Role of robot-assisted radical prostatectomy in the management of high-risk prostate cancer

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ABSTRACT

We aimed to evaluate the role of robot-assisted radical prostatectomy (RARP) in the management of high-risk prostate cancer (PCa), with a focus on oncological, functional and perioperative outcomes. Further, we also aimed to briefly describe our novel modification to conventional RARP that allows immediate organ retrieval and examination for intra-operative surgical margin assessment. A literature search of PubMed was performed for articles on the management of high-risk PCa. Papers written in English and concerning clinical outcomes following RARP for locally advanced and high-risk PCa were selected. Outcomes data from our own center were also included. A total of 10 contemporary series were evaluated. Biopsy Gleason score ≥ 8 was the most common cause for classification of patients into the high-risk PCa group. Biochemical failure rate, in the few series that looked at long-term follow-up, varied from 9% to 26% at 1 year. The positive surgical margin rate varied from 12% to 53.3%. Urinary continence rates varied from 78% to 92% at 1 year. The overall complication rates varied from 2.4% to 30%, with anastomotic leak and lymphocele being the most common complications. Long-term data on oncological control following RARP in high-risk patients is lacking. Short-term oncological outcomes and functional outcomes are equivalent to open radical prostatectomy (RP). Safety outcomes are better in patients undergoing RARP when compared with open RP. Improved tools for predicting the presence of organ-confined disease (OCD) are available. High-risk patients with OCD would be ideal candidates for RARP and would benefit most from surgery alone.

Key words: Functional outcomes, High–risk, oncological outcomes, prostate cancer, robotics,

INTRODUCTION

Prostate-specific antigen (PSA) screening was introduced in the US in the late 1980s for early detection of prostate cancer (PCa), and has resulted in both an increase in PCa diagnoses and an earlier identification of these tumors. Despite the downward stage migration associated with PSA testing and the growing number of low-risk and organ-confined (OC)

tumors, roughly 14.8% and 3.5% of men with newly diagnosed PCa are currently found to have high-risk and locally advanced disease (cT3NX/+M0), respectively.[1,2] Although these proportions have declined when compared with the pre-PSA screening era, they remain significant and have remained relatively stable over the past decade. Those men with high-risk PCa at the time of presentation have increased rates of secondary therapy and metastasis and contribute disproportionately to PCa mortality.[3-5] Improved treatments for such men would have a significant positive impact on overall morbidity and mortality due to this disease.

There is no consensus on the ideal management of these high-risk PCa patients. Multiple challenges exist in optimally treating men with high-risk disease, including, but not limited to, the biologic behavior of the cancer and the lack of staging accuracy of current diagnostic tools; furthermore, breakdown of various nomograms at these extremes make prognostic and outcome assessment difficult.[6] Significant differences may exist within the high-risk group because patients may have anywhere from one to three high-risk features and yet be similarly classified.[7]

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With robot-assisted radical prostatectomy (RARP) being increasingly utilized for PCa treatment,[8,9] in this review, we discuss oncological, functional and perioperative outcomes following RARP, the general role of surgery for the management of high-risk disease and technical modifications that may help improve patient outcomes.

MATERIALS AND METHODS

A literature search of PubMed was performed to retrieve all published articles on the management of high-risk PCa. We used the search terms "high-risk prostate cancer" AND "radical prostatectomy" OR "robotic radical prostatectomy." Papers written in English and concerning clinical outcomes following RARP for high-risk PCa were selected. Reference lists of retrieved papers were scrutinized for additional relevant articles. Outcomes data following RARP from our own center were also included.

Table 1 summarizes the studies evaluating outcomes of RARP in high-risk PCa. We found 10 studies evaluating the role of RARP in high-risk PCa. All studies represent contemporary experiences and were published between 2008 and 2013. In 90% of the studies, data were collected prospectively and the mean cohort size was 104 patients (range 30-160 patients).

