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Association Between Surgical Stress and Biochemical Recurrence After Robotic Radical Prostatectomy

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ABSTRACT

Background and Objectives: This study was conducted to identify whether surgical stress during the peri-operative period of robot-assisted radical prostatectomy might affect biochemical recurrence in patients with positive surgical margins.

Methods: Participants in the present study were 324 consecutive patients with localized prostate cancer who underwent robot-assisted radical prostatectomy between February 2013 and June 2018. Positive surgical margins were diagnosed in 61 of them. Patients with positive surgical margins were divided into those with (n = 19) and those without (n = 42) biochemical recurrence. Lymph node dissection, estimated blood loss, inhalation anesthetic volume, and surgical duration were evaluated as indicators of surgical stress. White blood cell count, C-reactive protein, body temperature, and usage of analgesics were postoperatively evaluated as surrogate markers of surgical stress. The associations between factors, including patients' characteristics and pathological features, and biochemical recurrence were investigated.

Results: In univariate analyses, surgical duration ($P = 0.004$), D'Amico risk class ($P = 0.002$), Gleason score ($P = 0.022$) and the number of positive cores in prostate biopsy ($P = 0.009$) were statistically significantly associated with biochemical recurrence. In multivariate analyses, only surgical duration was significantly associated with biochemical recurrence ($P = 0.042$), at a cut-off value of surgical duration of 228.5 minutes.

Conclusions: Prolonged surgical duration is associated with biochemical recurrence in patients with positive surgical margins. Thus, surgical duration should be limited as much as possible to reduce surgical stress, which might cause biochemical recurrence.

Key Words: Operative duration, Surgical stress, Prostate cancer, Positive surgical margin, Biochemical recurrence.

INTRODUCTION

Prostate cancer is one of the most common cancers in men, and radical prostatectomy is globally the usual treatment for localized prostate cancer.[1] However, 30% to 40% of patients experience biochemical recurrence (BCR) after radical prostatectomy.[2,3] Previous studies have demonstrated that one of the predictive factors for BCR is a positive surgical margin (PSM).[4–6] However, not all patients with a PSM after radical prostatectomy experience BCR despite the presence of residual cancer cells in all patients with PSM. Although certain other factors in addition to PSM, such as Gleason score,[6] lymph node metastasis,[6] pre-operative prostate-specific antigen (PSA) level,[7] and pathological stage,[6,8] have been reported to be associated with BCR, reports of their predictive ability for BCR are inconsistent and controversial.

While surgery is a critical treatment for many types of localized cancers, surgical stress has been considered to be associated with the development of cancer recurrence and metastasis.[9,10] In animal studies, it was shown that the stress of surgeries for ovarian cancer, colorectal cancer, melanoma, and lung cancer promotes cancer metastases immediately after surgery.[11–19] Therefore, we hypothesized that surgical stress during the peri-operative period might induce BCR after radical prostatectomy in patients with PSMs. To the best of our knowledge, no

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studies in humans have evaluated the association between surgical stress and cancer in general, or specifically for prostate cancer.

The aim of the present study was to identify whether surgical stress during the peri-operative period of robot-assisted radical prostatectomy (RARP) could affect BCR after RARP in patients with PSMs.

MATERIALS AND METHODS

Study Population and Study Design

Participants in this retrospective study were 324 consecutive patients with clinically localized prostate cancer, who underwent RARP performed by one of three surgeons at our institution from February 2013 to June 2018. As exclusion criteria, patients with other surgeries within 12 months after RARP, severe peri-operative complications (e.g., post-operative bleeding and colorectal injuries during surgery), and underlying systemic diseases were excluded.

