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ORIGINAL ARTICLE

Predictive factors for short-term biochemical recurrence-free survival after robot-assisted laparoscopic radical prostatectomy in high-risk prostate cancer patients

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Abstract

Background We aimed to assess the short-term oncological outcomes of robot-assisted laparoscopic radical prostatectomy to determine the predictive factors associated with biochemical recurrence in high-risk prostate cancer patients.

Methods A total of 331 patients with localized prostate cancer underwent robot-assisted laparoscopic radical prostatectomy. Of them, 113 patients were diagnosed with high-risk prostate cancer according to the D'Amico risk group classification. We evaluated the association between pre- or postoperative predictive factors and biochemical recurrence using Cox regression analysis.

Results The 2-year biochemical recurrence-free survival rate was 65.0% in the high-risk group. On univariate analyses, PSA level > 20 ng/mL, Gleason pattern 5 component on biopsy, pathological stage T3 or higher, perineural invasion, and positive surgical margin were predictive factors for biochemical recurrence. On multivariate analysis, PSA level > 20 ng/mL, Gleason pattern 5 component on biopsy, perineural invasion, and positive surgical margin were identified as independent predictive factors. The 2-year biochemical recurrence-free survival rate was 36.5% for patients with PSA level > 20 ng/mL and/or Gleason pattern 5 component on biopsy.

Conclusions PSA level > 20 ng/mL and/or presence of the Gleason pattern 5 component on biopsy are predictive factors for early biochemical recurrence after robot-assisted laparoscopic radical prostatectomy in high-risk prostate cancer patients. We considered that these patients require a combined modality therapy to improve their prognosis.

Keywords Gleason pattern · Prostate cancer · Prostatectomy · Prostate-specific antigen · Regression analysis

Introduction

Radical prostatectomy is one of the common treatment options for localized prostate cancer (PC), and it reduces the risks of metastasis and progression [1]. Robot-assisted laparoscopic radical prostatectomy (RARP) has become widely disseminated in Europe and the US because of the easier learning curve than open-radical prostatectomy (ORP) or laparoscopic radical prostatectomy (LRP). RARP was introduced in Japan in 2006, soon after which the number of RARP procedures increased substantially. This procedure has largely replaced ORP or LRP as the preferred surgical approach for treating PC [2].

The oncologic outcomes of RARP are equivalent to those of ORP or LRP [3]. Several studies have demonstrated that 10–25% of patients experience biochemical recurrence (BCR) within 5 years after radical prostatectomy [3–8], with a mean time from BCR to metastasis and metastasis to death of 8 and 5 years, respectively [9]. The risk classification defined by D'Amico is widely used clinically because of its simplicity [10]. It has been reported that 40–50% of patients with high-risk PC experience BCR within 5 years after radical prostatectomy [8, 11–13]. However, the D'Amico high-risk patients are a heterogeneous group and have varied risks for BCR [14]. Therefore, the determination of a more

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detailed risk classification may be useful for making treatment decisions.

Several institutions in Europe or the US have reported on the oncological outcomes after RARP, but limited oncological data are available in Japan [3]. The present study assessed the oncological outcomes of RARP to determine the predictive factors associated with BCR in high-risk PC patients.

Patients and methods

A total of 331 patients with localized PC underwent RARP at Iwate Medical University from May 2013 to December 2016. The surgical procedures were performed by four surgeons, using the daVinci Si system (Intuitive Surgical, Inc., USA). The initial cases of each surgeon were included. Risk assessment before treatment was performed in accordance with the D'Amico classification. Nerve sparing was performed on the side without cancer in low- or intermediate-risk PC patients, according to the patients' choice. Previously obturator lymph node dissection was performed, but now, extended lymph node dissection was performed in high-risk PC patients. Some patients were treated with neoadjuvant hormonal therapy if the waiting period until receiving RARP was very long. Prostate specimens were reviewed by two independent genitourinary pathologist according to ISUP 2014.

The PSA values were measured at 1 month and every 3 months after surgery. BCR was defined as having a PSA level of > 0.2 ng/mL after surgery, which was confirmed by at least two consecutive measurements. If the postoperative PSA values were not < 0.2 ng/mL, the surgery date was taken as the recurrence date.