RESULTS AND DISCUSSION

Definition of high-risk PCa and epidemiology

High-risk PCa is characterized by the following criteria [D'Amico], either

- PSA value >20 ng/mL or
- Biopsy Gleason score (GS) of ≥8 or
- Clinical stage (cT) of T2c or above
- A combination of either of these.[3]

The National Comprehensive Cancer Network (NCCN) and UCSF Cancer of the Prostate Risk Assessment (UCSF–CAPRA) classifications are other widely used criteria for defining high-risk PCa [Figure 1]. NCCN differs from the D'Amico criteria with regard to the clinical stage assignment for high risk,[20] where clinical stage T3a or higher is considered high risk. In the UCSF–CAPRA classification,[21] points (0-4) are assigned to individual risk factors and a score of ≥6 is considered high-risk disease. Most studies included in the current review utilized D'Amico risk stratification (70.0%) for defining high-risk PCa. Nguyen *et al.* compared the predictive value of six different definitions of high-risk PCa (consisting of varying combinations of clinical stage, serum PSA and GS) and found 5-year and 10-year BCRFS to range from 36% to 58% and 25% to 43% respectively, concluding that BCRFS for high-risk PCa did not differ significantly regardless of the definition used.[22]

With respect to epidemiology, as mentioned previously, the overall incidence of high-risk PCa has decreased since the advent of PSA screening, and currently stands at 14.8% as compared with 40.9% in the late 1980s. At present, approximately 9.8%, 8.1% and 3.5% of men newly diagnosed with PCa present with GS ≥ 8, PSA > 20 ng/dL and cT ≥ T2c, respectively.[1] Accordingly, GS is currently the major factor determining patient assignment to the high-risk category,

Parameters assessed	D'Amico	NCCN	UCSF-CAPRA
Age at diagnosis			Yes
PSA (ng/ml)	Yes	Yes	Yes
Clinical Stage	Yes	Yes	Yes
Gleason Score of the biopsy	Yes	Yes	Yes
Percent of biopsy cores involved with cancer			Yes

* D'Amico HR PCa (either or all)- PSA >20ng/ml; GS ≥ 8; cT ≥ T2c
* NCCN HR PCa (either or all)- PSA >20ng/ml; GS ≥ 8; cT ≥ T3
* UCSF-CAPRA HR PCa - Points (range 0-4) are awarded to individual parameters based on their value and a total score of > 6 is considered HR PCa

Figure 1: Different classification schemes of high-risk prostate cancer

Table 1: Summary of series evaluating outcomes after robot-assisted radical prostatectomy in patients with high-risk PCa

Study	Publication year	Study period	Data collection	High-risk definition	Cohort (*n*)	Mean cohort age (years)	Pre-operative disease characteristics %		
							cT >2c	GS 8-10	PSA >20 ng/mL
Ou *et al.*[10]	2013	2005-2012	Prospective	D'Amico	148	66.3	–	29.7	–
Rogers *et al.*[11]	2013	2001-2009	Prospective	D'Amico	69	73	36.2	62.3	15.9
Zugor *et al.*[12]	2012	2006-2010	Retrospective	PSA >20 ng/mL	147	63.1	–	–	100.0
Lavery *et al.*[13]	2012	Up to 2009	Prospective	D'Amico	123	–	9.8	81.0	17.1
Sagalovich *et al.*[14]	2012	2010-2011	Prospective	D'Amico	82	62	–	91.6	–
Yuh *et al.*[15]	2012	2010-2011	Prospective	D'Amico	30	63.7	13.3	73.3	23.3
Connolly *et al.*[16]	2011	2003-2010	Prospective	NCCN	160	–	23.8	75.0	30.0
Jayram *et al.*[17]	2011	2003-2009	Prospective	D'Amico	148	60.9	–	41.8	–
Yee *et al.*[18]	2009	2005-2008	Prospective	D'Amico	62	–	–	74.1	–
Shikanov *et al.*[19]	2008	–	Prospective	Gleason 8-10	70	63	5.7	100.0	–

