Prostate weight: an independent predictor for positive surgical margins during robotic-assisted laparoscopic radical prostatectomy

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Introduction: *Pre-operative prediction of pathological stage represents the cornerstone of prostate cancer management. Patient counseling is routinely based on pre-operative PSA, Gleason score and clinical stage. In this study, we evaluated whether prostate weight (PW) is an independent predictor of extracapsular extension (ECE) and positive surgical margin (PSM).*

Methods: *Between February 2003 and November 2006, 709 men underwent robotic-assisted laparoscopic radical prostatectomy (RLRP). Pre-operative parameters (patient age, pre-operative PSA, biopsy Gleason score, clinical stage) as well as pathological data (prostate weight, pathological stage) were prospectively gathered after internal-review board (IRB) approval. Evaluation of the influence of these variables on ECE and PSM outcomes were assessed using both univariate and multivariate logistic regression analysis.*

Results: *Mean overall patient age, pre-operative PSA and PW were 59.6 years, 6.5 ng/ml and 52.9 g (range 5.5 g-198.7 g), respectively. Of the 393, 209 and 107 men with PW < 50 g, 50 g-< 70 g and > 70 g, ECE was observed in 20.1%, 15.3% and 9.3%, respectively ($p = 0.015$). In the same patient cohorts, PSM was observed in 25.4%, 14.4% and 7.5%, respectively ($p < 0.001$). In a multivariate logistic regression analysis, PW, in addition to pre-operative PSA, biopsy Gleason score and clinical stage, was an independent risk factor for ECE ($p < 0.001$). Similarly, in multi-variate analysis, PW was observed to be a risk factor for PSM ($p < 0.001$).*

Conclusions: *PW is an independent predictor of both ECE and PSM, with an inverse relationship having been demonstrated between both variables. PW should be considered when counseling patients with prostate cancer treatment.*

Key Words: prostate cancer, prostate weight, laparoscopy, robotic, radical prostatectomy, extracapsular extension, positive surgical margins

Introduction

With the advent of PSA testing, a greater number of men are facing decisions in regards to prostate cancer (PCa) treatment. As we become more advanced in our surgical techniques, with minimally invasive surgery leading to less morbidity, radical prostatectomy, the gold standard for localized PCa, becomes a more appealing choice to patients. The ability to predict who will benefit from surgery is the cornerstone for counseling patients in regards to treatment options. Currently preoperative Gleason grade, serum prostate specific antigen and clinical stage are used in nomograms to predict pathological outcome.[1] Prostate weight (PW) could potentially be an additional preoperative factor to help improve prediction models.[2] Previous studies, based on open and laparoscopic prostatectomy series have shown that PW is inversely related to positive surgical margins (PSM).[2-7] In this study we examined the effect of PW on both PSM and extracapsular extension (ECE) in a large series of patients undergoing robotic-assisted laparoscopic prostatectomy (RLRP). To the best of our

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knowledge, this is the first comprehensive review of the predictive power of PW on pathological outcome in a large RLRP series.

Materials and methods

Patient selection

This is an IRB-approved, prospective collection and retrospective analysis of data obtained from patients undergoing RLRP. To date, over 900 procedures have been performed at our institution by two surgeons (ALS and GPZ). Between February 2003 and November 2006, 709 consecutive men underwent RLRP for clinically localized PCa. Patients requiring open conversion or who had aborted surgery were excluded from statistical analysis.

Surgical technique

RLRP was performed using the 3-arm, da Vinci Robotic System (Intuitive Surgical, Sunnyvale, CA) using our previously described technique.[8-10] Pelvic lymph node dissection (PLND) was routinely performed on men with a PSA ≥ 10 ng/mL, a primary Gleason grade of 4 or clinical stage ≥ T2b. All cases were approached transperitoneally with initial dissection of the seminal vesicles. The prostate was then exposed and dissected in an antegrade fashion. After bladder neck transection, nerve-sparing was performed using a clipless, interfascial technique without the use of monopolar cautery.[8,10] A running vesico-urethral anastomosis (VUA) was performed[11,12] using LapraTy clips to ensure a water-tight closure.

