ORIGINAL ARTICLE

Prediction of organ-confined disease after robot-assisted radical prostatectomy in patients with clinically locally-advanced prostate cancer

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Summary *Background:* Little is known about the preoperative predictive factors that could identify subsets of favorable patients who can be possibly cured with robot-assisted radical prostatectomy (RARP) alone in locally advanced prostate cancer (LAPCa). Our study was designed to identify clinical predictors of pathologic organ-confined disease (pOCD) in RARP setting.
Methods: Between 2007 and 2013, clinicopathological and oncological data from 273 consecutive men undergoing robot-assisted RP with extended PLND for clinically LAPCa were reviewed in a single-institution, retrospectively. After exclusion of patients who received neoadjuvant hormone treatment before surgery, 186 subjects satisfied the final inclusion criteria.
Results: Forty-three patients (23.1% of total cohort) with preoperative clinically LAPCa patients were down-staged to pOCD following RARP. Preoperative prostate-specific antigen (PSA)

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level, preoperative PSAD, positive core percent, maximal tumor volume in any core, and biopsy Gleason score were significantly associated with down-staging into pOCD following RARP. Multivariate logistic regression analysis revealed that lower preoperative PSA (≤ 10 ng/mL) and maximal tumor volume in any core ($\leq 70\%$) were independent predictors of pOCD following RARP.
Conclusions: Approximately 23% of preoperative clinically LAPCa patients were down-staged to pOCD following RARP. Preoperative PSA and maximal tumor volume in any biopsy core might be useful clinical predictors of pOCD in clinically LAPCa patients in RARP setting.
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1. Introduction

Despite the widespread application of prostate-specific antigen (PSA)-based screening leading to a profound stage migration in prostate cancer (PCa), as many as one-third of PCa cases have a high-risk feature that requires aggressive treatment.[1–3] Until recently, surgical treatment has not been commonly used to treat locally-advanced PCa (LAPCa).[4] Optimal disease management in these patients remains challenging, and strong advocates propose various treatment options, such as radical prostatectomy (RP), radiotherapy (RT), androgen deprivation therapy, and increasingly, a multimodal approach.[5] Surgery offers an attractive opportunity for tumor excision, either as definitive management or as a first step in multimodal therapy.[6] Surgery can also identify a substantial subset of men with favorable clinical features in whom additional therapy is not indicated.[1,7] Approximately 20%–30% of men undergoing RP for clinical stage T3 PCa have pathological organ-confined disease (pOCD).[8,9] A study conducted at Memorial Sloan-Kettering Center followed 176 men with cT3 over a 20-year period. Within this cohort, only 64 patients received neoadjuvant hormone therapy (HT), and more than one-half (52%) of patients remained free of disease recurrence following RP at a mean follow-up time of 6.4 years.[8] During the last several years, an increased number of publications have discussed the use of minimally invasive techniques, particularly robot-assisted radical prostatectomy (RARP), in high-risk or locally-advanced PCa patients. Numerous studies noted that RARP demonstrated similar oncological outcomes to open surgery and other minimally invasive surgeries in this clinical scenario.[10–13] Although recent published data illustrate of the therapeutic potential and technical feasibility of RARP in LAPCa patients, little is known about preoperative predictive factors that can identify subsets of favorable patients who may benefit from RARP monotherapy without any further treatment.

This retrospective study was designed to evaluate these predictive factors with respect to down-staging to pOCD in clinically LAPCa cases following RARP.

2. Materials and methods

2.1. Study population and data collection

We retrospectively reviewed the data of 1138 PCa patients who underwent extraperitoneal RARP performed by a single surgeon at Severance Hospital between January 2007 and December 2013. Of these men, 273 consecutive LAPCa cases (stages cT3-4) with no lymph node or distant metastasis (cT3-4N0M0) were identified. After excluding 70 patients who received neoadjuvant treatment before surgery and 17 patients whose lymph node metastasis was not verified by pathology, 186 men undergoing robot-assisted RP with extended PLND satisfied the final inclusion criteria.

