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Research Article

Changing trends in robot-assisted radical prostatectomy: Inverse stage migration—A retrospective analysis

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ABSTRACT

Background: With increasing availability of data on outcomes of surgery for prostate cancer, the profile of patients undergoing robot-assisted radical prostatectomy (RARP) has changed over the past decade. This impacts the decision-making process for surgeons and patients, particularly in low-incidence regions of Asia. Our institution was among the first in Asia to acquire a *da* Vinci surgical robot in 2005. We evaluated the changes in the clinical and pathology profile of patients undergoing RARP at our institution over the past 15 years (2005-2019).

Methods: A retrospective analysis of patients undergoing RARP between April 2005 and December 2019 was conducted from the hospital database. The patients were divided into two groups; patients undergoing RARP from April 2005 to December 2012 (Group I, first 8 years) and January 2013 to December 2019 (Group II, next 7 years). The perioperative characteristics were compared between these two groups to assess changes in their profile and outcome.

Results: Four hundred forty-seven patients were included in this study; 244 (54.6%) in Group I and 203 (45.4%) in Group II. The median prostate specific antigen in Group II was significantly higher than that in Group I (14.5 vs. 11.7 ng/ml, $P = 0.016$). Unfavorable pathological characteristics, i.e., Gleason Grade $\geq$3, perineural invasion, and the margin positivity rate increased substantially from 18.5% to 37.5%, 20.5% to 36.9%, and 15.2% to 26.6%, respectively, in Group II compared with Group I. More patients in Group II received adjuvant therapy than in Group I ($P < 0.001$).

Conclusion: There has been a change in profile of patients undergoing RARP and patients with more unfavorable disease characteristics such as higher prostate specific antigen and tumor grade are undergoing surgery. In line with international trends, the number of patients with low-grade disease undergoing surgery has substantially decreased. Multimodal treatment with adjuvant therapy is increasingly used, particularly in high-risk disease.

1. Introduction

Increasing availability of PSA testing, changing recommendations on screening, and improvements in surgical outcomes have affected the disease profile as well as utilization of radical prostatectomy in the management of prostate cancer (PCa) over the past 10-15 years.[1] Robot-assisted radical prostatectomy (RARP) has become the standard of surgical management with >85% of radical prostatectomies in the United States performed with robotic assistance.[2] Increasing data suggesting a limited benefit of surgery for low-risk localized PCa and adoption of 2012 United States Preventive Services Task Force (USPSTF) recommendation against PSA screening have impacted management strategies with the increasing use of active surveillance for low-risk PCa including Asia.[3–5] Some studies have suggested an increase in unfavorable PCa in patients managed with surgery.[6–10] However, in India and much of Asia, limited data are available on the change in patient profile undergoing RARP as the modality has become widely available only in the last few years. This information would be useful in determining the impact of new knowledge on practice and also in counseling patients on potential outcomes. Ours was among the first institutions in Asia to start RARP in 2005,[11] and we analyzed our data in two-time cohorts to assess change in trends of the utilization of RARP.

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2. Methods

In an institution review board–approved study (number: IECPG-402/30.08.2018), all patients who underwent RARP at our institution between July 2005 and December 2019 were retrospectively identified from hospital records, operating room records, and nursing records maintained in the hospital. The patients were then divided into two groups; patients undergoing RARP from April 2005 to December 2012 (Group I, first 8 years) and January 2013 to December 2019 (Group II, next 7 years). The patient profile and perioperative characteristics were compared between these two groups. The seventh edition of the American Joint Committee on Cancer-tumor-lymph node-metastasis classification was used to define clinical stage, and histopathological grading was performed according to the Gleason system. The modified Vattikuti Institute prostatectomy technique was used in most cases, while some surgeries were performed using the extraperitoneal and posterior-first approaches.[12] Preservation of the neurovascular bundle was attempted as clinically indicated for each patient. Standard pelvic lymphadenectomy was performed as per the risk stratification.