Pathologic analysis of the specimens

All biopsy specimens were reviewed by a single uropathologist. Furthermore, all surgical specimens were analyzed by dedicated uropathologists at our institution using our previously described technique.[13] In short, all prostates were coated with ink and fixed in formalin. The apical margin of the prostate was sectioned transversely in 1 mm sections and then sectioned longitudinally to allow precise examination of the apical margin. The remainder of the prostate was sectioned transversely into blocks at serial 3 mm intervals. Tissue blocks were further divided into quarters. Sections from each quarter were stained and examined on microscopy. Complete fresh specimen weight was calculated for PW. PSM was defined as tumor present at the inked margin. The sites of PSMs were classified as apical, base, posterolateral or any combination of sites. Patients with extension of the tumor through the prostatic capsule were considered to have ECE.

Statistical analysis

Chi-square analysis was used to test the effect of individual categorical preoperative variables on PSM and ECE. T-test analysis was used to evaluate the effect of continuous preoperative variables on PSM and ECE outcome. Furthermore, PSM and ECE rates were analyzed in both a continuous fashion and stratified into categorical cohorts based on PW < 50 g, 50 g-< 70 g and ≥ 70 g. Significant overall effect was followed by post-hoc, pair-wise comparative analysis using the Tukey test and Bonferroni adjustment of p-values. Multivariate logistic regression models were used to assess the effect of PW on PSM and ECE, controlling for other preoperative factors. All tests were performed as two-sided and a p-value of < 0.05 was considered statistically significant.

Results

Perioperative patient characteristics and pathological outcomes are summarized in Table 1. Mean pathological prostate weight was 53.0 grams (range 5.5-198). Mean

TABLE 1. **Perioperative patient characteristics and pathological outcomes**

Variables	**Mean**
Prostate weight (g)	53.0 (5.5-198.7)
Age (yrs)	59.6 (42-85)
PSA (ng/ml)	6.5 (0.6-52.5)
Pre-op Gleason score	
5-6	464 (65.4)
7	205 (28.9)
8-9	40 (5.64)
Clinical stage	
cT1c	542 (76.5)
cT2a/T2b	167 (23.5)
Post-op Gleason score	
6	421 (59.4)
7	247 (34.8)
8-9	41 (5.78)
Pathological stage (%)	
pT2	579 (81.6)
pT3	130 (18.3)
ECE	124 (17.5)
PSM (%)	
Overall	138 (19.5)
pT2	83 (14.3)
pT3	55 (42.3)

TABLE 2. **Univariate analysis of pre-operative risk factors for ECE and PSM**

Variables	ECE p-value	PSM p-value
Prostate weight (g)*	< 0.01	< 0.01
Age (yrs)*	0.04	0.37
PSA (ng/ml)*	< 0.01	< 0.01
Pre-operative Gleason score†	< 0.01	0.09
Clinical stage†	< 0.01	0.32

*t-test analysis
†Chi-test analysis

patient age and pre-operative PSA were 59.6 years and 6.5 ng/ml, respectively. The majority of patients (76.5%) had nonpalpable disease (cT1c). Overall PSM rate was 19.5%. Sub-stratified based on pathologic stage, pT2- and pT3-PSM rate was 14.3% and 42.3%, respectively.

Of the 393, 209 and 107 men with PW < 50 g, 50 g-< 70 g and ≥ 70 g, ECE was observed in 20.1%, 15.3% and 9.3%, respectively (p = 0.015). In the same patient cohorts, PSM was observed in 25.4%, 14.4% and 7.5%, respectively (p < 0.001).

On univariate analysis, Table 2, patient age was not predictive of PSM (p = 0.37), however PSA and PW related significantly with PSM (p = 0.007 and < 0.001, respectively). While PSA had a direct relationship with PSM, PW was inversely related to PSM. Age, PSA and PW were all associated with ECE (p = 0.049, 0.0008, and 0.0004, respectively) with PW again having an inverse correlation to ECE.

