striated muscle with fast and slow twitch fibres [14]. During radical prostatectomy surgeons attempt to identify and preserve the circular orientated horseshoe shaped urethral sphincter with its striated and smooth muscle components [7]. Due to the projection of muscle of the EUS onto the apex of the prostate, surgeons can attempt to preserve this by dissecting this off the prostate proximally [7]. A third component is the smooth muscle of the urethral musculature and preserving as much urethral length as possible remains an important factor in post-prostatectomy urinary continence [15].

The apical dissection of the prostate has long been recognised to be of crucial importance both in terms of positive margins and continence outcomes. There is a fine balance between taking too wide an apical margin and causing incontinence versus the alternative with leaving a positive surgical margin (PSM). The anatomical complexities as described above show the importance of the 3 step apical dissection procedure 1) Santorini plexus dissection, 2) dissection between the EUS striated and smooth muscle components and 3) dissection of the inner urethral muscular layer [7], this is summarised in Figure 5. With LRP, apical dissection is more difficult to do well given the lack of wristed instruments, the lack of space at the apex of the prostate, which lead to the possibility of greater traction on nerves [16]. This is supported by recent evidence of a shorter learning curve for apical PSM rates in robotic assisted radical prostatectomy (RARP) in comparison to LRP, with the robotic modality thought to improve a surgeons' apical dissection [2]. Another strength of our study is the fact that both groups of patients (continent and incontinent) were performed after a mean operative experience of over 300 cases which excludes the learning curve effect on outcomes [17]. This further strengthens the analysis and results of the study which clearly demonstrate that a higher percentage of muscle on the apical sections have a ROC of 0.76 for predicting long term UI. The results of the study show that increased excision of the EUS when dissecting the apex of the prostate, which may be affected by anatomical variation, leads to a greater defect in the EUS and increased likelihood of UI and reduced likelihood of early continence. The study also demonstrated that this additional histopathological parameter is the strongest independent predictor of UI and seems to be quantitative in nature, whereby an increased risk of urinary incontinence is associated with a greater amount of striated muscle at the apex, whilst a small amount is associated with early and long-term continence. It appears likely that difficult dissection of the apex (longer operative time being a surrogate for

this) in the study has resulted in higher apical PSMs, greater EUS injury all of which is associated with a high risk of UI after LRP.

Previously variables that have been reported as important predictors of urinary continence include age, PSA, nerve sparing and previous transurethral resection of the prostate (TURP) [18, 19]. The systematic review and meta-analysis by Ficarra et al [1] identified that age, body mass index (BMI), comorbidity index, lower urinary tract symptoms and prostate volume were the most relevant factors. In our series higher age, higher PSA, lack of a nerve sparing and higher percentage of muscle or extraprostatic tissue on the apical section were the most important predictors of predictors of UI, which is consistent with the landmark study by Eastham et al [20]. When PSA, nerve sparing procedure and percentage of extraprostatic tissue on the apical section were used as variables the CART model we created successfully predicted early continence with over 80% accuracy on internal validation of the model (ROC = 0.86). This extremely high predictive value in this model could be of great potential value in counselling patients in the early post-operative period. Ours is the most accurate model created for the prediction of early continence that we have found in the literature. A recent pre-operative predictive model on a much larger cohort of patients (2,849) which used patient pre-operative data including MRI urethral length (but not muscle on apical prostate sections) data yielded an AUC for their predictive model of 0.66 for regaining continence at 6 months [15], this did not use an estimation of striated muscle in the apical section of RP specimens.

Urinary incontinence following RP is a major cause for anxiety and decision regret for patients [5]. This anxiety is exacerbated and prolonged for many months because of the uncertain nature of the post-operative course and our inability to predict the return of urinary continence. The use of simple additional reporting of muscle and extraprostatic tissue on the apical sections of RP specimens can help to better predict the likelihood of continence return. Future studies should seek to validate these findings in a larger prospective study.

In conclusion, currently there is no consistent and reliable way to predict which patients will regain continence and which will remain incontinent after radical prostatectomy. Consequently patients usually have to play “a waiting game”. As patient satisfaction is closely linked to patient expectation, a more accurate predictive tool regarding the recovery of continence, such as this, may prove to be important in managing this group of patients.

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Table 1: Patient characteristics for continent and incontinence groups after radical prostatectomy at 12 months follow-up.

Parameter	Continent at 12 month group N = 38	Incontinent at 12 month group N = 42	Statistical significance (p =)
Mean Age (SD)	65 (11.3)	63 (6.1)	0.07 [^]
Mean PSA (µg/l)	6.4 (3.9)	8.8 (5.4)	0.03* [^]
cT stage			
cT1 (%)	19 (50%)	22 (52%)	0.8+
cT2 (%)	13 (34%)	13 (31%)	0.6+
cT3 (%)	6 (16%)	7 (17%)	0.8+
pT stage			
pT2 (%)	24 (63%)	29 (69%)	0.6+
pT3 (%)	14 (37%)	13 (31%)	0.6+
Median Gleason score	7	7	0.9 [^]
Mean Prostate Weight grams (range)	53.7 (19 – 166)	52.2 (22 – 164)	0.7 [^]
Pelvic Lymph node dissection (%)	21 (55%)	28 (67%)	0.14+
Operative Time in min (SD)	138 (34)	156 (38)	0.04* [^]
Estimated Blood loss in mls (SD)	190 (216)	250 (160)	0.1 [^]
Mean Surgeon case experience (SD)	313 (182)	303 (164)	0.8 [^]
Nerve sparing (%)	12 (32%)	19 (40%)	0.3+
Early continence (%)	14 (37%)	N/A	N/A

Apical Positive Margin rate (%)	6 (15.7%)	10 (23.8%)	0.15
Mean pads/day	N/A	2.5	N/A

*- statistically significant to a p value <0.05

^ - Mann Whitney U test

+ - chi squared test

Figure Legends:

Figure 1a: No striated muscle nor extra-prostatic tissue present at the apical margin

Figure 1b: Extraprostatic fibrous tissue and muscle present at the apical margin (red arrow)

Figure 1c: Extra-prostatic fat, fibrous tissue and blood vessels present at the apical margin (yellow arrow)

Figure 2: ROC curve for incontinence at 12 months

Figure 3: CART model for the prediction of early continence. Node 1 shows the first division if PSA is ≤ 6.7 ng/ml, Node 2 shows the percentage of extraprostatic tissue in cruciate section low (<10%), Node 3 shows presence of nerve sparing procedure (unilateral or bilateral).

Figure 4: ROC for the CART model for early continence: ROC 0.86

Figure 5: Different planes of apical dissection in radical prostatectomy. I-III “inadequate” horizontal section planes not respecting the anatomy of the striated sphincter and the prostatic apex:

I: horizontal transection plane caudal to the verumontanum preserves the striated sphincter ventrally, but apical parts of the prostate are left in situ dorsally.

II: ventral parts of the striated sphincter are harmed (white dashed line) and apical tissue of the prostatic apex is left in situ.

III: complete removal of the prostate but circumferential damage to the striated sphincter (white dashed line)

IV: ideal oblique transection plane respecting the ventral prostatic overlap of the striated sphincter. P=prostate, U=urethra, Uc=urethral crest, Ct=centrum tendineum