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## Benign Prostate Glandular Tissue at Radical Prostatectomy Surgical Margins

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### Abstract

**Objective**—To determine whether presence of benign glandular tissue at the radical prostatectomy surgical margin is associated with technique (open (ORP) or robotic assisted laparoscopic radical prostatectomy (RALRP)) and if benign glandular tissue increases the risk of biochemical recurrence.

**Methods**—Surgical specimens from men with clinical T1–T2 disease who underwent RP between 2004–2010 were re-reviewed by a single uropathologist, examining all sections from the prostate apex and base for the presence of benign glandular tissue and tumor at the margin. Regression analysis was utilized to examine associations of benign glandular tissue with surgical approach and biochemical recurrence.

**Results**—Of 934 cases reviewed, 431 were managed by ORP and 503 by RALRP with a median follow up of 48 and 25 months, respectively. Overall, benign glandular tissue was found in 274 (29%) cases: 98 (36%) at the apex, 138 (50%) at the base and 38 (14%) at both. Compared with those who underwent ORP, patients who underwent RALRP had 3-fold greater odds of benign glandular tissue at the margin ( $P<0.01$ ), including significantly greater number of cases with benign glandular tissue at the base ( $P<0.01$ ). However, recurrence-free survival rates were similar between patients with and without BGM regardless of surgical approach and across all clinical risk groups (log-rank  $P=0.20$ ).

**Conclusions**—Patients undergoing RALRP were more likely to have benign glandular tissue at the surgical margin. However, the presence of benign glandular tissue was not an independent risk factor for biochemical recurrence.

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## Keywords

Prostatic Neoplasms/pathology; Prostatic Neoplasms/surgery; Prostatectomy\*/Methods; Neoplasm Staging; Robotics

## INTRODUCTION

Prostate cancer remains the most common non-cutaneous malignancy in American men, with over 240,000 new diagnoses annually<sup>1</sup>. The majority of men are diagnosed early with organ-confined disease, for which radical prostatectomy (RP) is frequently performed with excellent, well-reported outcomes. In addition, robotic-assisted laparoscopic radical prostatectomy (RALRP) has intensified interest in surgical management and may be increasing the number of men undergoing RP<sup>(2)</sup>.

Careful pathologic analysis of the RP specimen provides critical information regarding prognosis, risk of biochemical recurrence (BCR), and indications for adjuvant treatment. It is well recognized that tumor at the surgical margin (PSM) adversely affects cancer-specific outcomes and significantly increases the risk of BCR<sup>3</sup>. As a tool in the surveillance for BCR, a high level of reliance is placed upon the validity of postoperative PSA values. The predictive value of postoperative PSA for BCR comes into question when considering the presence of *benign* prostate glandular tissue at the surgical margin (BGM). This tissue also secretes PSA and is not associated with prostate cancer. The presence of this benign PSA-secreting tissue could possibly elevate postoperative PSA, with levels meeting the criterion for BCR in the absence of cancer recurrence. Due to the paucity of literature on the topic, the clinical impact, if any, of finding BGM at the surgical margin is unknown. Some suggest that BGM may be identified in over 25% of RP specimens, with the incidence dependent on surgical technique<sup>4</sup>. We believe these issues are particularly relevant given: (a) changes in surgical approach with the proliferation of RALRP; (b) widespread use of ultra-sensitive PSA tests with thresholds as low as 0.001 ng/mL; and (c) improved appreciation of prostate and peri-prostatic anatomy<sup>4,5</sup>. Better understanding of BGM implications may directly impact contemporary surgical techniques, pathologic analysis of the specimen, and management of patients and PSA values postoperatively.

With one of the largest cohorts and longest follow-up periods in the literature, we sought to characterize the incidence, location and association of BGM with surgical approach in specimens in men undergoing both open (ORP) and RALRP and investigate the potential association between BGM and an increased risk of BCR.