cT = Clinical Stage, GS = Gleason Score on biopsy, PSA = Prostate-specific antigen, RARP = Robot-assisted radical prostatectomy

followed by PSA and then by clinical stage with 61.5%, 50.8% and 21.9% of high-risk patients having GS ≥ 8, PSA > 20 ng/dL and cT ≥ T2c, respectively.[1] This trend was evident in the current review as well, as in all the series reviewed that used > 1 risk factor to define high-risk PCa, 91.6-29.7% of patients had GS ≥ 8 and 30.0-15.9% had a PSA > 20 ng/dL [Table 1].

Literature review of outcomes following RARP in high-risk PCa patients

Oncological outcomes

Table 2 summarizes the oncological outcomes in patients with high-risk PCa. Long-term follow-up data were not available in all the series. In the studies that did assess long-term oncological control, the rate of biochemical recurrence (BCR) varied from 9% to 26% at 1 year.[11,13] At 3 years, it was between 14%[11] and 55%.[13] Sukumar *et al.* looked at the oncological outcomes of 4803 patients with PCa undergoing RARP, including 1556 patients with non-organ confined disease (OCD).[23] They demonstrated a BCR of 18.3% in this group of patients over a period of mean follow-up of 34.6 months (range 1-116.7 months). All studies used a PSA ≥ 0.2 ng/mL as the definition of BCR, except for Shikanov *et al.*,[19] who defined BCR as a PSA > 0.1 ng/mL and reported an 18% BCR rate at 1 year.

The positive surgical margin (PSM) rate varied from 12.0%[14] to 53.3%.[10] However, in most studies, the PSM rate was between 20% and 30%.[12,13,15,17-19] The lymph node positivity rate was also widely variable, from 1.4% to 33.3% overall. A 33.3% positivity rate was reported by Yuh *et al.*[15] in their study specifically assessing the role of robotic-extended lymph node dissection in intermediate and high-risk PCa, and might reflect the most accurate lymph node involvement rate in this subset of patients. That being said, the PSM and the lymph node positivity results from these reports should be interpreted cautiously as many of these studies did not provide details on the protocol used for sampling radical prostatectomy (RP) specimens and the extent of lymph node dissection performed, both of which are well-know factors affecting the PSM rate[24] and lymph node positivity rate.[15,25] respectively.

These BCR and PSM rates are comparable to the results reported by Briganti *et al.* in their review of open RP (ORP) outcomes, where they found a mean BCR rate of 31% at 5 years and a mean PSM rate of 45% following ORP in patients with high-risk disease.[26] Harty *et al.* compared the PSM rates for open versus minimally invasive RP in 445 high-risk PCa patients and found that they were not significantly different: 52.9% in ORP, 50% in RARP and 41.4% in laparoscopic RP (LRP) (*P* = 0.13).[27] The PSM rate did not differ when comparing ORP with a combined group of RARP and LRP (*P* = 0.16). Similar results were seen by Pierorazio *et al.* when they compared 913 men undergoing open versus minimally invasive RARP and LRP for high-risk PCa at a single center over a 10-year period and found no significant difference in the PSM or BCR rates across the groups.[28]

Sukumar *et al.*, in the study mentioned previously, looked at 99 patients with node-positive disease (N1), which, even though not strictly classified under high-risk PCa, represents an aggressive cohort with a relatively high risk of BCR.[23] In their series, this group had a mean PSA of 12.3 ng/mL; 46.5% of them had a biopsy GS of 8-10 and 15.2% had cT2c-cT3 disease. BCR for this cohort was 58.6% over a mean follow-up of 34.6 months (range 1-116.7 months). Actuarial 5-year BCR-free survival, metastasis-free survival and cancer-specific survival (CSS) were 26.3% (SE: 7.3), 77.7% (SE: 11.7) and 96.1% (SE: 2.7), respectively, for these patients with N1 disease.

