

# Benign prostate glands at the bladder neck margin in robotic vs open radical prostatectomy

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Accepted for publication 29 January 2010

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Study Type – Therapy (case series)  
Level of Evidence 4

## OBJECTIVE

To compare the prevalence and extent of benign glands at the bladder neck (BN) margin in a large population undergoing open retropubic radical prostatectomy (RRP) and robotic-assisted laparoscopic RP (RALP), as RALP was previously suggested to be associated with a higher rate of benign glands at the surgical margin than RRP.

## PATIENTS AND METHODS

From 2005 to 2008, 137 RRP and 152 RALP were performed by one surgeon. Pathology

slides were re-reviewed while unaware of origin to examine the extent of benign glands at the BN margin (minimal, moderate, or extensive). Statistical analysis was used to assess the prevalence and extent of benign glands in the two procedures.

## RESULTS

Benign prostatic glands were present at the margins in 89 (58.2%) RALP and 57 (41.6%) RRP specimens ( $P = 0.005$ ). There were also a significantly greater extent of benign glands in RALP vs RRP ( $P = 0.031$ ). After multivariate adjustment for prostate-specific antigen (PSA) level, clinical stage, and biopsy Gleason score, RALP maintained a significant association with both the presence ( $P = 0.019$ ) and extent ( $P = 0.018$ ) of benign glands at the BN. Two patients with organ-confined disease (no cancerous margins) with benign glands at the BN margin had an initially high postoperative PSA level.

## CONCLUSIONS

Benign prostate glands were present at the BN margin in a greater proportion of RALP than RRP specimens, possibly due to differences in the surgical approach to BN dissection. Additional study is necessary to determine the long-term biological significance, if any, of these histological differences.

## KEYWORDS

benign glands, positive margin, bladder neck, robotic, open prostatectomy

## INTRODUCTION

In 1997, Intuitive Surgical (Sunnyvale, CA, USA) developed the da Vinci robot, which has since gained considerable popularity for radical prostatectomy (RP). Based on claims from a 5% Medicare sample, the proportion of RP performed using a laparoscopic or robotic approach increased from 12.2% in 2003 to 31.4% in 2005 [1], and has continued to grow.

Advantages of robotic-assisted laparoscopic RP (RALP) include improved cosmesis and decreased intraoperative blood loss [2,3]. The da Vinci system also features magnified visualization and wristed movements with computer-assisted elimination of intention tremor. Other short-term outcomes, e.g. length of hospital stay and postoperative

narcotic usage, appear to be comparable between RALP and open retropubic RP (RRP) [4,5].

However, there is ongoing concern about the oncological efficacy of RALP. For example, Hu *et al.* [1] reported a 3.7 times greater rate of salvage therapy within 6 months of minimally invasive RP than for RRP. Other studies reported high positive (cancerous) surgical margin rates during the early experience for RALP [6].

Anecdotally we have also noted an increase in the proportion of cases with benign prostate glands at the surgical margin with RALP. A similar observation was made by Kohl *et al.* [7], who reported the presence of benign glands at the surgical margin in 54% of 25

consecutive RALPs, compared to 15% of 12 RRP specimens ( $P = 0.035$ ). The objective of the present study was to expand on these findings in a much larger contemporaneous single-surgeon comparison of RALP vs RRP. Our hypothesis was that benign prostate glands are present at the bladder neck (BN) margin in a greater proportion of RALP than RRP specimens.

## PATIENTS AND METHODS

From 2005 to 2008, 289 patients underwent RP by one surgeon (J.P.J.) of whom 137 (47.4%) and 152 (52.6%) had RRP or RALP, respectively. Clinical and pathological variables were prospectively recorded in a database. All patients provided written

**TABLE 1** The demographics of the study population

Variable	Mean (sd) or n (%)
Age, years	58.1 (5.6)
Race	
Caucasian	251 (86.9)
African American	24 (8.3)
Other	9 (3.1)
Unknown	5 (1.7)
Preoperative PSA level, ng/mL	5.4 (2.9)
Clinical stage	
T1c	220 (76.1)
T2	67 (23.1)
T3	1 (0.4)
Missing	1 (0.4)
Biopsy Gleason score	
6	199 (68.9)
7	73 (25.2)
8–9	17 (5.9)

informed consent and the study protocol received institutional review board approval.

Open RRP was performed in the standard anatomical fashion; notably, the BN was preserved during RRP, using a technique similar to that previously described by Latiff [8] and Gomez [9]. RALP was performed by various techniques but the prostatic dissection was always antegrade, with division of the BN from anterior to posterior.