## MATERIALS AND METHODS

Study participants were selected from our prospectively collected institutional clinical and patient-consented research database. Men diagnosed with cT1 or cT2 prostate cancer who underwent RP at UCSF between 2004–2010 were included. Men with cT3 or higher were excluded as these patients have extension of disease invading into and beyond the prostatic capsule; these findings would independently raise the BCR rates as well as the likelihood of BGM present at the surgical margin. Patients who received neo-adjuvant treatment were excluded to ensure specimens were free from treatment effect. Those receiving adjuvant radiation (within 6 months of surgery) or hormone therapy were also excluded as this would affect the assessment of BCR. Formalin-fixed paraffin-embedded surgical tissue was retained for all RP patients and those with complete sets of slides of the apex and base were included in the study cohort. Clinical, pathologic, and PSA outcomes were assessed. Clinical risk groupings were based upon the NCCN 2010 risk classification guidelines<sup>6</sup>.

All prostatectomies were performed by one of six surgeons at UCSF. ORP was performed by the standard retropubic technique without preservation of the bladder neck<sup>7</sup>. RALRP was performed using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) via a transperitoneal approach with division of the bladder neck from anterior to posterior. Robotic cases were all performed with bladder neck preservation. The operations were categorized as unilateral, bilateral, or non-nerve-sparing, as documented within the operative report. The specimens were received intact and inked for the left, right, and posterior regions of the prostate. Apical and basal margins were identified at the initiation of processing and specimens were serially cross-sectioned at 3–4 mm intervals perpendicular to the urethral axis. All cases had been analyzed previously as part of routine clinical care with locations of apex, bladder margin and prostatic/seminal vesicle junction noted. Cases were then reviewed for presence of tumor, Gleason score, extraprostatic extension, seminal vesicle invasion, lymph node involvement, margin status for tumor, and were staged using the AJCC 2002 TNM guidelines<sup>8</sup>.

Re-review was performed by a single experienced genitourinary pathologist (JPS), blinded to patient clinical data, surgical technique, and patient outcomes for the presence and extent (in mm) of BGM and PSM and the Gleason patterns of tumor found at margins. PSM was defined as tumor touching the inked margin. Presence of BGM was defined as benign prostatic glands touching the inked margin. Focal BGM was defined as BGM of less than 3mm in length. Established BGM was defined as BGM of length greater than 3mm<sup>9</sup>. BCR was defined as a two postoperative elevations of serum PSA  $\geq 0.2$  ng/mL at least 8 weeks after surgery or administration of non-adjuvant second treatment ( $\geq 6$  months after primary treatment)<sup>10</sup>. Detectable PSA was defined as an elevation in postoperative serum PSA  $> 0.03$  ng/mL at least 8 weeks after surgery or administration of non-adjuvant second treatment that did not meet criteria for BCR.

Frequency tables and chi-squared tests were used to describe categorical variables. Means and *t*-tests were used to describe continuous variables. Univariable analysis identified variables significantly associated with the presence of BGM. The effect of surgical experience was explored by comparing the outcomes of surgeries performed by the two most experienced surgeons (P.R.C. and C.K.) to those of the other surgeons operating upon this cohort. Multivariable logistic regression was used to determine associations between patient or disease characteristics and the presence of BGM. Forward stepwise selection identified statistically significant parameters in the multivariable logistic regression for BCR. BCR-free survival rates stratified by surgical approach were computed with life table estimates and plotted using Kaplan-Meier curves. Cox proportional hazards regression was utilized to determine factors independently associated with BCR-free survival. Year of surgery was highly correlated with surgical approach and thus excluded from multivariable analyses. As nearly 90% of cases used bilateral nerve-sparing, the cohort was insufficiently powered to assess the differences between types of nerve-sparing used. The two most experienced surgeons were grouped together and compared to all other operating surgeons to quantify the effect of surgical experience upon outcomes measured. Statistical analysis was performed using Stata 10 and SAS 9.2 for Windows. A  $p < 0.05$  was considered statistically significant.