Functional outcomes

Table 3 summarizes the functional outcomes. The 12-month continence rates using a 0-1 safety pad definition varied from 78% to 92%.[13,18] Ou *et al.*, using a 0 pad definition for continence, reported a 95% continence rate in men undergoing RARP for high-risk disease.[10] Potency rates varied from 52% to 60% at 12 months.[10,17] Rogers *et al.* reported a 33.3% potency rate at 26 months, but their study population was aged ≥ 70 years.[11] In select patients with high-risk disease who underwent bilateral nerve sparing, Ou *et al.* found potency rates of 71%.[10]

Perioperative outcomes

Table 4 provides details on the perioperative outcomes of RARP. The mean operative time was 168 min, with operative times ranging from 111 to 186 min and mean estimated blood loss was 189 mL (range 84-200 mL). Length of hospital stay (LOS) varied from 1 to 3.4 days. The overall complication rates ranged from 2.4% to 30%, although many series did not fulfill the Martin criteria requirement for reporting of complications,[29] and this could lead to underreporting of adverse events. The most common complications reported were urethrovesical anastomotic leaks in approximately 10% of the patients,[15] lymphocele (range 6.6-2.4%)[14,15] and deep venous thrombosis in approximately 3.3% of patients.[15] Rectal injuries were extremely rare.[15]

In a retrospective, propensity score-matched analysis comparing the perioperative outcomes of 1512 patients with high-risk PCa undergoing RARP versus ORP, Gandaglia *et al.* found no significant differences in complications (*P* = 0.6), PSM (*P* = 0.4) or additional therapy needed after surgery (*P* = 0.2) between patients treated with RARP and ORP.[30] In multivariable analyses, however, patients undergoing RARP were less likely to receive a blood transfusion (*P* = 0.002) or to experience a prolonged LOS (*P* < 0.001) compared with men treated with ORP.

Similar results were obtained by Punnen *et al.*, who retrospectively analyzed oncological and perioperative outcomes of 410 patients undergoing ORP versus RARP at

Table 2: Summary of oncological outcomes in series looking at robot-assisted radical prostatectomy outcomes in patients with high-risk PCa

Study	Cohort (*n*)	Stanford protocol used for evaluating the RARP specimen	PSM %	% of patients with NVB preserved	Unilateral | bilateral NVB preservation %	LN positivity %	Extent-LN dissection	% of patients with LN dissection	BCR rate %	Metastasis %	Median follow-up (months)
Ou *et al.*[10]	148	No comment	53.3	20.3	10.9 | 9.4	14.2	-	95.9	19.6 at 1 year	-	26.7
Rogers *et al.*[11]	69	Yes	42.0	-	-	1.4	-	-	9 at 1 year; 14 at 3 years	1.4%	37.7
Zugor *et al.*[12]	147	No comment	33.3	19.7	-	17.1	-	100.0	19.8 at 19.6 months	-	19.6
Lavery *et al.*[13]	123	No comment	31.0	73.0	15 | 58	2.4	-	100.0	26.0 at 12.5 months	-	12.5
Sagalovich *et al.*[14]	82	Yes	12.0	-	-	13.4	Extended	100.0	-	-	-
Yuh *et al.*[15]	30	No comment	26.7	-	-	33.3	Extended	100.0	-	-	-
Connolly *et al.*[16]	160	No comment	38.0	-	-	14.8	Limited	27.0	44 at 2 years; 55 at 3 years	-	26.2
Jayram *et al.*[17]	148	No comment	20.5	54.1	34.5 | 19.6	12.3	Standard	100.0	21.3 at 18 months	-	18
Yee *et al.*[18]	62	Yes	22.6	-	-	-	-	-	-	-	-
Shikanov *et al.*[19]	70	No comment	24.0	78.0	60 | 18	12.9	-	-	18 at 1 year	-	9.6