Preoperative characteristics, including age, body mass index, clinical stage, PSA, and prostate biopsy findings (Gleason grade, positive core percent, and maximal tumor volume in any biopsy core) were collected from electronic medical records. In most cases, TRUS-guided biopsy consisted of a minimum of 10 cores including a 2-core transition zone biopsy. Positive core percent were calculated using formulas: number of positive cores/total number of biopsy core. The clinical stages of all the prostate cancer patients included in this study were determined by 3.0T MRI system staging, and the upper normal limit for pelvic lymphadenopathy by prostate MRI was 5 mm.

The RARP and bilateral pelvic lymph node dissections (PLND) were carried out using our standardized extraperitoneal technique and protocol.[14] The indication for and use of a unilateral or bilateral nerve-sparing technique depended on individual patient characteristics. Clinical staging was assigned by the attending urologist according to the 2002 TNM system. Biopsy and pathological grading were performed according to the Gleason grading system, and Gleason scores were assigned by genitourinary pathologists.

2.2. Good clinical practice protocols

The study was carried out in agreement with the applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. The institutional review board of the hospital approved the study protocol (Approval number: 4-2014-0619).

2.3. Statistical analysis

Continuous variable values are presented as the median and interquartile range (IQR). Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann–Whitney U test. The Fisher exact or Chi-square tests were used to evaluate the association between categorical variables. We used univariate and multivariate logistic regression analysis to determine predictive variables of pOCD in 158 patients, excluding

those lacking prostate biopsy parameters. Variables yielding $P < 0.2$ after univariate analysis were included in the multivariate analysis. Receivers operating characteristic (ROC) curves were constructed to obtain the cut-off values of PSA, Gleason biopsy grade, positive biopsy core percent, and maximal tumor volume in any biopsy core that would confer optimal sensitivity and specificity for predicting the pOCD of prostatectomy specimens. Statistical significance was indicated if $P < 0.05$, and all reported *P*-values are 2-sided. Statistical analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

Table 1 lists the baseline characteristics and pathologic results of the 186 patients with clinically LAPCa. Median pre-biopsy PSA and PSA density (PSAD) levels were 10.87 ng/mL (IQR: 5.78–18.98) and 0.33 ng/mL/g (IQR: 0.19–0.73), respectively. Clinical stages included cT3a in 139 (74.7%), cT3b in 38 (20.4%), and cT4 in 9 (4.8%) patients.

After RARP, pathological Gleason scores were identical in 82 patients (44.1%). Compared to the biopsy-based Gleason score, pathologic over-grading and under-grading occurred in 66 (35.5%) and 38 (20.4%) patients, respectively. LN invasions and positive surgical margins (PSMs) were found in only 4 patients (2.2%) and in 64 (34.4%) patients, respectively.

3.1. Prediction of pOCD in clinically LAPCa patients after RARP

After RARP, 43 patients (23.1% of total cohort) with preoperative clinically LAPCa patients were down-staged to pOCD following RARP. PSMs were found in 6 (14.0%) of pOCD and 58 (40.6%) of pathologically LAPCa ($P = 0.001$). Preoperative serum PSA ($P < 0.001$), preoperative PSAD ($P < 0.001$), positive core percent ($P = 0.019$), maximal tumor volume in any core ($P = 0.005$), and biopsy Gleason score ($P = 0.002$) were significantly associated with downstaging into pOCD after RARP (Table 2). The area under the curve (AUC) for the discriminative ability of pOCD in clinically LAPCa patients was 0.680 for preoperative PSA and 0.617 and 0.641 for positive core percent and maximal tumor volume in any core, respectively ($P < 0.05$ for each variable). After grouping Gleason biopsy scores into five categories (6, 7 with primary Gleason pattern 3, 7 with primary Gleason pattern 4, 8, and ≥9), the AUC of biopsy Gleason score related to the discriminative ability of pOCD in clinically LAPCa was 0.647 ($P = 0.004$).

Table 3 shows results from univariate and multivariate logistic regression analyses used to predict pOCD in clinically LAPCa after RARP. The cut-off values conferring optimal sensitivity and specificity for the discriminative ability of pOCD in LAPCa patients using ROC curve were PSA at 10 ng/mL, positive core percent at 33.3%, maximal tumor volume in any core at 70%, and biopsy Gleason score at 7 with primary Gleason pattern 3. In univariate analyses, preoperative PSA level (≤10 ng/mL), positive core percent (≤33.3%), Maximal tumor volume in any core (≤70%), and biopsy Gleason score (≤7 with primary Gleason pattern 3)

Table 1 Clinicopathologic characteristics of study patients.