## RESULTS

Of 1,382 eligible patients within the database, 296 were excluded because follow-up after RP was conducted by urologists outside this institution, making thorough assessment of BCR unobtainable. An additional 154 had incomplete pathologic specimens, typically lacking slide mounts of the prostate apex and/or base. The final non-randomized study cohort consisted of 934 patients meeting criteria with complete RP specimens available for

review; they were different from those excluded with respect to high risk disease (24% vs. 31% for study cohort vs excluded), the number undergoing ORP (46% vs 12%), the proportion without post-surgery follow-up at this institution (9% vs 33%) and number of cases by the less experienced surgeons (14% vs 43%) (all,  $p<0.01$ ).

Disease characteristics of the study cohort are summarized in Table 1. The mean age was 59.2 (SD 6.8) years at diagnosis. Clinical risk classification was distributed amongst the three categories: 38% low risk, 37% intermediate risk, and 23% high risk. Average CAPRA score was 2.9 for the cohort. Overall, BGM were present in 29% and PSM in 13% of specimens. Median extent of BGM was 2.5mm (IQR 2–4) at the apex and 4mm (IQR 2–6) at the base. Of those with BGM, BGM was focal in 81 (30%) cases at the apex and 73 (27%) cases at the base. BGM was established in 51 (19%) cases at the apex and 101 (37%) cases at the base. The extent of BGM at the base was greater in RALRP cases compared to ORP ( $p<0.01$ ).

Table 1 further stratifies patients by surgical approach and the presence of benign glands. Those undergoing RALRP were more likely to have cT1c disease (54% vs 34%,  $p<0.01$ ), although clinical risk classification by approach was similar. Average CAPRA scores did not differ significantly between surgery types (2.9 for both,  $p=0.9$ ) Robotic surgeries were predominantly in the latter part of the series and conducted by less experienced surgeons (20% vs 7% for RALRP vs ORP) (both,  $p<0.01$ ). PSM differed significantly by surgical approach (18% for ORP vs 39% for RALRP,  $p<0.01$ ). BGM occurred more frequently in later years ( $p<0.01$ ) and in patients who were cT1c, had a smaller maximum percentage positive of a single core, had a lower maximum length of benign tissue present, and had a bilateral nerve sparing procedure (all,  $p<0.05$ ). There was no significant variation in the overall BGM rate when stratified by level of surgical experience. More experience surgeons conducted roughly 93% of open cases and 80% of robotic cases ( $p<0.01$ ). Surgical experience was associated with significantly higher rates of BGM in robotic surgeries (86% with BGM vs 14% without,  $p=0.004$ ) not observed with open cases (93.7% with BGM vs 13% without,  $p=0.8$ ) When compared to cases without BGM, prostate volume and prostate tumor volume did not differ significantly.

In multivariable logistic regression analysis (Table 2), compared to ORP, RALRP was associated with 3-fold greater odds of BGM ( $p<0.01$ ). Caucasian men had significantly greater odds of BGM ( $p=0.03$ ). An increase in prostate volume was associated with a slight, but significant, increase in odds of BGM ( $p<0.01$ ). Age at diagnosis and clinical risk did not significantly impact the odds of BGM. Surgical experience, though associated with 50% increase in the odds of BGM, was found not to be an independent predictor of BGM ( $p=0.2$ ).

The proportion of cases with BGM in robot assisted cases decreased over time, from 48% of cases in 2004–5 to 30% by 2009. The large decrease came at the base, decreasing from 28% to 11%, with a slight increase at the apex (12% to 15%). Among patients with BGM who underwent RALRP, glands were most often found at the base. In ORP, the proportion of cases in which BGM were noted stayed stable during the course of the study, ranging from 19–20% of cases.

852 patients had long-term follow-up, with median follow-up of 49 months (range <1–97) after ORP and 28 months (range <1–84) after RALRP. Biochemical failure (PSA 0.2 ng/ml) occurred in 72 (8%) men within five years after RP. Nearly all patients had undetectable postoperative PSA values within six months after RP (89%). A detectable PSA that did not yet reach PSA failure (0.2 ng/ml) was observed in 11% of cases; higher rates of BGM were observed in robotic cases (36% for RALRP vs 14% for ORP,  $p<0.0003$ ).