PSM = Positive surgical margin, NVB = Neurovascular bundle, LN = Lymph Nnode, BCR = Biochemical recurrence, RARP = Robot-assisted radical prostatectomy

Table 3: Summary of functional outcomes in series looking at robot-assisted radical prostatectomy outcomes in patients with high-risk PCa

Study	Cohort (*n*)	Potency definition	Potency rate at 12 months (%)	Continence definition	Continence rate at 12 months (%)
Ou *et al.*[10]	148	Erection adequate for sexual intercourse	60.0	0 pads	95.2
Rogers *et al.*[11]	69	Erection adequate for sexual intercourse	33.3*	0-1 pads/day	81.5*
Zugor *et al.*[12]	147	-	-	-	-
Lavery *et al.*[13]	123	IIEF 5 score>16	56.0	0-1 pads/day	78.0
Sagalovich *et al.*[14]	82	-	-	-	-
Yuh *et al.*[15]	30	-	-	-	-
Connolly *et al.*[16]	160	-	-	-	-
Jayram *et al.*[17]	148	IIEF 5 score>17	52.0	0-1 pads/day	92.0*
Yee *et al.*[18]	62	-	-	0-1 pads/day	92.0
Shikanov *et al.*[19]	70	-	-	-	-

*These data are from beyond 12 months (18-36 months); IIEF = International index of erectile function, RARP = Robot-assisted radical prostatectomy

a single center and found that, beside a longer LOS, more blood loss and higher transfusion rate (all *P* < 0.01), more men undergoing RARP had a complete nerve-sparing procedure compared with men undergoing ORP (54% vs. 34%, *P* < 0.01).[31] Oncological outcomes measured, in terms of PSM and BCR-free survival, did not differ significantly between the two groups.

Role of surgery in high-risk PCa

Randomized studies specifically looking at the comparative effectiveness of different treatment modalities for high-risk PCa are lacking, but significant information may be gleaned from high-risk subsets of randomized controlled trials (RCTs)

evaluating various treatment modalities for all-risk PCa. In the supplement to the landmark paper published by Wilt *et al.* in 2012 comparing RP versus observation for treatment of localized PCa, they performed a subset analysis of patients with high-risk PCa.[32] The subset analysis [Figure 2] showed that cancer-specific mortality (CSM) was greatly reduced in high-risk PCa patients who underwent RP versus those who underwent observation (11.5% vs. 20.0%, respectively, *P* = 0.05). The overall mortality was also lower in patients undergoing RP as compared with observation, although it was not statistically significant (55% vs. 59%, respectively, *P* = 0.25). Their subset analysis showed survival benefit after RP was greater in patients with high-risk PCa

Table 4: Summary of perioperative outcomes in a series looking at robot-assisted radical prostatectomy outcomes in patients with high-risk PCa

Study	Cohort (*n*)	Operative time (min)	Estimated blood loss (mL)	Length of stay (days)	Overall complication rate %
Ou *et al*.[10]	148	153.8	167	3.4	7.4
Rogers *et al*.[11]	69	175	150	1	5.8
Zugor *et al*.[12]	147	164	183	-	14.2
Lavery *et al*.[13]	123	147	84	1.6	-
Sagalovich *et al*.[14]	82	111	150	-	2.4*
Yuh *et al*.[15]	30	186	200	1	30.0
Connolly *et al*.[16]	160	-	-	-	-
Jayram *et al*.[17]	148	-	150	1	4.0
Yee *et al*.[18]	62	-	-	-	-
Shikanov *et al*.[19]	70	-	-	-	-

*Only comments on lymphocele incidence, RARP = Robot-assisted radical prostatectomy

Figure 2: (a) Overall survival trend in patients with high-risk prostate cancer. (b) Cancer-specific survival trend in patients with high-risk prostate cancer (Adapted with permission from Supplementary Data to Wilt *et al.*, 2012 New England Journal of Medicine. All rights belong to the Massachusetts Medical Society.)