The following information was determined from the case records: demographic details, baseline PSA, Gleason grade on biopsy, clinical stage, intraoperative details including operative time, blood loss, duration of hospital stay, and final histopathological details along with the adjuvant therapy.

2.1. Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range) as appropriate. Categorical variables were compared using the chi-square test or Fischer Exact test, and continuous variables were compared using Student's t-test, multiple analysis of variance, Mann-Whitney test, or Kruskal-Wallis test as appropriate. All statistical tests were two-sided. Statistical significance was taken as $P < 0.05$. Data were analyzed using IBM SPSS Statistics software (version 20.0; Chicago, IL). The authors confirm the availability of and access to all data reported in this study.

3. Results

Between 2005 and 2019, 447 patients underwent RARP at our center. Among these 447 patients, 244 (54.6%) patients were included in Group I while 203 (45.4%) were included in Group II. The mean age (±SD) was 64.3 (±5.9) years and was similar in both groups. Most patients (83.8%) presented with lower urinary tract symptoms. However, 14.4% of patients in Group I were asymptomatic and detected on PSA screening as compared to 5.9% patients in Group II ($P = 0.015$). The median PSA was significantly higher in Group II than that in Group I (14.5 ng/ml vs. 11.7 ng/ml, $P = 0.016$). In Group I, 92.6% of patients were diagnosed on transrectal ultrasound (TRUS)-guided prostate biopsy. With the availability of magnetic resonance imaging–guided biopsy, 13.8% of patients underwent MRI-TRUS fusion biopsy while 4 patients (1.9%) underwent in-bore MRI targeted biopsy in the second group (Table 1).

The Gleason grade on biopsy differed significantly with 57.3% of patients in Group I having Gleason Grade Group I disease compared with 31.5% in Group II. Similarly, the number of patients with Gleason Grade Group ≥3 was significantly lower in Group I (36 patients [14.7%]) than that in Group II (71 patients [34.9%]; $P = 0.001$). Assessing the D'Amico risk category, patients in Group I had a

Table 1
Demographic characteristics of patients undergoing robot-assisted radical prostatectomy (RARP) between 2005 and 2019.

Parameter	Overall	Group I (2005–2012)	Group II (2013–2019)	*P* value
Number	447	244 (54.6%)	203 (45.4%)	
Mean age, y (±SD)	64.3 ± 5.9	64.6 ± 6.1	64.3 ± 5.9	0.743
Presentation				0.015
LUTS, n (%)	375 (83.8)	195 (79.9)	180 (88.7)	
Screening, n (%)	47 (10.5)	35 (14.4)	12 (5.9)	
Other symptoms, n (%)	25 (5.7)	14 (5.7)	11 (5.4)	
Comorbidities				0.213
Diabetes mellitus, n (%)	55 (12.3)	33 (13.5)	22 (10.8)	
Hypertension, n (%)	125 (27.9)	76 (31.1)	49 (24.1)	
Coronary artery disease, n (%)	21 (4.7)	10 (4.1)	11 (5.4)	
COAD, n (%)	23 (5.2)	18 (7.4)	5 (2.5)	
Previous TURP, n (%)	43 (9.6)	34 (13.9)	9 (4.4)	<0.001
Mean prostate volume on USG, cc ± SD	41.1 ± 18.9 (n = 230)	38.4 ± 16.0 (n = 66)	42.2 ± 19.9 (n = 166)	0.167
Median PSA (IQR), ng/ml	13 (8.3-20)	11.7 (7.7-19.1)	14.5 (8.9-23)	0.016
PSA category				0.147
<10 ng/ml, n (%)	174 (38.9)	105 (43.0)	69 (33.9)	
10-20 mg/ml, n (%)	161 (35.7)	82 (33.6)	78 (38.5)	
>20 ng/ml, n (%)	113 (25.4)	57 (23.4)	56 (27.6)	
Mode of biopsy				0.001
TRUS biopsy, n (%)	395 (88.4)	226 (92.6)	169 (83.4)	
MRI-TRUS fusion biopsy, n (%)	26 (5.8)	0	26 (13.8)	
In-bore MRI biopsy, n (%)	4 (0.9)	0	4 (1.9)	
TURP chips, n (%)	22 (4.9)	18 (7.4)	4 (1.9)	
Preoperative Gleason Grade Group				0.001
Group 1, n (%)	204 (45.7)	140 (57.3)	64 (31.5)	
Group 2, n (%)	134 (29.9)	66 (27.1)	68 (33.5)	
Group 3, n (%)	53 (11.9)	17 (6.9)	36 (17.8)	
Group 4, n (%)	41 (9.1)	15 (6.2)	26 (12.7)	
Group 5, n (%)	13 (2.9)	4 (1.7)	9 (4.5)	
Variant, n (%)	2 (0.5)	2 (0.8)	0	
Preop D'Amico Risk Stratification				0.001
Low, n (%)	97 (21.7)	71 (29.2)	26 (12.9)	
Intermediate, n (%)	240 (53.7)	121 (49.5)	119 (58.6)	
High, n (%)	110 (24.6)	52 (21.3)	58 (28.5)	