Life table estimates of BCR-free survival at 5 years were 93% for low risk, 90% for intermediate-risk and 67% for high-risk patients (log-rank  $p<0.01$ ). No statistically significant difference in recurrence-free survival was found between patients with and without BGM (log-rank  $p=0.6$ ), regardless of surgical approach and clinical risk groups (Figure 1).

In multivariable Cox proportional hazards regression predicting recurrence (Table 3), there was no significant association between BGM and BCR ( $p=0.7$ ). As expected, higher PSA at diagnosis ( $p<0.01$ ), PSM ( $p=0.02$ ) and increasing pathologic Gleason grade ( $p<0.01$ ) were associated with BCR.

## COMMENT

Over the past three decades, surgical management of prostate cancer has evolved significantly. A greater understanding of peri-prostatic anatomy has led to techniques allowing for safe and meticulous gland resection while preserving urinary and sexual function. Despite increased use of both radiation therapy and active surveillance, the popularization of the robotic-assisted approach has led to renewed interest in surgery and analysis of operative details and outcomes. Careful pathologic examination of the prostatectomy specimen provides critical information regarding tumor size and grade, pathologic stage, and status of surgical margins with respect to malignant glands, all of which play a role in prognosis and subsequent decision-making. Standardized assessment of the surgical specimen and reporting of findings are important<sup>11</sup>. With further standardization more accurate differentiation between true pathologic recurrence and elevated postoperative PSA values due to BGM may develop. Nevertheless, the presence and significance of benign prostate glands at the surgical margin remains poorly characterized.

Our analysis of contemporary patients undergoing radical prostatectomy reveals that BGM is identified in a significant number of cases (29%), which is consistent with previous reports<sup>12–20</sup>. Moreover, surgical approach (RALRP) had the strongest association with BGM (OR 3.1, 95% CI 2.1–4.6), adjusting for sociodemographic and clinical characteristics. Other variables associated with BGM included ethnicity, prostate volume at biopsy. We also noted the rate of BGM in men undergoing RALRP decreased over time, suggesting a learning curve contributed to the ability to prevent this occurrence. Together, these observations highlight that the presence of BGM may be directly related to both surgical technique and experience of the surgeon, rather than patient or disease characteristics. The surgeon must be aware of the potential for BGM, particularly at the bladder neck in patients undergoing robotic-assisted surgery. This supports the fact that the bladder neck dissection is one of the most challenging aspects of RALRP, where it may be difficult to precisely identify the junction between prostatic and bladder tissue early in a surgeon's experience. It is interesting to note that bladder neck preservation during ORP yielded BGM in 42% of cases, suggesting that proximity to the prostate-bladder junction, whether via open or robotic-assisted approach, results in an increased occurrence of benign glandular tissue at margin of the specimen<sup>21</sup>.

Conversely, the rate of BGM at the apex was consistently low (10%) overall as well as in both surgical groups. Although this may reflect similar (and unchanging) techniques in apical approach, it also emphasizes the importance of understanding peri-prostatic anatomy. Despite frequent reference, the gland lacks a discrete capsule. This is particularly true on the anterior third at the apex, where the tissue is in reality a fibromuscular stroma: an amalgamation of striated muscle, prostate glands, and elastic fibers<sup>22,23</sup>. It is therefore unsurprising, due to variations in the shape and the known presence of extraprostatic glands in this area despite complete prostate excision, that glands may be found at this anterior

apical margin where the dorsal venous complex is divided. With this level of dissection there is a delicate balance between the risk of BGM at the apical margin and detrimental impact on continence and potency with wider dissection.