in comparison with patients with low-risk PCa. Similarly, Bill-Axelson *et al.* in their Scandinavian Prostate Cancer Group-4 RCT showed that patients who have high-risk PCa are benefited by surgery as compared with watchful waiting.[33]

In addition to the aforementioned RCTs, multiple other studies[34,35] substantiate the favorable outcomes of surgery for high-risk disease patients. A recent study by Briganti *et al.*, which evaluated outcomes in 1366 patients after RP with 15 years of follow-up, found that the CSS was as high as 91.0% at 10 years.[26] Boorjian *et al.* in their study looking at the comparative effectiveness of RP vs. external-beam radiotherapy (EBRT) in high-risk PCa patients found that overall survival (OS) was significantly better in patients who underwent RP compared with patients who underwent EBRT with or without androgen-deprivation therapy (ADT) (RP OS: 77% compared with the patients who received EBRT + ADT OS: 67% or EBRT alone OS: 52%; $P < 0.001$).[36] Similarly, Abdollah *et al.*[37] showed that the 10-year CSM rates were significantly better in patients who underwent RP as compared with radiotherapy or observation (3.6%, 6.5% and 10.8%, respectively; $P < 0.001$).

RP offers several distinct advantages. First, and most importantly, it provides pathologic specimens for more accurate staging. Recent studies have shown that up to 35% of patients are staged inaccurately,[38] and up to 50% of high-risk, post-RP patients have more favorable disease on final pathological review.[39] Thus, RP allows clinicians to offer targeted therapy based on more accurate staging and to avoid morbidity associated with unnecessary adjuvant treatment. Second, RP provides excellent local cancer control. Inman *et al.* reported a recurrence rate of
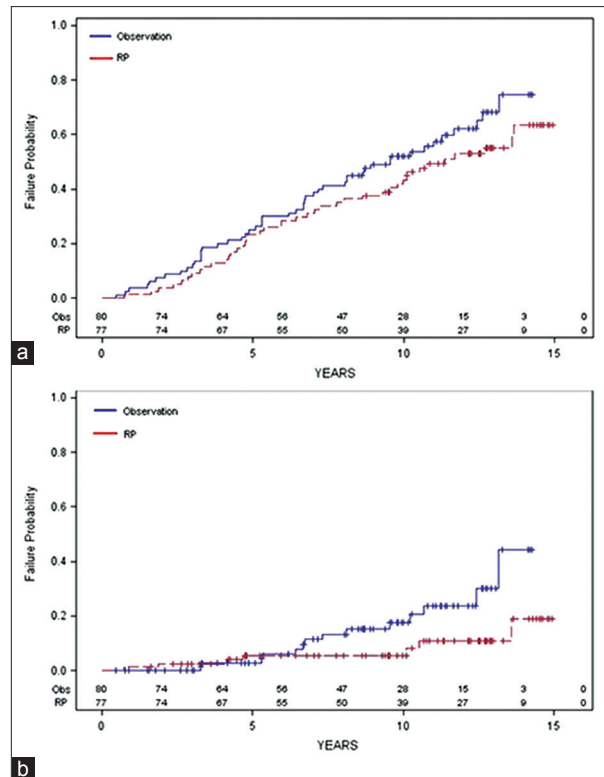
just 13% in men who underwent RP as compared with a recurrence rate of 41-61% in men who underwent EBRT.[40] Third, EBRT, which is considered the main alternative to RP, is associated with significant morbidity including late-onset erectile dysfunction, chronic bladder irritation, hemorrhagic cystitis, infertility, strictures, bowel/bladder incontinence and secondary risk of cancer [Ischia *et al.*,]. In addition, men undergoing RP are 3.5 times less likely to require ADT, and they also have significantly longer intervals of ADT-free survival compared with men undergoing EBRT.[41] ADT is associated with significant morbidity including hyperlipidemia, metabolic syndrome, diabetes, cardiovascular disease, anemia, osteoporosis, periodontal disease, infertility, sexual dysfunction, fatigue, hot flashes and/or cognitive deficits.[42] Finally, primary tumors play a significant role in tumor shedding and cytokine/growth factor production. Therefore, RP provides definitive tumor debulking (i.e. removal of the primary tumor) and may improve overall outcomes.[43]