We retrospectively analyzed the association of various clinical factors with BCR. *T* test, Chi-square test, and Mann–Whitney *U* test were used for between-group comparisons. The BCR-free survival was estimated using the Kaplan–Meier method. Cox regression analysis was used to evaluate the association of pre- or postoperative predictive factors with BCR. Covariates included preoperative parameters [age, body mass index (BMI), preoperative PSA, biopsy Gleason score, Gleason pattern 5 component, percent positive core, clinical stage, and neoadjuvant hormonal therapy] and postoperative parameters [prostatectomy Gleason score, pathological stage, perineural invasion, surgical margins, and lymph node invasion]. Covariates were tested for significance in the univariate model and included in the multivariate model if the *P* value was < 0.05. All statistical analyses were performed using JMP® (SAS Institute Inc., USA).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Results

The mean postoperative follow-up period was 15.7 months (range 6–45 months). All patient characteristics based on the D'Amico classification are listed in Table 1. There were statistically significant differences in all clinical and pathological characteristics except for age, BMI, and neoadjuvant hormonal therapy between patients categorized according to the D'Amico classification. Three cases (2.7%) in the high-risk group showed positive lymph node invasion.

Of the 331 patients, 56 (16.9%) had BCR, and none died during the follow-up period. The 2-year BCR-free survival rate was 79.6% in all patients. BCR curves according to the different risk groups are shown in Fig. 1. The 2-year BCR-free survival rate was 92.7% in the low-risk group, 82.5% in the intermediate-risk group, and 65.0% in the high-risk group. There were statistically significant differences in the BCR-free survival rate among groups ($P < 0.0001$).

Table 2 shows the results of univariate and multivariate analyses for the various preoperative predictors in all patients. In multivariate analysis, PSA > 20 ng/mL, Gleason score ≥ 8 on biopsy, and percent positive core were independent predictors of BCR. These results suggested that high-risk PC tends to recur.

Table 3 shows the results of univariate and multivariate analyses for the various pre- and postoperative predictors in the high-risk group. In multivariate analysis, PSA > 20 ng/mL, presence of Gleason pattern 5 component on biopsy, perineural invasion, and positive surgical margin (PSM) were independent predictors of BCR.

Considering that PSA > 20 ng/mL and presence of Gleason pattern 5 component on biopsy are preoperative predictors, it is important to be able to predict the prognosis before surgery. Figure 2 shows the BCR curves of the high-risk groups subdivided according to the preoperative predictors. The 2-year BCR-free survival rate was 80.2% in the "favorable" high-risk group and 36.5% in the "poor" high-risk group. There were statistically significant differences in the BCR-free survival rates between the subdivided high-risk groups ($P = 0.0017$). BCR of the "favorable" high-risk group was equivalent to that of the intermediate-risk group in our cohort.

Discussion

Several studies have demonstrated that the PSM rate following ORP, LRP, and RARP is 11–52%, 10–46%, and 6.5–32%, respectively [3–8]. Eastham et al. and Roehl

Table 1 Patients' characteristics

	All patients	D'Amico risk classification			*P* value
		Low	Intermediate	High	
Number of patients, *n* (%)	331 (100)	84 (25.4)	134 (40.5)	113 (34.1)	
Mean age, years (SD)	65.2 (5.7)	65.1 (5.5)	65.2 (6.0)	65.2 (5.4)	0.9902
BMI, kg/m^2 (SD)	24.0 (3.1)	23.6 (3.2)	23.7 (2.6)	24.5 (3.6)	0.0756
PSA, ng/mL (SD)	8.3 (5.5)	5.8 (1.6)	8.2 (3.8)	10.2 (8.0)	< 0.0001
Biopsy Gleason score, *n* (%)					< 0.0001
− 6	127 (38.4)	84 (100)	30 (22.4)	13 (11.5)	
7	126 (38.1)	–	104 (77.6)	22 (19.5)	
8–10	78 (23.5)	–	–	78 (69.0)	
Percent positive core, % (SD)	29.0 (18.0)	22.1 (15.1)	28.0 (16.0)	35.1 (21.8)	< 0.0001
Clinical stage, *n* (%)					< 0.0001
T1c	159 (48.0)	58 (69.0)	69 (51.5)	32 (28.3)	
T2a	79 (23.9)	26 (31.0)	35 (26.1)	18 (15.9)	
T2b	47 (14.2)	–	30 (22.4)	17 (15.0)	
T2c	36 (10.9)	–	–	36 (31.9)	
T3a–	10 (3.0)	–	–	10 (8.9)	
Neoadjuvant hormonal therapy, *n* (%)	28 (8.5)	7 (8.3)	7 (5.2)	14 (12.4)	0.1306
Prostatectomy Gleason score, *n* (%)					< 0.0001
− 6	116 (35.0)	52 (61.9)	50 (37.3)	14 (12.4)	
7	133 (40.2)	27 (32.1)	63 (47.0)	43 (38.0)	
8–10	82 (24.8)	5 (6.0)	21 (15.7)	56 (49.6)	
Pathological stage, *n* (%)					0.0011
− T2a	58 (17.5)	19 (22.6)	26 (19.4)	13 (11.5)	
T2b	8 (2.4)	0 (0)	4 (3.0)	4 (3.5)	
T2c	204 (61.6)	57 (67.9)	83 (61.9)	64 (56.6)	
T3a	43 (13.0)	5 (6.0)	19 (14.2)	19 (16.8)	
T3b	18 (5.5)	3 (3.5)	2 (1.5)	13 (11.6)	
Perineural invasion, *n* (%)	164 (49.6)	26 (31.0)	67 (50.0)	71 (62.8)	< 0.0001
Positive surgical margin, *n* (%)	110 (33.2)	18 (21.4)	46 (34.3)	46 (40.7)	0.0166
Positive lymph node invasion	3 (0.9)	–	–	3 (2.7)	