The most interesting finding of this study is the identification of BGM after both ORP and RALRP was not associated with recurrence, either biochemical or clinical, during a median follow-up interval of 49 months after ORP and 28 months after RALRP. As expected, factors associated with recurrence included PSA at diagnosis, primary Gleason 4, tumor volume, and detectable PSA during the first six months after surgery. In addition, BGM was not significantly associated with PSM. Thus, the potential presence of residual benign prostate glands after surgery suggested by BGM does not seem to imply the presence of residual tumor that may lead to biochemical failure, highlighting the need for differentiation between pathologic recurrence and PSA biochemical recurrence. It is important to note the follow-up for those with BGM is relatively short, and sufficient time for cellular proliferation and resultant increase in serum PSA may not have elapsed<sup>24</sup>. Extending followup further should clarify whether BGM leads to low, detectable levels of PSA that may not meet threshold for defining biochemical failure. This may be particularly relevant with the widespread availability of ultra-sensitive PSA assays. The routine use of ultra-sensitive tests after treatment has not been validated and remains controversial in clinical practice, and may be particularly true in patients at low risk of disease recurrence and potentially in those with BGM.

Strengths of our study include the large cohort of patients treated at an academic center with extensive experience performing RP, as well as long-term clinical follow-up and prospective collection of data. In addition, a single experienced genitourinary pathologist re-reviewed all cases ensuring the consistent evaluation of all specimens. Nevertheless, quantification of BGM is difficult and not yet standardized. We postulated that cases with more slides per site led to greater detection of BGM, although this could not be confirmed. Within our cohort, longer follow-up may reveal detectable levels of PSA associated with BGM that may not reflect actual prostate cancer recurrence but rather a clinically benign elevation of PSA. Significant differences in biopsy Gleason grade, clinical risk, year of surgery, surgical experience and approach and the length of follow-up introduce bias that could underestimate BGM rates. Of note, RALRP was associated with a higher incidence of cT1c. Our study shows increasing rates of robotic cases over time, which coincides with an increase in cT1c over time previously observed. This increasing incidence of cT1c could contribute to the higher rates of BGM in seen in the robotic cases. Interestingly, this significant increase in cT1c disease incidence has been previously reported to trend with significant rise in Gleason 6 disease, decreasing concern of a potential confounding effect on BCR rates in our cohort<sup>25</sup>. Potentially, a portion of the ORP learning curve excluded from the study cohort may contain cases of less precise dissection at the apex, contributing to higher rates of BGM. Further quantification of the level of dissection at the apical margin may better define the optimal length necessary to ensure a lower rate of BGM without compromising the post-operative potency and continence.

## CONCLUSIONS

Patients undergoing RALRP had greater odds of BGM than those undergoing ORP, although this number decreased over time with increased experience. However, BGM was not independently associated with BCR, and therefore raises the issue of the clinical significance of BGM.