These RCTs and cohort studies constitute level-1b and 2b evidence, respectively, and clearly demonstrate the beneficial role of surgery in high-risk PCa. Having said that, we should recognize that the high-risk PCa group is a heterogeneous group, as shown by Yossepowitch *et al.*, Yossepowitch *et al.* compared eight high-risk subsets in nearly 6000 men undergoing RP and found varying rates

of BCRFS, need for secondary therapy and metastatic progression, with 10-year PCa-specific mortality ranging from 3% to 11%.[5] Thus, patients falling under the umbrella of high-risk PCa should ideally be treated on a case-to-case basis, as a patient with high PSA and high GS but with an OCD would benefit most from surgery alone while a patient with non-OCD might benefit more from a non-surgical option.

This review demonstrates many points. First, outcomes following RARP for the management of high-risk PCa are equivalent to ORP in terms of functional and short-term oncological outcomes, but better in terms of safety outcomes. Second, RARP is an effective and safe option for select high-risk patients. Third, functional outcomes for patients with high-risk PCa are highly variable, and in general are inferior when compared with all-risk or low-risk PCa.[44] Fourth, surgery as part of a multimodal management strategy seems to offer the best survival rates as compared with other modalities alone or in combination, but there is a need for better stratification of these high-risk patients for their optimal management, which can only be achieved by devising better modalities of stage assessment and prediction of biological behavior of the disease utilizing various imaging and translational tumor markers, which are still in discovery and testing phase. At this time, it can be said that RARP is as effective as other available modalities, but may be the best choice for select patients with localized, high-risk PCa.

RARP for high-risk PCa - Our MORE technique

We recently developed a Modification to the Vattikuti Institute Prostatectomy technique[45-49] of RP, which allows immediate Organ Retrieval after excision for intra-operative Examination and frozen-section analysis (the MORE technique).

Briefly, with the help of a GelPOINT™ platform (Applied Medical, Rancho Santa Margarita, CA, USA), a hand-access platform, the excised RP specimen, is easily extracted without needing to undock the robot or any loss of pneumoperitoneum. The specimen is then examined on-table by the surgeon. Frozen-section biopsies may be taken from areas that appear suspicious for PSM on inspection and/or bimanual examination, and after carefully marking the samples for anatomical orientation they are sent for analysis. Biopsies that are positive or suspicious for cancer result in *more* tissue being removed. While waiting for the results of the frozen section analysis, the surgeon continues with lymph node dissection and hence there is no increase in the overall operative time.

With this technical modification, we showed an absolute risk reduction of 26.6% (*P* = 0.04) in the PSM rate in patients with pT3a disease. MORE is a promising technique and a prospective trial is currently underway in our institution.

CONCLUSIONS

There is substantial evidence to support that RP with or without robotic assistance achieves extremely favorable oncological outcomes in patients with high-risk PCa compared with other treatment modalities. In addition, patients who are considered to have high-risk disease are an internally heterogeneous group, and all patients should not be treated alike. The key is to predict which patients, despite having high-risk characteristics, may harbor OCD. The current literature suggests that at least 40%[26] of patients classified as high risk fall into this category, but the proportion may be as high as 80%.[1] With new nomograms specifically tailored for predicting OCD in high-risk disease patients,[26] and the improvement in the accuracy of magnetic resonance imaging technology in assessing nodal disease/non-OCD, patients with a high likelihood of having OCD, despite being high risk, would be ideal candidates for RP and would gain the most benefit from surgery alone.

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