RP specimens were processed at our institution as follows: Prostates were inked to determine the surgical margins and then injected with formalin for rapid fixation in a microwave oven. The proximal (BN) margin was removed from the proximal urethral area as a 1-mm, thin-shave margin, and any tumour on the BN margin slice was considered positive. The distal 5–8 mm of the prostate was amputated and then sectioned parallel to the urethra in 2–3 mm thick slices; tumour at the inked perpendicular margins was considered as a positive margin. After removing the apical distal and proximal margins, the remaining prostate was sectioned at 2–3 mm intervals and entirely submitted for histological examination. All pelvic lymph nodes were also submitted for pathological examination.

All 289 cases were re-reviewed by an expert pathologist (J.I.E.) for the current study to

Extent	Total	RALP	RRP	P
None	143 (49.5)	63 (41.5)	80 (58.4)	0.031
Minimal	31 (10.7)	19 (12.5)	12 (8.8)	
Moderate	36 (12.5)	19 (12.5)	17 (12.4)	
Extensive	79 (27.3)	51 (33.5)	28 (20.4)	

**TABLE 2** Prevalence and extent of benign glands at the surgical margin in RALP vs RRP**TABLE 3** Multivariable models for predicting the presence and extent of benign glands at the bladder neck margin

Variable	Odds ratio or coefficient (95% CI)	P
<b>Presence</b>		
RALP (vs RRP)	1.78 (1.1–2.9)	0.019
PSA level	0.94 (0.9–1.02)	0.157
Biopsy Gleason score	0.91 (0.6–1.4)	0.656
Clinical stage	0.89 (0.5–1.6)	0.707
<b>Extent</b>		
RALP (vs RRP)	0.37 (0.1–0.7)	0.018
PSA	–0.04 (–0.09–0.02)	0.176
Biopsy Gleason score	0.003 (–0.3–0.3)	0.981
Clinical stage	–0.13 (–0.5–0.2)	0.476
Constant	1.2 (0.8–1.6)	<0.001

assess the presence and extent of benign glands specifically at the BN. Based on semiquantitative visual estimation, benign glands were quantified as: 0, no benign glands represented; minimal, benign glands fit into one  $\times 10$  high-power field (hpf) or two  $\times 20$  hpf; moderate, benign glands fit into two  $\times 10$  hpf or five  $\times 20$  hpf; extensive, benign glands fit into more than two  $\times 10$  hpf or more than  $5 \times 20$  hpf.

Descriptive statistics were used to examine the clinical and pathological features of the study cohort. In addition, the chi-square test was used to compare the prevalence and extent of benign glands between RRP and RALP. Logistic regression was used to examine the relationship between RP technique (RRP vs RALP) with the presence or absence of benign glands, adjusting for PSA level (continuous variable), clinical stage, and biopsy Gleason score. Similarly, linear regression was used to examine the association between RP technique (RRP vs RALP), PSA level, clinical stage, and biopsy Gleason score with the extent of benign glands. Finally, we examined the distribution of initial postoperative PSA levels in 266 (92%) men with follow-up data. Recurrence was defined as a PSA level of  $>0.2$  ng/mL after RP, or early salvage therapy.

## RESULTS

Table 1 shows the demographic details of the study cohort; the mean age was 58 years and the mean (range) preoperative PSA level was 5.4 (0.2–24) ng/mL. Most patients had clinical stage T1c disease (76.1%) and a biopsy Gleason score of 6 (68.9%). At RP most patients had organ-confined disease; extraprostatic extension, seminal vesicle invasion and lymph node metastases were present in 80 (27.8%), five (1.7%) and two (0.7%) men, respectively. Positive surgical margins were present in 47 (16.3%) patients, including 22 (14.5%) RALP and 25 (18.2%) RRP ( $P = 0.411$ ). Among men with organ-confined disease, there was also no significant difference in the positive surgical margin rate (6.0% RALP vs 9.1% RRP,  $P = 0.4$ ).

Overall, 50.3% of the study population had benign glands at the BN, including 89 (58.2%) RALP and 57 (41.6%) RRP specimens ( $P = 0.005$ ). Table 2 compares the proportion of cases with minimal, moderate and extensive benign glands between RALP and RRP. RALP was associated with a significantly greater extent of benign glands than RRP ( $P_{\text{trend}} = 0.031$ ).

Table 3 shows the results of multivariate analysis. After adjusting for PSA level, clinical

stage and biopsy Gleason score, RALP was associated with a significantly greater odds of benign glands at the BN margin than RRP (odds ratio 1.8,  $P=0.019$ ). Similarly, RALP was associated with a significantly greater extent of benign glands in the multivariable model ( $P=0.018$ ).

