Original Article

Changes in pathologic outcomes and operative trends with robot-assisted laparoscopic radical prostatectomy

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ABSTRACT

Introduction: We hypothesized that there is a reverse stage migration, or a shift toward operating on higher-risk prostate cancer, in patients undergoing robot-assisted laparoscopic prostatectomy (RALP). We therefore evaluated the stage of disease at the time of surgery for patients with prostate cancer at a large tertiary academic medical center.

Materials and Methods: After institutional review board approval, we reviewed all patients that had undergone robotic prostatectomy. These patients were separated into three categories: An early era of 2005-2008, intermediate era of 2009-2010, and a current era of 2011-2012.

Results: A total of 3451 patients underwent robotic prostatectomy from 2005 to 2012. The proportion men with clinical T1 tumors declined from 88.3% in the early era to 72.2% in the current era ($P < 0.0001$). Men with preoperative biopsy Gleason 6 disease decreased from the early to the current era ($P < 0.0001$), while men with preoperative biopsy Gleason ≥ 8 showed the opposite trend, increasing from the early to the current era ($P = 0.0002$). From the early to the current era, the proportion of patients with National Comprehensive Cancer Network (NCCN) low risk prostate cancer decreased, while those with NCCN intermediate and high-risk disease increased. The proportion of pathologic T3 disease increased from 15.5% in the early to 30.6% in the current era ($P < 0.0001$). On the other hand, the proportion of pathologic T2/+ SMS (surgical margin status) decreased from 6.6% in the early era to 3.1% in the current era ($P = 0.0002$).

Conclusions: We have demonstrated a reverse stage migration in men undergoing robotic prostatectomy. Despite the increasing proportion of men with extra-capsular disease undergoing RALP, the surgical margin status has remained similar. This could reflect both the changing dynamics of the population opting for surgery as well as the learning curve of the surgeons.

Key words: Prostate cancer, robotics, stage migration

INTRODUCTION

Although Prostate-specific antigen (PSA) testing for prostate cancer screening has lowered death rates due to prostate cancer,[1] there is growing concern that clinically insignificant prostate cancer would be detected in many men in the population, and also at an earlier age, leading to therapies that otherwise would have not changed the course of the disease.[2,3]

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Access this article online

Quick Response Code:

Website: www.indianjurol.com

DOI: 10.4103/0970-1591.142054

Studies have demonstrated a general trend of downward stage and grade migration after institution of PSA testing.[4-6] The overtreatment of low-grade disease in prostate cancer in the population is largely due to stage migration,[7,8] and approximately 80% of American men had organ-confined disease after radical prostatectomy in 2001.[9]

To sum up, PSA screening has played a major role in the over-diagnosis and over-treatment of clinically insignificant prostate cancer.[10,11] The objective of our analysis was to evaluate our series for a shift in the operative volume on low and high-risk prostate cancer as well as the pathologic changes seen over time in patients undergoing robot-assisted laparoscopic prostatectomy (RALP).

MATERIALS AND METHODS

We performed an institutional review board-approved, retrospective review of 3451 consecutive patients who underwent robot-assisted prostatectomy by a single surgeon from 2005 to 2012 for localized prostate cancer. Patients who had received preoperative radiation therapy

or androgen-deprivation therapy were excluded from the analysis. Patient data were collected and entered into a prospective prostate cancer database. The seventh edition of the American Joint Committee on Cancer tumor-lymph node (LN)-metastasis classification was used to define clinical stage, and histopathologic grading was done according to the Gleason system. Biopsies performed at referring facilities were reviewed by dedicated genitourinary pathologists at our institution. All patients underwent robot-assisted radical prostatectomy and pelvic LN dissection in this series.

Patients were stratified according to year of operation based on surgeon experience, 2005-2008, 2009-2010, 2011-2012 (early, intermediate, and current groups for robot-assisted prostatectomy). These categories were determined on volume and surgeon learning curve. Patients also were stratified according to National Comprehensive Cancer Network (NCCN) guidelines into the following risk categories: Low risk (PSA ≤10 ng/mL, ≤T2a, and Gleason score ≤6), intermediate risk (PSA 10-20 ng/mL, or T2b-T2c, or Gleason score 7), or high risk (PSA >20 ng/mL, or ≥T3a, or Gleason score ≥8).[12]

Postoperative pathologic reports were identified for all patients, and high-risk characteristics of extracapsular extension (ECE), positive nodal status (N1), and positive surgical margins (PSM) (+SMS) were determined and sorted by the above year stratification system.