Sixty-one of the patients in the present cohort had PSMs. These patients were divided into two groups, those with and without BCR (n = 19 and 42, respectively) (**Figure 1**). Since previous animal investigations have evaluated cancer development and metastasis several weeks to months after surgery,[9,12,13,19] and factors other than surgical stress might be involved in BCR with longer observation periods, the observation period was restricted to only 12 months in the present study. PSA was measured at least four times within 12 months after RARP. BCR was defined as follows: If PSA was less than 00.2 ng/ml at one month or more after RARP, the patient was considered to be free of BCR; if not, they were diagnosed with BCR.[20] When PSA exceeded ≥ 00.2 ng/ml in two tests performed at 2 to 4 week intervals after RARP, the first day when PSA exceeded ≥ 00.2 ng/ml was defined as the date of BCR, or, if PSA was never ≤ 00.2 ng/ml after RARP, the day of surgery was defined as the date of BCR.

Intra-operatively, inhalation anesthesia with either sevoflurane of desflurane was used in addition to intravenous anesthesia with propofol. Lymph node dissection, estimated blood loss (EBL), inhalation anesthetic volume, and surgical duration were evaluated as peri-operative factors related to surgical stress. Lymph node dissection was only performed in cases in which the probability of lymph node involvement was more than 5% according to a preoperative nomogram.[21] Surgical duration was defined as knife to skin time, including robot docking time.

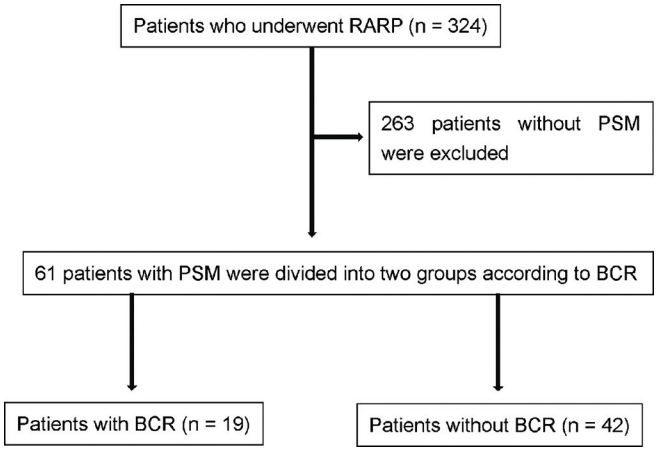


Figure 1. Flow chart of patient selection in the present study.

White blood cell count, C-reactive protein (CRP) level, fever with a temperature of > 38°C, and total usage of analgesics after surgery were evaluated as postoperative factors related to surgical stress. White blood cell count and CRP were examined immediately after surgery and on the next day. The analgesics used in the present cohort were nonsteroidal anti-inflammatory drugs (NSAIDs) and pentazocine, and the amount of both oral and intravenous administrations were evaluated as their total usage.

As clinical and histopathological variables, age, body mass index (BMI), pre-operative PSA, clinical stage, D'Amico risk class, Gleason score, number of positive cores in prostate biopsy, neoadjuvant androgen-deprivation therapy, pathological stage, extracapsular tumor invasion, seminal vesicle invasion, vascular invasion, lymphatic invasion, perineural invasion, and lymph node involvement were evaluated from our electronic health record system.

The protocols in the present study were approved by the ethics committee of our institution (clinical trial registration number: 2334). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all subjects. In the present study, to identify whether surgical stress might induce BCR in patients with PSMs, the association between BCR and surgical stress, and between BCR and patients' characteristics were investigated.

Statistical Analysis

Surgical stress and clinical and histopathological factors were statistically evaluated using the Mann-Whitney u test in univariate analyses. Next, significant factors according

Table 1A.
Comparison of Characteristics Between Patients With and Without Biochemical Recurrence Among Those With Positive Surgical Margins After Robot-Assisted Radical Prostatectomy