Variables	Value
Patients, n	186
Follow-up period, months (median, IQR)	34.1 (21.5–45.1)
Preoperative variables	
Age at operation, years (mean, IQR)	68.0 (62.0–72.0)
BMI, kg/m² (median, IQR)	24.1 (22.0–25.4)
PSA, ng/mL (median, IQR)	10.87 (5.78–18.98)
PSAD, ng/mL/cm³ (median, IQR)	0.33 (0.19–0.73)
Positive core percent (median, IQR)	33.3 (16.7–54.4)
Maximal tumor volume in any core (median, IQR)	60.0 (30.0–80.0)
Gleason biopsy score, n (%)	
6	54 (29.0)
7 (3 + 4)	41 (22.0)
7 (4 + 3)	30 (16.1)
8	56 (30.1)
≥9	5 (2.7)
Clinical T stage, n (%)	
T3a	139 (74.7)
T3b	38 (20.4)
T4	9 (4.8)
Postoperative pathological variables	
High-grade PIN	82 (44.1)
Lymphovascular invasion	15 (8.1)
Pathologic Gleason score	
6	31 (16.7)
7 (3 + 4)	57 (30.6)
7 (4 + 3)	49 (26.3)
8	20 (10.8)
≥9	29 (15.6)
Pathologic T stage	
T2a	16 (8.6)
T2b	0 (0.0)
T2c	27 (14.5)
T3a	108 (58.1)
T3b	30 (16.1)
T4	5 (2.7)
Pathologic N stage	
N0	182 (97.8)
N1	4 (2.2)
Positive surgical margin	64 (34.4)

BMI, body mass index; IQR, interquartile range; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PIN, prostatic intraepithelial neoplasia.

were associated with pOCD. Multivariate analysis revealed that lower preoperative PSA (≤10 ng/mL) and maximal tumor volume in any core (≤70%) were independent predictors of pOCD following RARP.

4. Discussion

The optimal treatment regimen for men with LAPCa is controversial. At this stage the tumors appears to extend

Table 2 Comparison of preoperative variables between pathologically organ-confined and non-organ confined groups after robot-assisted radical prostatectomy in patients with clinically locally-advanced prostate cancer.

Variables	Final pathology		P
	Organ-confined	Non-organ confined	
Patients, n (%)	43 (23.1)	143 (76.9)	
Preoperative variables			
Age at operation, years (mean, IQR)	67.0 (61.0−71.0)	68.0 (62.0−72.0)	0.519*
BMI, kg/m^2 (median, IQR)	24.2 (21.5−26.1)	24.0 (22.3−25.4)	0.991*
PSA, ng/mL (median, IQR)	6.00 (4.92−11.70)	12.23 (6.91−20.93)	<0.001*
PSAD, ng/mL/cm^3 (median, IQR)	0.20 (0.12−0.33)	0.38 (0.23−0.78)	<0.001*
Positive core percent (median, IQR)	23.5 (8.3−41.7)	37.5 (16.7−58.3)	0.019*
Maximal tumor volume in any core (median, IQR)	40.0 (20.0−70.0)	70 (30.0−90.0)	0.005*
Biopsy Gleason score, n (%)			0.002†
6	22 (51.2)	32 (22.4)	
7 (3 + 4)	6 (14.0)	35 (24.5)	
7 (4 + 3)	7 (16.3)	23 (16.1)	
8	6 (14.0)	50 (35.0)	
≥9	2 (4.7)	3 (2.1)	
Clinical T stage, n (%)			0.464†
T3a	35 (81.4)	104 (72.7)	
T3b	7 (16.3)	31 (21.7)	
T4	1 (2.3)	8 (5.6)	

IQR, interquartile range; BMI, body mass index; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; *P*-values were obtained from the *Mann−Whitney U test or †Fisher's exact test.