Microsoft Excel 2013 (Microsoft Corporation, Seattle WA) and GraphPad Prism 5 (Graph-Pad Software Inc., La Jolla, CA) software were used to perform all statistical calculations with $P < 0.05$ considered as statistically significant. Two analyses were used to compare factors between the different eras.

RESULTS

RALP for prostate cancer was performed on a total of 3451 patients all of whom met the inclusion criteria and had preoperative characteristics available from 2005 to 2012. Baseline characteristics are listed in Table 1.

Preoperative markers

PSA levels did not demonstrate any significant changes over time in either the total cohort or the individual era in which RALP was performed. The proportion of clinical T1 tumors in the operative cohorts declined from the early to current eras (88.3% of patients were clinical T1 in the early group, 72.2% were T1 in the current group; $P < 0.0001$).

Similarly, the percentage of patients in each era that represented Gleason 6 disease at biopsy was statistically decreased from the early to the current group (63.5% of cases in the early group, 38.7% of cases in the current group; $P < 0.0001$). Preoperative biopsy Gleason 7 disease showed the opposite trend to that of Gleason 6 disease, and the proportion of Gleason 7 disease was also statistically significantly higher from the early (30.1%) to the current group (50.5%) ($P < 0.0001$). Preoperative biopsy Gleason 8 disease showed a similar trend to that of Gleason 7, and there was a statistically significant difference between the early (6.4%) and current group (10.8%) ($P = 0.0002$).

Stratification by National Comprehensive Cancer Network Category

Figures 1 and 2 demonstrate the trends seen from the early, intermediate and current groups with respect to NCCN classification. A downward trend is seen in the proportion of NCCN low risk patients undergoing

Table 1: Baseline characteristics of the sample categorized by era

Characteristic	No. of patients (%)		
	2005-2008	2009-2010	2011-2012
Number of patients	1492	1082	877
Age: Median (IQR), year	60 (55, 65)	60 (54, 64)	60 (55, 65)
PSA at diagnosis median (IQR), ng/mL	4.9 (3.8, 6.6)	4.9 (3.8, 6.7)	5 (3.9, 7.0)
Clinical stage, *n* (%)			
T1	1318 (88.3)	798 (73.7)	633 (72.2)
T2a	121 (8.1)	281 (26)	236 (26.9)
≥T2b	53 (3.6)	3 (0.3)	8 (0.9)
Biopsy gleason score, *n* (%)			
≤6	948 (63.5)	568 (52.5)	339 (38.7)
7	449 (30.1)	421 (38.9)	443 (50.5)
>8	95 (6.4)	93 (8.6)	95 (10.8)
National Comprehensive Cancer Network category, *n* (%)			
Low risk	834 (55.9)	496 (45.8)	281 (32.0)
Intermediate risk	546 (36.6)	484 (44.7)	483 (55.1)
High-risk	112 (7.5)	102 (9.5)	113 (12.9)

IQR=Interquartile range, PSA=Prostate-specific antigen

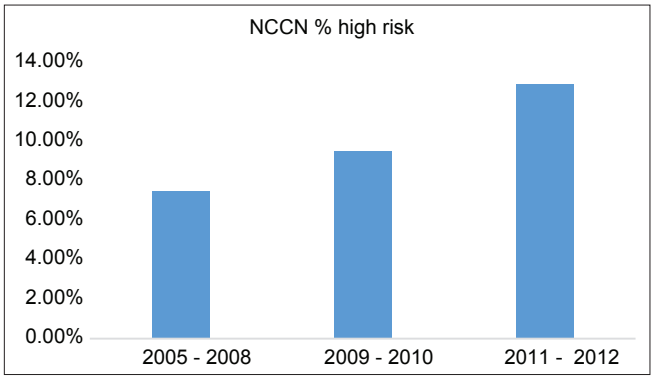

Figure 1: Percentage of sample categorized as National Comprehensive Cancer Network low risk categorized by era

RALP from the early (55.9%) to current groups (32.0%) ($P < 0.0001$) [Figure 1]. An upward trend is seen in both the NCCN intermediate risk patients from the early (36.6%) to high-risk patients (55.1%) ($P < 0.0001$) and high-risk patients from early (7.5%) to current groups (12.9%) ($P < 0.0001$) [Figure 2].