	BCR		
Variables	Positive	Negative	P Value
No. of patients	19	42	
Age (Mean ± SD) (years)	68.2 ± 3.8	66.4 ± 6.1	0.41
BMI (Mean ± SD)	25.3 ± 2.1	23.7 ± 4.6	0.19
Preoperative PSA (Mean ± SD) (ng/ml)	15.0 ± 11.3	10.0 ± 3.6	0.13
Clinical stage (n)			0.11
cT1c	5	17	
cT2a	3	10	
cT2b	4	9	
cT2c	2	6	
cT3a	5	0	
cT3b	0	0	
D'Amico risk classification (n)			0.002*
Low	0	0	
Intermediate	5	29	
High	14	13	
Gleason score (n)			0.022*
≤ 6	2	5	
≤ 7	4	24	
≤ 8	9	9	
≤ 9	3	4	
≤ 10	1	0	
No. of positive cores in prostate biopsy (Mean ± SD)	5.5 ± 2.7	3.8 ± 2.8	0.009*
Neoadjuvant androgen-deprivation therapy (n)	1	9	0.12
Pathological stage (n)			0.068
pT2a	3	8	
pT2b	0	2	
pT2c	3	12	
pT3a	7	16	
pT3b	6	4	
Extracapsular tumor invasion (n)	12	23	0.54
Seminal vesicle invasion (n)	5	5	0.16
Vascular invasion (n)	6	13	0.96
Lymphatic invasion (n)	5	8	0.84
Perineural invasion (n)	16	32	0.97

*$P < .05$.
BCR, biochemical recurrence; PSM, positive surgical margin; RARP, robot-assisted radical prostatectomy; SD, standard deviation; BMI, body mass index; PSA, prostate-specific antigen.

Table 1B.
Comparison of Surgical Stress Factors between Patients With and Without Biochemical Recurrence Among Those With Positive Surgical Margins After Robot-Assisted Radical Prostatectomy

	BCR		
Variables	Positive	Negative	*P* Value
No. of patients	19	42	
Lymph node dissection (n)	16	26	0.084
Estimated blood loss (Mean ± SD) (ml)	245.0 ± 240.8	282.8 ± 244.2	0.40
Inhalation anesthetic volume (Mean ± SD) (ml)	76.0 ± 54.0	67.8 ± 35.2	0.32
Surgical duration (Mean ± SD) (minutes)	324.3 ± 40.2	289.0 ± 52.6	0.004*
White blood cell count (Mean ± SD) (103/μl)			
On the day of surgery	13.5 ± 3.3	13.3 ± 3.5	0.86
POD1	11.1 ± 2.6	10.0 ± 1.9	0.11
CRP (Mean ± SD) (mg/dl)			
On the day after surgery	0.09 ± 0.11	0.16 ± 0.19	0.38
POD1	3.4 ± 1.6	2.8 ± 1.3	0.64
Fever of > 38°C (n)	3	14	0.13
Total analgesic consumption			
NSAIDs (Mean ± SD) (mg)	84.9 ± 100.0	52.6 ± 71.6	0.54
Pentazocine (Mean ± SD) (mg)	0.8 ± 3.3	3.2 ± 8.4	0.22

*$P < .05$.
BCR, biochemical recurrence; PSM, positive surgical margin; RARP, robot-assisted radical prostatectomy; SD, standard deviation; POD, postoperative day; CRP, C-reactive protein; NSAIDs, nonsteroidal anti-inflammatory drugs.

to univariate analyses were included in multivariate logistic regression analyses. The receiver operating characteristic (ROC) curve was created using the Youden index method to investigate cut-off values. BCR-free survival was calculated using the Kaplan-Meier method and comparisons were made using the log-rank test. All statistical analyses were performed using SPSS software package version 26 (SPSS, Chicago, IL, USA). P values < 0.05 were considered significant.

RESULTS

Table 1A shows a comparison of the characteristics of patients with PSMs with and without BCR after RARP. Of the 61 patients with PSMs, 19 (31%) patients experienced BCR within 12 months after RARP. As shown in Table 1A, D'Amico risk class (P = .002), Gleason score (P = .022), and the number of positive cores in prostate biopsy (P = .009) were statistically significantly associated with BCR in univariate analyses. Conversely, there was no statistically significant association between BCR and age, BMI, pre-operative PSA levels, clinical stage, neoadjuvant androgen-deprivation therapy, pathological stage, extracapsular tumor invasion, seminal vesicle invasion, vascular invasion, lymphatic invasion, and perineural invasion. Table 1B shows a comparison of surgical stress factors between patients with and without BCR after RARP among patients with PSMs. Surgical duration (P = .004) was the only factor significantly associated with BCR on multivariate analysis. On the other hand, the effects of lymph node dissection, EBL, inhalation anesthetic volume, white blood cell count, CRP level, fever of > 38°C, and total usage of analgesics did not reach statistical significance.