Using Chi-square analysis, clinical stage was not associated with PSM (p = 0.32) while pathological stage did predict PSM (p = < 0.0001). The biopsy Gleason score was not predictive of PSM (p = 0.09) but pathological Gleason score was found to be related (p = < 0.001).

On multivariate analysis, PSA, PW, and pathological stage were risk factors for PSM, Table 3. Biopsy and pathological Gleason score as well as clinical stage were not. Risk factors for ECE on multivariate analysis were PW, PSA, and clinical and pathological stage.

Discussion

There is no distinct cutpoint or threshold to define a large prostate in the prostatectomy literature. Most studies examining the effect of prostate weight on prostatectomy outcomes utilize a value of ≥ 70 g for defining a large prostate.[2,3,5] We have found a significant difference in both PSM and ECE in our series when the patients were divided into three groups based on prostate weight: < 50 g, 50 g-70 g and ≥ 70 g. Such results are consistent with large open and laparoscopic series which have demonstrated an inverse relationship between PW and both PSM and ECE. [2-5]

Should prostate size be a component of preoperative nomograms for risk assessment? In a comprehensive, multi-institutional review by Freedland et al of 1602 men who underwent open RP, men with smaller prostate sizes (< 20 g) were observed to have increased rates of PSM and ECE (all p ≤ 0.004).[2] In addition, these patients had higher Gleason grade cancers and a greater risk of disease progression than those with larger prostates (> 100 g). Upon comparing PW < 20 g versus ≥ 100 g, a relative risk of 8.43 for biochemical progression was observed (95% CI, 2.9 to 24.0; p < 0.001). The authors suggest that PW may be a useful prognostic variable that should be evaluated during pre-operative patient counseling. Such data is further supported by similar findings in other large open retropubic RP series examining PW. [3,4] Chang et al observed an inverse correlation between PW (< 75 g versus ≥ 75 g) and PSM (p = 0.01) in 400 men undergoing laparoscopic RP as well. [5] We offer yet another study, this time in a large

TABLE 3. **Multivariate analysis of pre-operative risk factors for ECE and PSM**

Variables	PSM p-value	PSM Hazard ratio	PSM 95% Wald confidence interval	ECE p-value	ECE Hazard ratio	ECE 95% Wald confidence interval
Prostate weight	< 0.01	1.032	1.01-1.04	< 0.001	1.025	1.01-1.04
Age	0.43	1.012	0.98-1.04	0.25	0.981	0.95-1.014
PSA	< 0.01	0.914	0.87-0.95	< 0.001	0.928	0.89-0.97
Biopsy Gleason score	0.14	1.663	0.73-3.79	< 0.001	5.082	2.36-10.96
Clinical stage	0.96	0.989	0.62-1.57	< 0.001	2.314	1.48-3.63

RLRP series, demonstrating that men with smaller prostates are at greater risk for PSMs. The pT2-PSM rates, a result of surgical technique with inadvertent capsular violation, has been previously observed to be increased in men with small PW undergoing RLRP.[7] A lack in haptic feedback and improper patient selection for nerve preservation may account for this observation, particularly for pT3-PSM patients.

In our experience, dissection of a smaller prostate does not appear to increase the technical level of difficulty during RLRP. We have previously demonstrated that there is no significant difference in surgical time, estimated blood loss, transfusion rate, hospital stay or complications. However, a significantly higher rate of overall and pT2-PSMs were noted in men with smaller PW.[7]

Results from the current study suggest a greater risk for ECE in men with smaller PW. Two notable explanations for this observation can be described: 1) using a mathematical, geographic model analyzing the distance from tumor to prostatic capsule; 2) by a time-lead bias when a PSA cut-off of 4 ng/ml is used. To better illustrate our first rationalization, Figure 1 depicts two hypothetical patients with 30 g and 100 g PWs, respectively, however with similar PSA levels and comparable tumor volumes. In the smaller volume prostate, there is a substantially decreased peripheral zone volume when compared to the patient with a much larger PW. Based on mathematical principles, there is a greater chance that a given tumor mass will lie in closer proximity to the capsule in the smaller gland when compared to the larger prostate. Furthermore, in the patient with the smaller prostate, there is less distance required for the tumor to traverse in order to reach the capsule, leading to a greater incidence of ECE and PSM.