Pathologic markers

Pathologic characteristics from men in this cohort are shown in Tables 2 and 3. Pathologic T3 disease increased from the early to current groups (from 15.5% in 2005-2008 to 30.6% in 2011-2012; $P < 0.0001$) [Figure 3]. Pathologic surgical margin status remained similar from the early to current groups (from 10.6% in 2005-2008 to 8.8% in 2011-2012; $P = 176$). On the other hand, the proportion of T2/+SMS findings on pathologic specimens decreased from the early to current groups (from 6.6% in 2005-2008-3.1% in 2011-2012; $P = 0.0002$) [Figure 4].

DISCUSSION

In this study, we examined the preoperative baseline characteristics and stages of risk as well as the postoperative pathologic rates of ECE as well as LN and SMS positive rates in RALP patients over an 8-year period in men with localized prostate cancer. From the early to current groups of RALP, we found an increase in the proportion of preoperative high-risk patients undergoing surgery, as well as an increase in the high-risk pathologic characteristics. These trends suggest a shift with operative emphasis on higher risk disease as well as the learning skills gained as RALP became an established practice. The increasing trend toward operating on higher risk patients could also be explained by increasing use of active surveillance as a treatment option for low risk prostate cancer. Active surveillance could lead to patients being upstaged as a result of repeat biopsies performed.

Table 2: Pathologic characteristics of the sample categorized by era

Period	Total	T3a/T3b	T3a/T3b %	T2/PSM	T2/PSM %	N1	N1%
2005-2008	1492	231	15.48	98	6.57	9	0.60
2009-2010	1082	207	19.13	51	4.71	15	1.39
2011-2012	877	268	30.56	27	3.08	13	1.48

PSM=Positive surgical margin

Table 3: Breakdown of pathologic Gleason scores by era

Operative time period	Pathologic Gleason 6 (%)	Pathologic Gleason 3+4 (%)	Pathologic Gleason 4+3 (%)	Pathologic Gleason 8 (%)	Pathologic Gleason 9-10 (%)
2005-08	532 (35.6)	681 (45.6)	181 (12.1)	37 (2.5)	62 (4.2)
2009-10	234 (21.6)	525 (48.5)	208 (19.3)	37 (3.4)	78 (7.2)
2011-12	132 (15.1)	435 (49.5)	199 (22.7)	28 (3.2)	83 (9.5)

The advent of PSA-based screening has led to a significant shift in the presentation and treatment of prostate cancer. PSA screening has led to patients presenting with prostate cancer at a significantly earlier age[13] and with lower-risk disease.[14] In line with this, the pathological makeup of prostate cancer specimens from early RALP showed a trend of lower-stage disease. This is largely due to the high increase in surgical intervention for lower-risk prostate cancers with the intent to cure all prostate cancer disease,[15] despite the fact that many of these patients with low risk cancer are unlikely to benefit from surgical intervention.

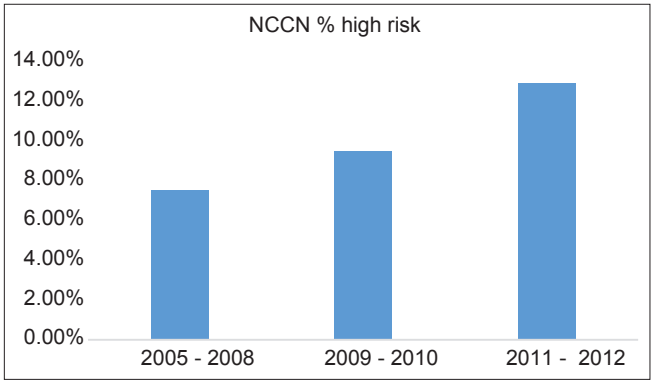

Figure 2: Percentage of sample categorized as National Comprehensive Cancer Network high-risk categorized by era