As shown in **Table 2**, in multivariate analyses, surgical duration (odds ratio [OR], 1.016; 95% confidence interval [CI], 1.001–1.031; P = .042) was the only significant predictive factor of BCR. On the contrary, D'Amico risk class, Gleason score, and the number of positive cores in prostate biopsy were not statistically significantly related to the risk of BCR.

ROC analysis was performed to elucidate the optimal cut-off value of surgical duration for predicting BCR within 12 months after RARP. The cut-off value of 2280.5 minutes yielded the best accuracy in ROC analysis, with an area under

Table 2.
Multivariate Analyses of Factors Predictive of Biochemical Recurrence Within Twelve Months in Prostate Cancer Patients With Positive Surgical Margins After Robot-Assisted Radical Prostatectomy

Variables	OR	95% CI	*P* Value
D'Amico risk classification	6.201	0.654–58.840	0.11
Gleason score	0.832	0.259–2.676	0.76
No. of positive cores in prostate biopsy	1.193	0.962–1.479	0.11
Surgical duration	1.016	1.001–1.031	0.042*

*$P < .05$.
BCR, biochemical recurrence; PSM, positive surgical margin; OR, odds ratio; CI, confidence interval.

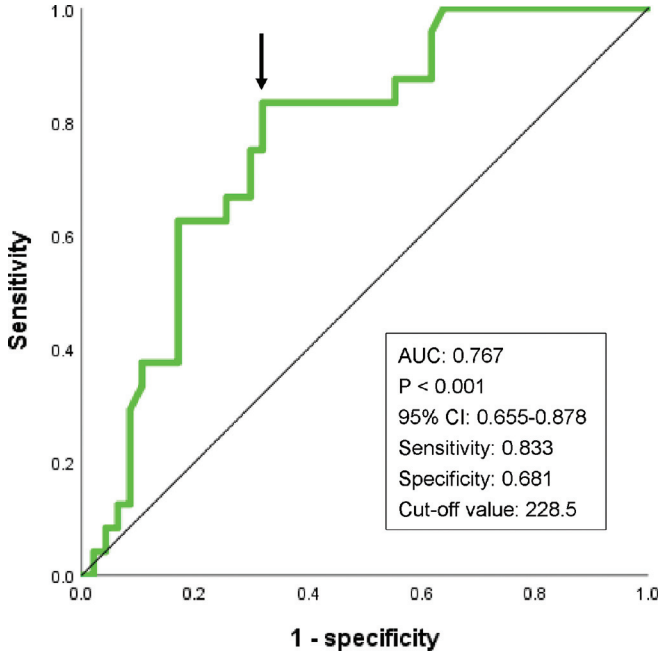


Figure 2. Receiver operating characteristic curve for calculating the cut-off value of surgical duration for predicting biochemical recurrence within 12 months after robot-assisted radical prostatectomy. The black arrow indicates the cutoff point of 228.5 Minutes.