COAD, chronic obstructive airway disease; LUTS, lower urinary tract symptoms; MRI, magnetic resonance imaging; PSA, prostate specific antigen; TRUS, transrectal ultrasonography; TURP, transurethral resection of prostate; USG, ultrasonography.
$P < 0.05$ is considered as significant.

Table 2
Perioperative characteristics of the study population.

Parameter	Overall	Group I (2005–2012)	Group II (2013–2019)	*P* value
Number	447	244 (54.6)	203 (45.4)	
Conversion to open, n (%)	9 (2.0)	7 (2.8)	2 (1)	<0.001
Surgical approach				0.001
Transperitoneal, n (%)	359 (80.3)	211 (86.5)	148 (72.9)	
Extraperitoneal, n (%)	88 (19.7)	33 (13.5)	55 (27.1)	
Mean operative time (SD), min	190.6 (47.9) [n = 437]	185.8 (44.1) [n = 237]	196.3 (51.7) [n = 200]	0.024
Median blood loss (IQR), ml	200 (150–400) [n = 437]	200 (100–350) [n = 237]	250 (200–400) [n = 200]	0.002
Mean hospital stay (SD), d	5.1 (2.8) [n = 437]	5.5 (4.8) [n = 237]	4.7 (2.3) [n = 200]	0.002
Mean duration of catheter removal, (SD), d	15.0 (3.9) [n = 437]	16.3 (4.4) [n = 237]	13.5 (3.6) [n = 200]	0.001

$P < 0.05$ is considered as significant.

significantly lower risk category than those in Group II. In Group I, 29.2% of patients belonged to the low-risk category as compared to 12.9% in Group II. Similarly, 49.5% and 21.3% of patients in Group I belonged to the intermediate and high-risk category as compared to 58.6% and 28.5% in Group II, respectively ($P = 0.001$).

Among the intraoperative parameters, there was a significant risk of conversion to open surgery in Group I (7 patients, 2.8%) as compared to Group II (2 patients, 1%) ($P < 0.001$) [Table 2]. However, the mean operative time ($P = 0.024$) and the median blood loss ($P = 0.002$) were significantly higher in Group II than those in Group I. On the other hand, the mean hospital stay (5.5 [4.8] days in Group I vs. 4.7 [2.3] days in Group II; $P = 0.002$) and the mean duration of catheter (16.3 [4.4] days in Group I vs. 13.5 [3.6] days in Group II, $P = 0.001$) in the postoperative period were significantly lower in Group II than those in Group I.