beyond the prostatic capsule with invasion into the pericapsular tissue, apex, bladder neck, or seminal vesicle but is not associated with lymph node involvement or distant metastases.[15,16] Until recently, surgical management was often disregarded in these individuals due to their increased risk of BCR, systemic progression, and worsening oncologic outcomes.[17−19] However, several recent studies related to high-risk PCa have presented alternative views.[7,20−22] In a Mayo Clinic study of men undergoing RP, cT3 was found in 841 (15%) of the 5662 patients. Of the cT3 patients, 661 (79%) men did not receive neoadjuvant HT. After a pathological review of these patients, 223 (27%) had pathologic stage T2 disease, again highlighting the high prevalence of clinical over-staging.[23] Moreover, Tai et al reported that even patients with pathological T3 or higher stages, there are still optimistically high chances of 3-year recurrence-free survival at 81.1% (pT3a), and 62.6% (pT3b-4), and concluded that radical prostatectomy is curative even for some locally advanced prostate cancers in a midterm follow-up.[24] In our cohort, approximately 22% of preoperative clinically LAPCa patients were down-staged to pOCD following RARP. However, according to the Surveillance, Epidemiology, and End Results data, only 6% of men with locally advanced, nonmetastatic disease are treated

Table 3 Prediction of organ-confined disease after robot-assisted radical prostatectomy in patients with clinically locally-advanced prostate cancer.

Parameters	Univariate analysis		Multivariate analysis	
	OR (95%, CI)	P	OR (95%, CI)	P
Age (continuous)	0.991 (0.945−1.040)	0.722		
BMI (continuous)	0.957 (0.851−1.077)	0.468		
PSA (<10 ng/mL)	3.898 (1.849−8.216)	<0.001	2.670 (1.194−5.969)	0.017
Positive core percent (≤33.3%)	2.620 (1.247−5.505)	0.011	1.060 (0.442−2.542)	0.896
Maximal tumor volume in any core (≤70%)	5.338 (1.983−14.367)	0.001	3.837 (1.296−11.354)	0.015
Biopsy GS (≤7 with primary Gleason pattern 3)	2.117 (1.043−4.298)	0.038	1.631 (0.761−3.496)	0.209
Clinical T stage				
T3a	—			
T3b	0.671 (0.271−1.659)	0.388		
T4	0.371 (0.045−3.075)	0.358		

OR, odds ratio; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; GS, Gleason score.

surgically. Even among the youngest patients, only 19% are treated with radical prostatectomy. In the context of such significant clinical challenges, pretreatment prediction model which can help guide decision making is essential for appropriate management in men with LAPCa. Concentrated efforts of several research groups has been developed a nomogram based on clinical stage, Gleason's score of the prostate needle biopsy, and serum PSA to assist physicians in making clinical recommendations for men with clinically localized PCa. On the contrary, this issue has not been sufficiently addressed in LAPCa. Recently, Joniau et al analyzed single center data for 200 patients with clinically unilateral T3a PCa underwent a radical prostatectomy (RP).[25] The authors presented a table combining preoperative serum PSA and biopsy GS to predict histopathologic results in clinically unilateral T3a PCa. And then, this table was successfully validated in multicenter retrospective cohort.[26] We evaluated preoperative predictive factors, such as PSA levels, positive core/total biopsy core percent, maximum cancer involvement in positive cores, and biopsy Gleason score, that can identify subsets of favorable pathologic outcomes in RARP setting. To the best of our knowledge, no previous RARP series has reported a preoperative predictive factors for predicting pathologic outcome after RARP in LAPCa. Our results indicated that lower preoperative PSA ($\leq$10 ng/mL) and maximal tumor volume in any core ($\leq$70%) were independent predictors of pOCD following RARP. When patients with LAPCa are well selected, RARP can offer an attractive opportunity for complete tumor excision without any further treatment.

This study has several potential limitations. First, its retrospective design may produce some sampling bias. Also, the study included data from patients treated at a single tertiary institution by one surgeon, the time frame of which encompassed the surgical learning curve and development of the robot technology. Another concern relates to missing biopsy variables from some patients, further decreasing the size of our cohort. Notwithstanding the limitations, this study identified relevant clinical evidence supporting the role of RARP in LAPCa patients for whom surgical intervention had been previously abandoned due to potentially over-staged based on clinical staging.

In conclusion, clinically LAPCa is still frequently over-staged based on pre-treatment clinical staging criteria. Preoperative variables, including PSA levels and maximum cancer involvement in positive cores might identify subsets of favorable patients who can be possibly cured with robot-assisted radical prostatectomy (RARP) alone in clinically LAPCa.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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