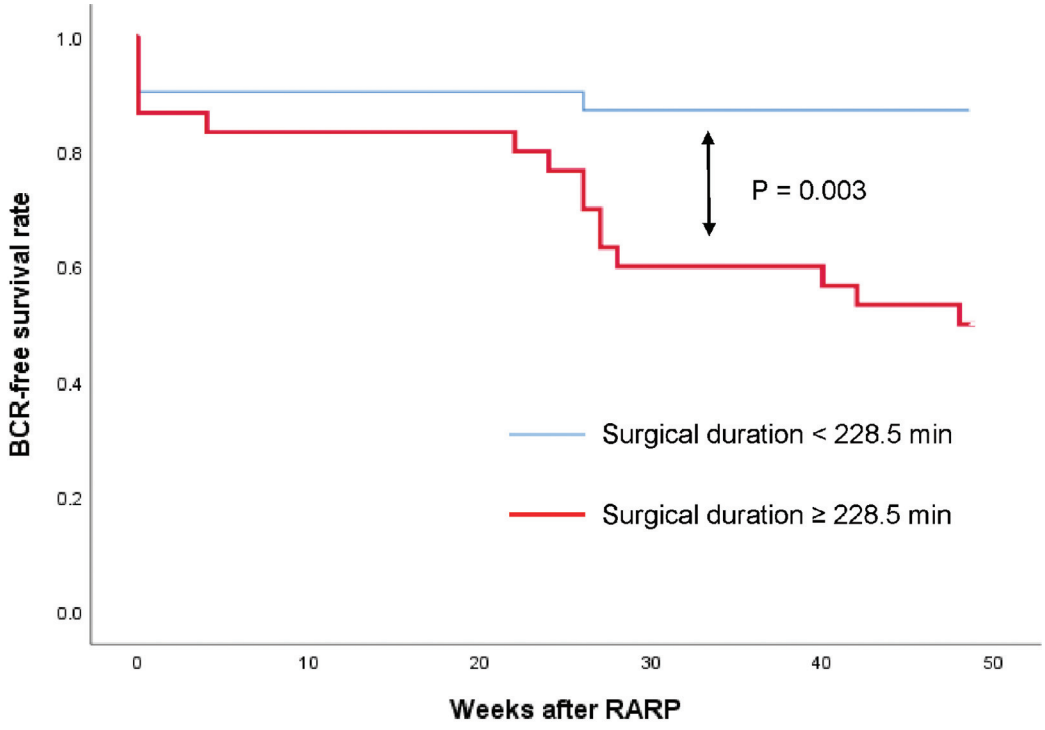
the curve, sensitivity and specificity of 0.77, 0.83, and 0.68, respectively (**Figure 2**). Surgical duration ≥ 2280.5 minutes was significantly associated with BCR within 12 months after RARP (**Figure 3**) ($P = .003$).

DISCUSSION

In the present study, to elucidate the contributory factors for BCR in patients with PSMs after RARP in the early postoperative period, we focused on the association between surgical stress and BCR. Factors such as surgical duration, bleeding during the peri-operative period and postoperative pain were generally considered to be representative of surgical stress in previous studies.[22,23] The present study demonstrated that prolonged surgical duration was the only contributing factor for BCR within 12 months after RARP in patients with PSMs. Since increase in the value of PSA in the early postoperative period is reportedly significantly associated with overall survival after radical prostatectomy in patients with PSMs,[24] surgical duration should be minimized as far as possible. In several studies, factors such as high Gleason score in the transition zone,[25] pre-operative PSA level,[26] prostate volume,[27] and pathological stage[26,28] were reported to be significantly associated with PSMs. Our results suggest that particularly in such patients, surgical duration should be as short as possible. To the best of our knowledge, this is the first report to demonstrate the association between prolonged surgical duration and recurrence of prostate cancer in a clinical study.

In patients with PSMs, the putative mechanism by which prolonged surgery increases the rate of BCR is as follows. Naturally, a fraction of cancer cells might remain in the surgical field after RARP owing to incomplete resection margins. Some of these cancer cells disseminate via hematogenous and lymphatic routes, leading to an increase in circulating tumor cells after surgery.[23] In addition, the stress evoked by prolonged surgery leads to immunosuppression,[12] providing the circulating tumor cells with opportunities for both distant metastasis and local recurrence. As a result, BCR might occur in patients with prolonged surgical duration.