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## Abbreviations

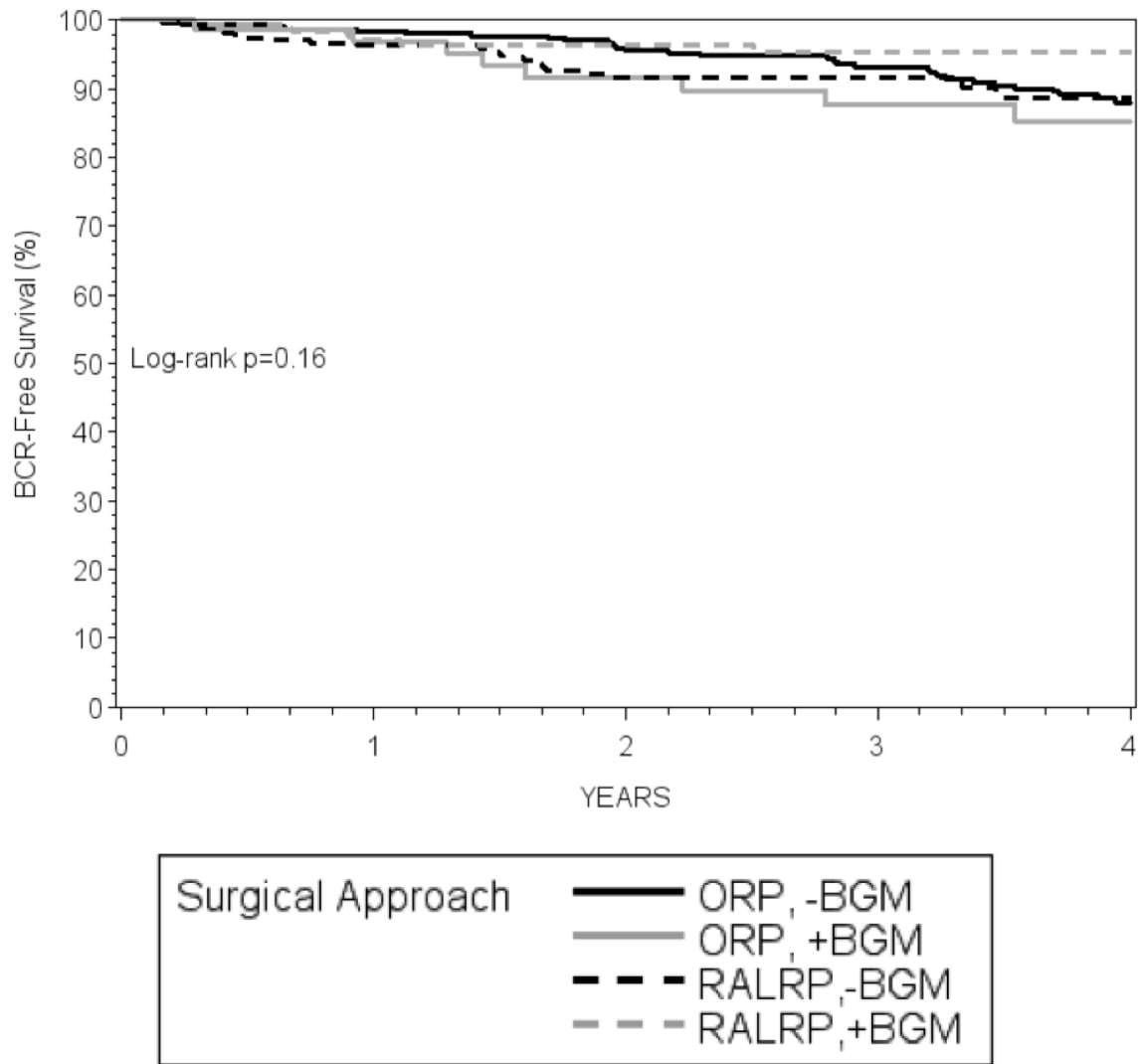
<b>RP</b>	Radical Prostatectomy
<b>ORP</b>	Open Radical Prostatectomy
<b>RALRP</b>	Robotic Assisted Laparoscopic radical Prostatectomy
<b>BGM</b>	Benign Glands at the Surgical Margins
<b>PSM</b>	Positive Surgical Margins
<b>BCR</b>	Biochemical Recurrence

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**Figure 1.**

Surgical Approach	Total at risk (n)	1yr	2yr	3yr	4yr
ORP, -BGM	324	300	263	215	166
ORP, +BGM	70	61	49	41	31
RALRP, -BGM	278	242	166	82	34
RALRP, +BGM	180	163	115	66	26