The final histopathology also revealed unfavorable disease characteristics, i.e., the higher risk features of higher Gleason Grade group in Group II as compared to Group I (Table 3). Of 447 patients, 8 patients (1.8%) did not reveal any evidence of malignancy on radical prostatectomy specimens. Among the remaining 439 patients, the overall margin positivity rate was 20.2%. The margin positivity rate was 15.6% in Group I versus 26.2% in Group II ($P = 0.004$). The pathological tumor stage was significantly higher in Group II than that in Group I. Similarly, extracapsular extension was present in 11.4% of patients in Group II compared to 5.5% in Group I ($P = 0.019$). The perineural invasion and seminal vesicle invasion was also significantly higher in Group II than that in Group I (Table 3). Consistent with the higher risk disease profile and higher margin positivity disease in Group II, significantly more number of patients received adjuvant therapy either in the form of radiation therapy or both radiation and androgen deprivation therapy in Group II (20.8% in Group II vs. 6.3% in Group I, $P < 0.001$).

4. Discussion

We found a significantly higher-risk disease with poorer prognostic features in the most recent cohort of men undergoing RARP at our institution than in an earlier cohort. Several factors have affected the contemporary practices of radical prostatectomy. The adoption of active surveillance for patients with low-risk cancer, on the one hand, coupled with increasing surgical experience leading to increased acceptance of high-risk and locally advanced disease for surgery on the other is possibly contributory to this stage migration.

In the early years of radical prostatectomy, most men undergoing surgery had a disease that would now be classified as low risk.[13] Higher risk disease was considered not amenable to surgical cure and referred for multimodal management including radiation.[14,15] Although USPSTF guidelines of 2012[3] are not rigidly followed in the Indian subcontinent, its recommendation against PSA screening could have influenced clinical practice. In addition, large data sets suggesting a limited benefit of screening or surgery in low-risk disease would have contributed to decreasing surgery in such patients.[16,17] These factors are probably contributory to the shift to the management of high-risk disease with radical prostatectomy while favoring active surveillance for low-risk disease.

Our study tries to assess the trends in our practice patterns for RARP. The group division, apart from coinciding with the publication of the USPSTF's 2012 statement, also coincides with the period when surgical robots started to become more widely available in the country and an increasing number of institutions started offering this surgery. Before this, this surgery was available at a limited number of institutions.

We found significantly more symptomatic men with higher PSA and unfavorable disease being managed with surgery in

Table 3
Pathological characteristics of the population undergoing robot-assisted radical prostatectomy (RARP).

Parameter	Overall	Group I (2005–2012)	Group II (2013–2019)	*P* value
Number	447	244 (54.6%)	203 (45.4%)	
Gleason Grade Group on radical prostatectomy specimen				**0.001***
Group 1, n (%)	161 (36.1)	98 (40.1)	63 (31.1)	
Group 2, n (%)	151 (33.8)	89 (36.5)	62 (30.5)	
Group 3, n (%)	67 (14.9)	26 (10.7)	41 (20.1)	
Group 4, n (%)	36 (8.0)	14 (5.7)	22 (10.8)	
Group 5, n (%)	18 (4.0)	5 (2.1)	13 (6.5)	
HGPIN, n (%)	4 (0.9)	3 (1.3)	1 (0.5)	
Benign, n (%)	8 (1.8)	7 (2.8)	1 (0.5)	
Variant, n (%)	2 (0.5)	2 (0.8)	0	
pT stage, n (%)	**N = 439**	**N = 237**	**N = 202**	**0.042***
pT2, n (%)	393 (89.5)	219 (92.4)	174 (86.1)	
pT3a, n (%)	32 (7.3)	13 (5.5)	19 (9.4)	
pT3b, n (%)	14 (3.2)	5 (2.1)	9 (4.5)	
Presence of ECE, n (%)	36 (8.2)	13 (5.5)	23 (11.4)	**0.019***
Margin positivity, n (%)	90 (20.5)	37 (15.6)	53 (26.2)	**0.004***
Seminal vesicle invasion, n (%)	14 (3.2)	5 (2.1)	9 (4.5)	0.189
Perineural invasion, n (%)	125 (28.5)	50 (21.1)	75 (37.1)	**0.001***
pN + disease, n (%)	25 (5.7)	11 (4.5)	14 (6.9)	0.145
Patients receiving adjuvant therapy, n (%)	57 (12.9)	15 (6.3)	42 (20.8)	**<0.001***

ECE, extracapsular extension; HGPIN, high-grade prostate intraepithelial neoplasia.
*$P < 0.05$ is considered as significant.