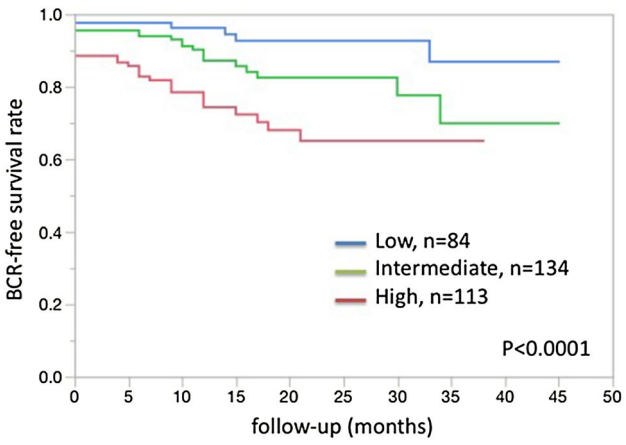

Fig. 1 Kaplan–Meier analysis of BCR-free survival rates according to the D'Amico classification

Table 2 Results of uni- and multivariate analyses in all patients

	Univariate	Multivariate		
	P value	HR	95% CI	*P* value
Age				
≤ 65 vs > 65	0.8381			
BMI				
< 25 vs ≥ 25	0.9483			
PSA				
≤ 20 vs > 20	< 0.0001	3.29	1.45–6.72	0.0060
Biopsy Gleason score				
≤ 7 vs ≥ 8	< 0.0001	2.34	1.35–4.00	0.0030
Percent positive core				
< 50 vs ≥ 50	0.0004	1.83	1.00–3.24	0.0483
Clinical stage				
< cT2c vs ≥ cT2c	0.1006			
Neoadjuvant hormonal therapy				
Received vs not received	0.6348			

Table 3 Results of uni- and multivariate analyses in high-risk patients

	Univariate	Multivariate		
	P value	HR	95% CI	*P* value
Age				
≤65 vs > 65	0.0837			
BMI				
< 25 vs ≥ 25	0.8055			
PSA				
≤20 vs > 20	0.0015	2.87	1.23–6.17	0.0165
Biopsy Gleason score				
≤7 vs ≥ 8	0.3422			
Biopsy Gleason pattern 5				
Absence vs presence	0.0235	3.82	1.82–7.38	0.0008
Percent positive core				
< 50 vs ≥ 50	0.1168			
Clinical stage				
< cT2c vs ≥ cT2c	0.6276			
Neoadjuvant hormonal therapy				
Received vs not received	0.2062			
Pathological Gleason score				
≤7 vs ≥ 8	0.1312			
Pathological Gleason pattern 5				
Absence vs presence	0.1426			
Pathological stage				
≤pT2 vs ≥ pT3	0.0208	1.47	0.78–2.69	0.2338
Perineural invasion				
Absence vs presence	0.0079	2.07	1.15–3.87	0.0145
Positive surgical margin				
Absence vs presence	0.0407	2.22	1.25–3.94	0.0062

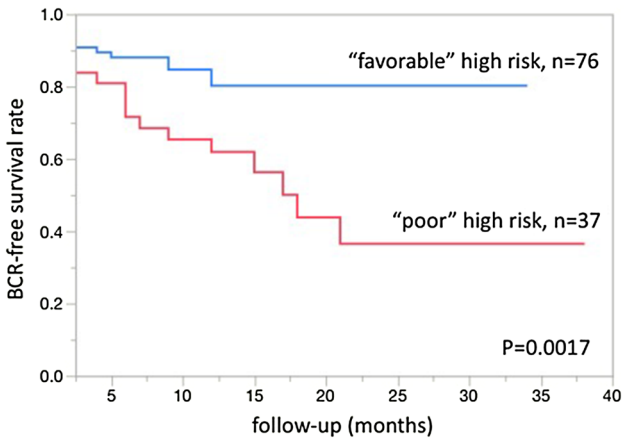

Fig. 2 Kaplan–Meier analysis of BCR-free survival rates according to the subdivision of the high-risk groups. We defined patients with PSA ≤ 20 ng/mL and Gleason pattern < 5 as the "favorable" high-risk group, and patients with PSA > 20 ng/mL and/or Gleason pattern = 5 as the "poor" high-risk group