**Table 1**  
Clinical, pathologic and demographic factors stratified by surgical approach and by benign glands status

	ORP	RALRP	p	BGM absent	BGM present	p
Year of Surgery median (IQR)	2005 (2004–06)	2007 (2006–08)	<0.01	2006 (2005–07)	2006 (2005–08)	<0.01
Age (years), mean (SD)	59 (6.5)	59 (6.9)	0.8	59 (6.6)	59 (7.1)	0.1
Caucasian, n (%)	384 (89)	444 (88)	0.8	579 (88)	249 (91)	0.3
PSA (ng/mL) median (IQR)	5.5 (4.4–7.6)	5.7 (4.5–7.7)	0.8	0.85.6 (4.4–7.6)	5.6 (4.5–7.7)	0.4
Clinical Stage T1, n (%)	147 (34)	271 (54)	<0.01	276 (42)	142 (52)	0.02
Prostate volume (cc) median (IQR)	29 (23–39)	29 (23–39)	0.6	28 (22–38)	30 (25–39)	0.1
Biopsy Gleason Grade n (%)	2–6	260 (52)		338 (51)	153 (56)	
	7	172 (35)	0.3	224 (34)	82 (30)	0.7
	8–10	70 (14)		91 (14)	38 (14)	
% Cores positive, Median (IQR)	42 (20–67)	42 (21–67)	0.6	43 (22–67)	38 (19–60)	0.04
Type of Surgery n (%)	ORP	431 (46)	-	352 (53)	79 (28)	<0.01
	RALRP	-	503 (54)	308 (46)	195 (71)	
Nerve Sparing n (%)	None	8 (2)	9 (2)	15 (2)	2 (1)	
	Unilateral	47 (11)	27 (5)	60 (9)	14 (5)	0.01
	Bilateral	375 (87)	459 (93)	577 (87)	258 (94)	
Pathologic Gleason Grade n (%)	6	152 (35)	165 (33)	212 (32)	105 (38)	
	7 (3+4)	189 (44)	235 (47)	306 (46)	118 (43)	0.2
	7 (4+3)	68 (16)	81 (16)	107 (16)	42 (15)	
	8–10	22 (5)	21 (4)	34 (5)	9 (3)	
Pathologic Stage n (%)	T2	333 (78)	409 (81)	512 (78)	229 (84)	0.4
	T3a	81 (19)	70 (14)	119 (18)	32 (12)	
	T3b	13 (3)	20 (4)	23 (3)	10 (4)	
	T4	4 (1)	5 (1)	6 (1)	3 (1)	

**Table 2**

Multivariable logistic regression analysis of benign glands at the surgical margin

<b>Patient Characteristics</b>	<b>OR (95% CI)</b>	<b><i>p</i></b>
Age (per year increase)	0.98 (0.95 – 1.01)	0.2
Caucasian (vs. other)	2.31 (1.14 – 4.64)	0.03
CAPRA Clinical Risk (0–10 scale)	0.94 (0.84 – 1.06)	0.3
Prostate volume (per cc increase)	1.02 (1.00 – 1.03)	0.01
RALRP (vs. ORP)	3.07 (2.06 – 4.58)	<b>&lt;0.01</b>
Surgical experience	1.52 (0.08 – 2.89)	0.2

OR Odds ratio; CI Confidence Interval

**Table 3**

Cox proportional hazards regression predicting disease recurrence

<b>Patient Characteristics</b>	<b>HR (95% CI)</b>	<b><i>p</i></b>
Age (per decade inc)	1.5 (1.0–1.1)	0.06
Caucasian (vs other)	1.4 (0.6–3.3)	0.4
PSA (per ng/ml inc)	1.0 (1.0–1.1)	<b>&lt;.01</b>
Prostate volume (per 10cc inc)	1.0 (0.8–1.1)	0.2
RALRP (vs ORP)	1.0 (0.6–1.7)	1.0
Surgical Experience	0.8 (0.3–1.8)	0.5
Pathologic Gleason Grade (vs. 6)		
7 (3+4)	3.7 (1.5–9.1)	<b>&lt;.01</b>
7 (4+3)	6 (2.3–15.3)	<b>&lt;.01</b>
8–10	10.5 (3.6–30.5)	<b>&lt;.01</b>
Pathologic T3/4 (vs T2)	1.5 (0.9–2.5)	0.1
Positive margins (vs none)	2 (1.1–3.4)	0.02
Benign glands (vs none)	0.9 (0.5–1.6)	0.7