Group II than in Group I. Presentation of asymptomatic men diagnosed on screening declined as did the number of men diagnosed on transurethral resection of prostate chips, who often have low-risk disease. We found a significantly higher PSA in the second cohort of men. This was similar to a large study that looked at 10,000 cases from 2002 to 2017 and noted a significant increase in initial PSA from 6.01 ng/ml in the initial 1000 cases to 8.53 ng/ml in the last 1000 cases.[6] This study, similar to ours, crossed the threshold of a time when the USPSTF guideline and the studies on screening and outcomes of radical prostatectomy appeared.[3] However, studies that do not span this threshold often do not report any change in the trend of patients undergoing surgery. Silberstein et al performed a retrospective analysis of 6,624 patients with localized PCa undergoing radical prostatectomy from 2000 to 2010 and found no significant difference in mean PSA in the entire cohort or individual risk groups.[18] Similar results were reported by Bernie et al for patients undergoing RARP between 2005 and 2012.[7]

The utility of MRI has been emphasized by the PRECISION trial where MRI targeted biopsy significantly increased the detection of clinically significant PCa.[19] With the acquisition of the MRI-TRUS fusion platform for prostate biopsy in 2013, 13.8% of patients undergoing radical prostatectomy had MRI-TRUS fusion biopsy in Group II, and the use of this biopsy technique resulted in a higher yield of cancer detection.[20]

In the initial years of robotic surgery, RARP was mainly confined to low-risk disease. As surgical restrictions diminish with experience and time, patients with unfavorable disease characteristics were being better managed with surgery. This was further strengthened with good long-term outcomes of RARP in intermediate and high-risk disease when coupled with multimodality treatment.[21] Bernie et al analyzed disease characteristics of 3,451 patients undergoing RARP from 2005 till 2012 and found a significant decline in grade group (GG) 1 cancers from 63% to 38.7% and an increase in GG $\geq$ 4 cancers from 6.4% to 10.8%.[7] Silberstein et al also noted a revere stage migration with a significant decline in GG1 cancers from 66% in 2000 to 32% in 2010.[18] Budaus et al analyzed 8,916 patients in Germany undergoing radical prostatectomy between 2000 and 2009.[10] They reported an inverse stage migration with a significant decline in favorable-risk disease (organ confinement and Gleason 3 + 3 grade) from 53% in 2003 to 17% in 2009. This trend was accompanied by an increase in the number of patients with non–organ-confined PCa from 19% in 2003 to 33% in 2009.[10] Gnanapragasam et al also studied the change in patient profile in 1500 patients undergoing RARP between 2005 and 2015 in a United Kingdom tertiary referral center and observed a progressive increase in the proportion of high-risk cases from 11.6% in 2005-2008 to 33.6% in 2013-2015 with a corresponding decline in low-risk disease from 48.6% to 17.3%.[22]