et al. reported that 5- and 10-year BCR-free survival rates underwent ORP were 90% and 68%, respectively [15, 16]. Guillonneau et al. and Touijer et al. reported that 3-, 5-, and 8-year BCR-free survival rates underwent LRP were 91, 78, and 71%, respectively [17, 18]. Several studies have demonstrated that 5-year BCR-free survival rate underwent RARP were 74–90% [3–8]. Oncological outcomes appear to be primarily determined by the malignancy of PC and less so by surgical approach [7]. Since the PSM rate and the 2-year BCR-free survival rate in our study were 33.2% and 79.6% in all patients, it was considered that PSM and BCR rate almost equivalent to described in the previous reports regardless of ORP, LRP, and RARP.

The BCR-free survival rate was low in the high-risk group according to the D'Amico classification. Diaz et al. reported that BCR-free survival rates in the high-risk group at 2, 5, and 10 years were approximately 60, 55, and 40%, respectively [11], whereas Abdollah et al. reported these rates to be approximately 70, 63.2, and 51.2%, respectively [8]. Although there were a few differences in the reports, it was considered that BCR-free survival in our study was almost equivalent to those described in the previous reports.

PSA and Gleason score are widely accepted as predictive factors of BCR. In our study, PSA > 20 ng/mL and Gleason score ≥ 8 on biopsy were also independent predictive factors of BCR in all patients.

It is known that the high-risk group has a wide variety of patients with BCR risks [19]. In the high-risk group, some cases can be cured by surgery alone, whereas other cases need combined modality therapy to achieve a good prognosis [20, 21]. Therefore, we only analyzed the high-risk group patients who underwent RARP to identify the predictive factors for BCR. We identified that PSA > 20 ng/mL, presence of Gleason pattern 5 component on biopsy, perineural invasion, and PSM were important predictive factors for BCR in the high-risk group on multivariate analysis.

The presence of Gleason pattern 5 including tertiary pattern 5 is a well-known poor prognostic factor [22, 23]. Sundi et al. reported that the presence of biopsy Gleason pattern 5 component tends to cause early BCR, which supports our results [24]. In our study, only nine patients had tertiary Gleason pattern 5 on prostatectomy specimens. We did not demonstrate that the presence of tertiary Gleason pattern 5 was associated with BCR (data not shown).

Perineural invasion as a postoperative factor was also identified as a predictive factor for BCR in the high-risk group. Perineural invasion is widely recognized as an important adverse pathological feature of many malignancies, such as pancreatic and head and neck cancers, and is associated with a poor prognosis [25, 26]. Some studies have indicated that perineural invasion in pathological specimens is also associated with BCR [27–29]. Tanaka et al. also reported that perineural invasion was associated with BCR in

Japanese high-risk PC patients who underwent open-radical prostatectomy [30]. In addition, perineural invasion in biopsy specimens is also associated with a poor prognosis [27–29]. However, we could not detect any perineural invasion in the biopsy samples assessed in this study.

Several studies have reported that PSM was significantly associated with BCR [3, 31, 32]. In our study, PSM was also predictive factor for BCR in the high-risk group (multivariate analysis, $P = 0.0062$).

Four surgeons in this study encountered 134, 84, 74, and 39 RARP cases. Therefore, our study included many initial cases. However, there was no significant difference between the initial and subsequent cases in terms of BCR (Supporting figure, $P = 0.8581$).

The limitations of this study are the retrospective design, small sample population, including initial cases of each surgeon, and lack of analysis of overall survival because of the short-term follow-up duration. In addition, 28 patients (8.5%) were treated with neoadjuvant hormonal therapy, which may be the limitation of this study, although neoadjuvant hormonal therapy was not associated with BCR in our study. However, the "poor" high-risk group defined according to our predictors is likely to cause early BCR.

In conclusion, a PSA level of > 20 ng/mL, the presence of Gleason pattern 5 component on biopsy, perineural invasion in an RARP specimen, and PSM were independent predictive factors for BCR in high-risk PC patients. The use of only preoperative factors to subdivide the high-risk group according to the D'Amico classification may help identify patients with a poorer prognosis before surgery and to develop treatment strategies.

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Compliance with ethical standards

Conflict of interest We have no conflict of interest to declare.

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