Blood loss and the need for blood transfusion during surgery reportedly worsened the rate of disease-free survival in another cancer.[29] However, lack of a significant association between EBL and the rate of BCR in our study could have been because none of our patients required blood



No. at risk						
Surgical duration < 228.5 min	31	28	28	27	27	27
Surgical duration ≥ 228.5 min	30	26	25	18	17	15

Figure 3. Biochemical recurrence-free rate after robot-assisted radical prostatectomy stratified by the cut-off value of surgical duration. Blue Line: Patients with surgical duration ≥ 228.5 Minutes; Red Line: Patients with surgical duration < 228.5 Minutes.

transfusion during the peri-operative period due to the lower EBL. Also, in the present study, two types of analgesics, i.e., NSAIDs and pentazocine, were used after surgery. NSAIDs reportedly inhibit the development of metastasis due to prevention of tumor-associated inflammation.[23] On the other hand, pentazocine, which is an opioid analgesic, has been recognized to promote tumor cell migration and facilitation of angiogenesis due to suppression of immunity.[30] However, because the present cohort did not use large amounts of either of the analgesics, there was no significant association between the total usage of analgesics and the rate of BCR in this study.

Several limitations must be considered in the present study. First, the odds ratio of surgical duration in multivariate analyses was 1.016, which, although not high, was statistically significant. However, this value might not be clinically important. Second, because the data were retrospectively evaluated, this study might entail a selection bias. Third, the difference in experience level among surgeons can affect surgical duration and oncologic outcomes. In this study, the number of years of urology experience were not very different and the incidence rates of BCR were not significantly different among the three surgeons (**Table 3** and **Figure 4**), suggesting that this factor was likely to have affected our study results. However, subtle differences which have not been recognized in the analyses might have influenced the present study. Fourth, the observation period of 12 months was short compared with other studies that investigated BCR after RARP. Although this follow up period was selected with reference to previous animal studies, based on the fact that the study aim was mainly to evaluate the effects of surgical stress on BCR,[9,12,13,19] further observations might be needed in the future. Fifth, the

Table 3.
Experience Level and Incidence of Biochemical Recurrence for Each Surgeon Who Performed Robot-Assisted Radical Prostatectomy

	Surgeon		
	1(Chief)	2	3
Experience as urologist (as of Jun 2018) (years)	23	26	21
No. of RARP (n)			
2013	107	0	0
2014	45	17	7
2015	10	11	15
2016	31	14	20
2017	36	0	19
2018	18	0	22
No. of RARP with PSMs in the present study (n)	31	16	14
BCR in the present study (n) (%)	9 (29%)	6 (38%)	4 (29%)

BCR, biochemical recurrence; RARP, robot-assisted radical prostatectomy; PSM, positive surgical margin.

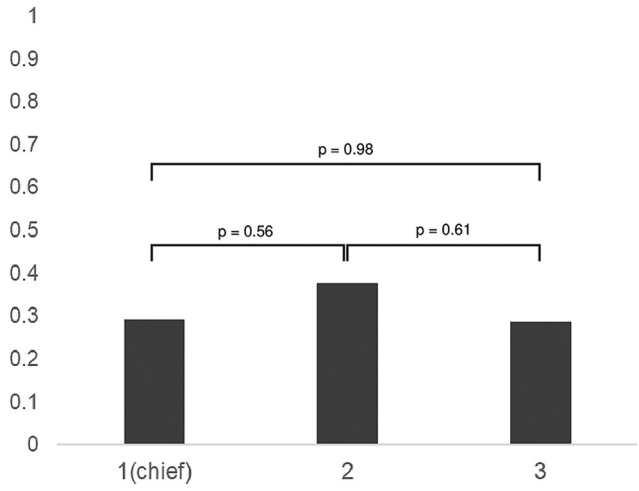


Figure 4. The incidence of biochemical recurrence was not significantly different among the three surgeons.

present study was conducted at a single center and the sample size was small. Sixth, disease aggressiveness, which can affect both longer surgical duration and BCR, might be a potential confounder. Although none of the characteristics except surgical duration was associated with BCR in the present study, highly aggressive cancers are often associated with recurrence. Finally, our hypothesis was not verified because the mechanisms of BCR were not directly evaluated and confirmed in this study. Further research with more participants and a longer observation period is needed to confirm the results of this study and our hypothesis.

CONCLUSIONS

In the present study, prolonged surgical duration, which is a determinant of surgical stress, was significantly associated with the risk of BCR in RARP patients with PSMs. From this perspective, surgical duration should be shortened as much as possible, especially in patients with other risk factors for PSMs.

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