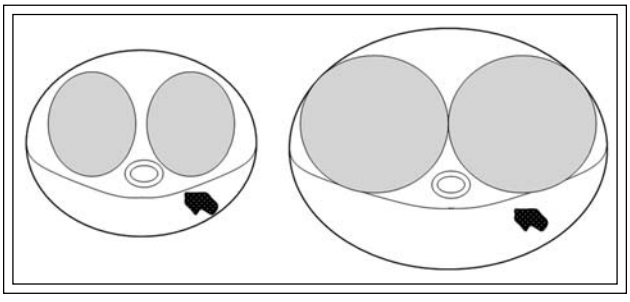

Figure 1. Schematic representation of two patients with similar pre-operative PSA and tumor volume. Both men however vary in prostate weights (30 g versus 100 g). Relative to the peripheral-zone volume, there is a greater mathematical chance that the edge of tumor mass will lie in proximity to the prostatic capsule in a patient with a smaller gland. As such, patients with small prostate size have a greater likelihood for ECE and PSM.

Another explanation for increased ECE rates in men with smaller PW is the likelihood of greater tumor volume and increased PSA density at the time of diagnosis. Larger prostate volumes, in general are associated with higher serum PSA levels due to the substantial contribution of benign hyperplastic tissue.[5] A larger prostate with elevated PSA from mainly benign tissue prompts a biopsy earlier when the cancer is at a lower clinical stage, leading to less ECE and PSM.[14] In a multivariate analysis of 325 patients, Freedland et al noted that PSA density calculated from the pathologic prostate specimen weight accurately predicted non-organ confined disease ($p < 0.001$) and PSM ($p < 0.001$) after retropubic RP, as well as biochemical recurrence($p < 0.001$).[15] Since PSA density takes into account the total volume of the prostate, it may reflect a better value for preoperative assessment. In study by the same group, it was noted that upon using PSA density rather than PSA in multivariate analysis, smaller PW was still associated with increased risk of biochemical progression.[2]

This study, however, has several limitations, including the retrospective nature of the study based on data from a single institution. Similarly, in the current study, we assessed the pathological PW rather that the pre-operative prostate volume calculations from transrectal ultrasonography (TRUS). TRUS volume calculations were not routinely available during patient consultation and being a tertiary RLRP referral center, the majority of the TRUS sizings were performed by a wide array of community urologists. Therefore, we could not ensure the accuracy of those measurements provided in our database collection and we were unable to correlate preoperative ultrasound prostate volume measurements to postoperative prostate specimen weights. TRUS imaging has routinely been the method of choice for preoperative size determination using the volume calculation of an elliptical model ($\pi/6*xyz$) with relatively good accuracy.[16,17] Advances in technology, including endorectal MRI, may lead to better estimates of PW to allow for more accurate preoperative risk assessment. Long-term follow-up studies in this RLRP cohort should examine the biochemical recurrence rate in relation to PW.

Conclusion

This study was the first comprehensive investigation of the effect of PW on pathologic outcomes in a large RLRP

series. Our data suggests that PW is an independent risk factor for both ECE and PSM, with an inverse relationship being demonstrated between both variables. As such, PW should be considered when counseling patients with prostate cancer. In addition to other pre-operative variables such as PSA, Gleason score and clinical stage, PW may empower the urologist and strengthen currently accepted nomograms, to more accurately predict pathological stage and better guide patients when discussing definitive treatment options for localized disease. □

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