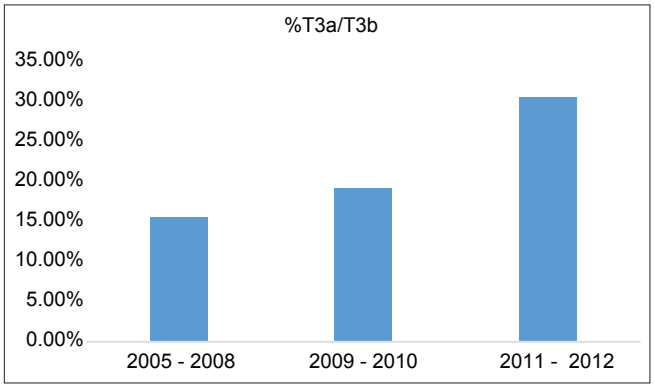

Figure 3: Percentage of sample with pathologic T3 disease categorized by era

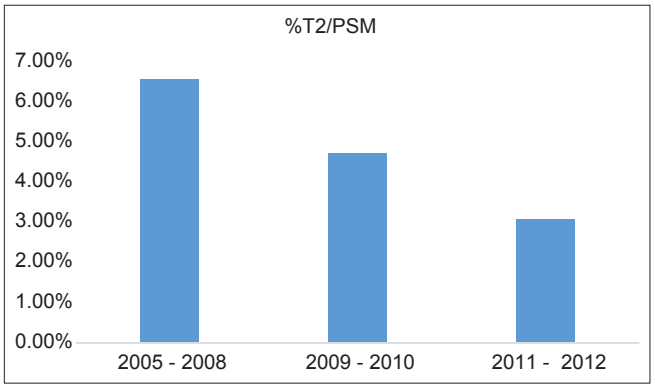

Figure 4: Percentage of sample with pathologic T2/positive surgical margin disease categorized by era

It has been previously demonstrated that ECE serves as an excellent marker for the likelihood of tumor progression because of its lack of variation with surgeon experience or skill,[16] and that rates of ECE significantly declined after the advent of PSA testing, in line with the increase in operative pathology suggesting more low risk disease after radical prostatectomy.[17,18] The fact that ECE declined so dramatically in these studies between the pre and current PSA testing era widely suggested that there was in fact a stage migration toward operating on more low-risk and potentially clinically insignificant prostate cancer.

Using this same concept, we were able to demonstrate an increase in the rate of high-risk preoperative and pathologic factors from groups of early to current RALP. The use of AS, alternative therapies for low risk prostate cancer and the learning curve with skills gained after the initial experience of RALP would explain a shift, or reverse stage migration, from the surgical treatment of low risk and potentially clinically insignificant prostate cancer to the treatment of only high-risk prostate disease. This shift suggests that PSA and prostate cancer screening are used diligently at our center, with operative intervention only on those cancers that impose a potentially significant health risk to the patient.

Furthermore, we used two more pathologic markers as well as high-risk preoperative factors to demonstrate our point. The rate of N1 disease, another clinical marker for potential tumor progression,[16] demonstrated similar trending to that of ECE, rising at a statistically significant rate from the early to current RALP era. The rate of PSM status initially rose from the early to intermediate era and then again fell in the current era, which would be expected as surgeons performing the procedure have become more skilled with RALP and are achieving similar SMS rates to that seen with initial RALP despite the fact that they are now operating on a higher grade disease. Similarly, there was a trend seen with NCCN guideline criteria of operating on higher risk disease from the early to the current era.

We are limited in our analysis by several variables. As this study was performed at a tertiary care center and many of these patients return to their local urologists for follow-up, the biochemical recurrence rate of these patients cannot be assessed. Furthermore, several genitourinary pathologists were involved in interpretation of the specimens and staging and could have potentially contributed to the variation identified. Similarly, this could have led to a skewing of the groups of patients presenting, in that those with low risk disease are much less likely to come for consultation at our institution as they have already been educated about low risk disease in a community setting.

CONCLUSIONS

We have demonstrated an increase in favorable pathologic outcomes with a decrease in operative intervention on low risk prostate cancer in men who opted to undergo robot-assisted radical prostatectomy. Despite the increasing proportion of men with extra-capsular disease undergoing RALP, the surgical margin status has remained similar. This could reflect both the changing dynamics of the population opting for surgery as well as the learning curve of the surgeons.

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How to cite this article: Bernie A, Ramasamy R, Ali A, Tewari AK. Changes in pathologic outcomes and operative trends with robot-assisted laparoscopic radical prostatectomy. Indian J Urol 2014;30:378-82.

Source of Support: Nil, **Conflict of Interest:** None declared.