Among intraoperative characteristics, there was a remarkable decrease in risk of conversion to open surgery from 2.8% in Group I to 0.1% in Group II ($P < 0.001$). Sharma and Meeks analyzed the Nationwide Inpatient Sample database of 134,398 minimally invasive radical prostatectomies from 2000 to 2010 and reported a conversion rate of 1.8%.[23] Luzzago et al studied the time trends for the conversion of minimally invasive radical prostatectomy to open surgery in 57,078 patients undergoing surgery between 2008 and 2015 and reported a significant decline in conversion rate from 1.8% in 2008 to 0.38% in 2015.[24] There was a significant increase in operative time and median blood from Group I to Group II. Onol et al reported decreased blood loss from 154 ml in the first 1000 cases to 86 ml in the last 1000 cases with a stable operative time over the period.[6] Jaulim et al also reported a decline in blood loss and operative time with increasing experience of three surgeons studied independently.[9] However, our study reports an increase in operative time and blood loss. This could be attributed to the increase in disease risk characteristics and the learning curve of surgeons. Being an academic institution, there was a different cohort of surgeons during the two time periods. These results are affected by the learning curve of various surgeons, and our study reflects the trends according to the experience of an institution rather than trends by a single surgeon over time. Mean hospital stay and duration of the catheter decreased significantly over time with experience, although these remained significantly longer than those in studies published from more experienced western centers of excellence.[6]

The histopathological analysis affirmed the preoperative disease characteristics with higher stage and grade disease in Group II than in Group I. Onol et al reported an increase in pT3 disease from 14% in the first 1000 RARP cases performed to 42.4% in the last 1000 cases.[6] Similarly, Bernie et al also reported an increase in pT3 disease from 15.5% in 2005-2010 to 30.6% in 2011-2012.[7] The PSM rate also appeared to change with time and experience. We observed an

increase in the margin positivity from 15.6% in Group I to 26.2% in Group II ($P = 0.004$). Onol et al also observed an increase in PSM rate from 14% in the first 1000 cases to 20.3% cases in the last 1000 cases.[6] Ahlering et al studied clinicopathological profile in 19,602 patients undergoing RARP at nine high-volume referral centers in the United States between 2008 and 2016 and found a significant increase in PSM rate from 16.4% to 19.8%.[25] It has been observed that higher Gleason grade, clinical stage, and preoperative PSA directly influence PSM rate.[26] However, a few studies did not find a significant increase in PSM rate,[8,9,22] and Bernie et al reported a significant decrease in PSM rate despite high-risk characteristics.[7] This could be attributed to increasing surgical experience, particularly in high-volume centers, despite the increase in high-risk characteristics.

With the evolution of the multimodal approach in the management of high-risk PCa, there was a significant increase in the utilization of adjuvant therapy from 6.1% in Group I to 20.7% in Group II. Although recommendations for adjuvant therapy remain variable, most patients receive adjuvant radiation therapy in pT3a disease, margin positive disease, Gleason Score (GS) $\geq$ 8, and disease persistence.[27] The fear of overtreatment and radiation toxicity has been countered with improved biochemical recurrence-free survival and low rates of acute and long-term radiation toxicities.[28] Hence, the acceptance of adjuvant radiation therapy has gradually increased over the past few years.

This study has several limitations. The retrospective study design comes with an inherent bias. The number of surgeons performing RARP increased from two to six from 2005 to 2019 at our institution. Thus, our results are affected by the learning curve of various surgeons. The histopathology reporting was not performed by a single pathologist; however, all reporting was performed by experienced pathologists. As the study reports the temporal trends in patients undergoing RARP, the reported inverse stage migration reflects changes in treatment selection and decision and not changes in patients diagnosed with PCa. Although the decision for radical prostatectomy is often taken by a multidisciplinary board, the data of patients opting for other modalities were beyond the purview of this article. Despite these shortcomings, our study represents the first report studying the time trends in RARP over the past decade in the Indian sub-continent. The study has incorporated clinical as well as the surgical and pathological profile of patients undergoing RARP in the past decade.

In conclusion, we found significant changes in RARP practice with the pattern of inverse stage migration over time. With the increasing experience in RARP, patients with more unfavorable disease characteristics, i.e., higher PSA and higher grade of the disease, are being managed with surgery while the proportion of patients with low-grade disease undergoing surgery has substantially decreased. The multimodal treatment in the form of adjuvant therapy is increasingly used, particularly in high-risk disease.

Conflict of interest

All authors have no conflict of interest to declare.

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