In the 266 men with follow-up data, 14 (5.3%) had an elevated initial postoperative PSA level, including seven after RALP and seven after RRP. Of these men, five had no evidence of cancer at the surgical margin, but two in the RALP group had benign glands at the BN margin. Both patients had clinical stage T1c, pathologically organ-confined disease, with RP Gleason scores of 6 and 7, respectively.

## DISCUSSION

The recent widespread use of the da Vinci robot has generated controversy as to its oncological efficacy compared to the standard open RRP. Numerous studies have described the positive (cancerous) surgical margin rates in RALP and RRP, with conflicting results. Smith *et al.* [10] reported positive margins in 9.4% of RALP vs 24.1% of RRP in men with pathological stage T2 disease ( $P < 0.001$ ). However, other large RRP series have reported positive margin rates as low as 1.8% in men with organ-confined disease [11].

Another interesting issue is the presence of benign glands at the surgical margin. In 2007, Kohl *et al.* [7] reported a small series (38 men) with a significantly higher rate of benign glands at the margin in RALP than RRP ( $P=0.035$ ). In the present study, we validated these findings and confirmed our initial hypothesis that RALP was associated with a significantly greater likelihood of benign glands at the BN margin. When present, benign glands were also significantly more extensive in RALP than RRP.

However, an unsuspected finding was the prevalence of benign glands at the BN margin in 41.6% of open RRP. A potential explanation for this finding is that the BN was preserved in our series. It is likely that not sparing the BN during RRP would be associated with a lower risk of benign glands at the BN, which would further increase the disparity between RALP and RRP. Another potential factor is that the BN was removed as

a thin (1 mm) shave (*en face*) margin, where in some cases an intraprostatic section might have been taken that would not have shown benign glands at the ink had the margin been taken perpendicularly. The advantage of the shave margin is that the entire surface area is examined microscopically, as opposed to perpendicular margins where only a 5 µm section of the margin is examined histologically for every 3 mm gross section processed.

That notwithstanding, the clinical significance of benign glands at the BN margin is unclear. A theoretical concern is that residual benign tissue could lead to a high PSA level after RP. Indeed, two patients in our series with organ-confined disease (no cancer at the surgical margin) with benign glands at the BN margin had an initially high PSA level after RP. This might lead to patient anxiety and/or secondary therapy, with its associated cost and potential side-effects. Other theoretical possibilities are that the tissue could continue to grow, leading to obstructive symptoms, or that prostate cancer could subsequently develop in the residual tissue.

Previous studies suggested that 1 g of benign prostatic tissue raises the serum PSA level by  $\approx 0.3$  ng/mL [12]. Although macroscopic residual benign tissue could therefore potentially lead to a high PSA level after RP, the time required for a few microscopic cells to trigger a detectable serum PSA level is unknown. Furthermore, the ability of PSA to gain access to the circulation might differ in the setting of altered anatomy after RP.

A possible reason for the different proportion of benign glands between RRP and RALP is the technique and vantage point of the surgeon for the BN dissection. In an open RRP, the surgeon looks directly down at the BN and can use tactile feedback to guide the posterior dissection, whereas in RALP the perspective of the camera is always cranial to caudal. Although we did not routinely switch to a 30° down lens in our series, it is possible that this might provide improved visualization for the posterior BN dissection in RALP.

A limitation of our study is that the sample size was relatively small, limiting statistical power, particularly for biochemical progression. Also, the presence of benign glands at the margin of the specimen does not necessarily imply residual prostate tissue inside the body. In addition, because we

studied this issue in a contemporary population, the follow-up was limited and therefore we are unable to address the long-term prognostic significance of benign glands at the BN margin. Furthermore, as this was not a randomized study, there might have been bias in the selection of patients who had RRP or RALP. Finally, the learning curve for RALP might have affected the results, as the surgeon had performed  $>1000$  open RRP before the study. Nevertheless, additional adjustment for date of surgery did not alter the statistically significant relationship between RALP and benign glands (data not shown).

However, the strengths of our study include the uniform pathological examination, minimizing bias due to differences in specimen handling and interpretation, and including quantification of benign glands. In addition, all RALP and RRP were performed by one experienced surgeon contemporaneously, thereby minimizing bias due to temporal trends or differences in technique between surgeons.

In conclusion, our results show a significantly higher proportion and greater extent of benign glands at the BN margin in RALP than in a bladder neck-preserving RRP. Additional study is warranted to determine the relationship of this finding to long-term treatment outcomes.

## CONFLICT OF INTEREST

None declared.

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**Abbreviations:** (R)RP, (open retropubic) radical prostatectomy; RALP, robotic-assisted laparoscopic RP; BN, bladder neck; hpf, high-power field.