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RESEARCH

Biochemical recurrence after chemohormonal therapy followed by robot-assisted radical prostatectomy in very-high-risk prostate cancer patients

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Abstract

Robot-assisted radical prostatectomy (RARP) has become one of the standard radical treatments for prostate cancer (PCa). A retrospective single-center cohort study was conducted on patients with PCa who underwent RARP at Gifu University Hospital between September 2017 and September 2022. In this study, patients were classified into three groups based on the National Comprehensive Cancer Network risk classification: low/intermediate-risk, high-risk, and very-high-risk groups. Patients with high- and very-high-risk PCa who were registered in the study received neoadjuvant chemohormonal therapy prior to RARP. Biochemical recurrence-free survival (BRFS) after RARP in patients with PCa was the primary endpoint of this study. The secondary endpoint was the relationship between biochemical recurrence (BCR) and clinical covariates. We enrolled 230 patients with PCa in our study, with a median follow-up of 17.0 months. When the time of follow-up was over, 19 patients (8.3%) had BCR, and the 2 years BRFS rate for the enrolled patients was 90.9%. Although there was no significant difference in BRFS between the low- and intermediate-risk group and the high/very-high-risk group, the 2 years BRFS rate was 100% in the high-risk group and 68.3% in the very-high-risk group ($P=0.0029$). Multivariate analysis showed that positive surgical margins were a significant predictor of BCR in patients with PCa treated with RARP. Multimodal therapies may be necessary to improve the BCR in patients with very-high-risk PCa.

Keywords Prostate cancer · Robot-assisted radical prostatectomy · Very-high-risk prostate cancer · Neoadjuvant chemohormonal therapy · Positive surgical margin

Introduction

According to the National Comprehensive Cancer Network (NCCN) guidelines [1], high-risk prostate cancer (PCa) is defined as PCa with at least one of the following characteristics: initial prostate-specific antigen (PSA) > 20 ng/mL, Gleason grade (GG) ≥ 4 based on the International Society for Urological Pathology (ISUP) 2014 guidelines [2], and clinical T stage ≥ T3a. In addition, very-high-risk PCa is defined as having at least one of the following: clinical T stage T3b or T4, two or more definitions of high-risk PCa, including Gleason pattern 5 in biopsy specimens, and ≥ 5 cores with ISUP grade group 4/5 in biopsy specimens [2]. Robot-assisted radical prostatectomy (RARP) is the recommended treatment modality for patients with organ-confined diseases including very low-, low-, and intermediate-risk PCa, with an estimated survival of at least 10 years [3]. Currently, there is no consensus regarding

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the optimal treatment for patients with high- and very-high-risk PCa, although these patients have a significantly higher rate of biochemical recurrence (BCR) [1, 3]. For patients with high- and very-high-risk localized PCa, RARP is currently the treatment of choice, but only for select patients, and the NCCN and European Association of Urology (EAU) guidelines recommend the use of a combination of various modalities [1, 3].

In a recent report, patients diagnosed with very-high-risk PCa, as classified by the NCCN, had markedly worse oncological outcomes after RARP than those in other risk groups [4]. Although treatment options for high-/very-high-risk PCa include androgen deprivation therapy (ADT) and/or external-beam radiation therapy (EBRT), ADT and/or EBRT and/or brachytherapy (BT), neoadjuvant/adjuvant therapy and/or surgery, and ADT alone [3, 5–7], patients with very-high-risk PCa have extremely poor oncologic outcomes, with a 5 years cancer-specific survival (CSS) rate of 58% and 5 and 10 years overall survival (OS) rates of 29% and 18%, respectively [8, 9]. Recent meta-analyses have reported that radical prostatectomy (RP) contributes to improved OS and CSS compared with radiotherapy (RT), and the trend is similar in patients with high- and very-high-risk PCa [10–12]. However, the combination of RT and ADT has been associated with improved biochemical recurrence-free survival (BRFS) and metastasis-free survival (MFS), making the long-term administration of ADT mandatory [10–12]. However, neoadjuvant therapy has been attempted in patients with high-/very-high-risk PCa because of the difficulty in cancer control using RP alone [13–18]. However, neoadjuvant hormone therapy (NHT) is not recommended by several guidelines or in the literature because it does not affect oncologic outcomes, although it reduces the rate of positive margins compared with RP alone [1, 2, 17, 18]. Therefore, it has been suggested that patients with high-/very-high-risk PCa may have improved oncological outcomes with combined neoadjuvant chemohormonal therapy (NCHT), including ADT plus anticancer agents, prior to RP [13–16]. However, to date, no effective therapeutic approach has been established for patients with very-high-risk PCa, especially regarding the optimal surgical treatment strategy.

Therefore, we designed this study to determine the differences in BCRs between high-risk and very-high-risk PCa by considering patients who underwent neoadjuvant therapy followed by RARP at our institution.

Methods

Patients

This research was conducted with the approval of the Institutional Review Board of Gifu University (Approval Number: 2022-191) and the Institutional Review Boards of the participating institutions. This study obtained consent for all enrolled patients, including those with low-, intermediate-, and high-risk PCa, undergoing RARP. Details of this study can be found at https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/2018-212.pdf (accessed on March 26, 2023).

This retrospective single-center cohort study included 285 patients with PCa who underwent RARP at Gifu University Hospital between September 2017 and September 2022. The participants had histologically confirmed PCa with no lymph node involvement or distant metastases, Eastern Cooperative Oncology Group (ECOG) performance status [17], adequate bone marrow function (absolute neutrophil count > 1500/microliter and platelet count > 100,000/microliter), and adequate renal function (creatinine < 2.0 mg/dL and/or creatinine clearance > 40 mL/min) and liver function (total bilirubin < 1.5 mg/dL). The following clinical data were collected from the enrolled patients: age, height, weight, initial PSA level, prostate volume, biopsy GG, clinical stage, and risk classification according to the NCCN criteria [2]. Console time (time from the start to the end of RARP using the robotic surgical system), estimated blood loss (EBL), whether lymph node dissection was performed, GG and T stages of the surgical specimen, presence of lymph node involvement, lymphovascular and perineural invasion, and positive surgical margins (PSM) were also evaluated as surgical and pathological outcomes. The staging of PCa was carried out in accordance with the American Joint Committee on Cancer, 8th Edition, "Cancer Staging Manual" [19]. The GG of biopsy and surgical specimens were classified into five groups referring to the ISUP 2014 guidelines [2]. We divided the enrolled patients into three risk groups using the NCCN guidelines [1]: low/intermediate-risk-group, high-risk group, and very-high-risk group.

Surgical procedure and neoadjuvant chemohormonal therapy

The RARP surgical procedure has been described in detail previously [20]. Six trocars were used, and the patient was operated on in the Trendelenburg position (25°). None of the enrolled patients underwent pelvic lymph node dissection (PLND) for reasons previously reported [20, 21].

All patients in the high-/very-high-risk group received a gonadotropin-releasing hormone (GnRH) antagonist (degarelix at a starting dose of 240 mg for 1 month, followed by a monthly maintenance dose of 80 mg) and tegafur-uracil (UFT; 300 mg/day) as NCHT for at least 3 months prior to RARP. All patients underwent computed tomography and magnetic resonance imaging (MRI) prior to RARP to confirm the absence of levator muscle involvement, regional and distant lymph node involvement, and distant metastases.

Follow-up schedule

All patients were evaluated for BCR by monitoring serum prostate-specific antigen (PSA) and testosterone levels at 3 months intervals after RARP during the first 2 years and at 6 months intervals during the following 5 years. The PSA assay kit was manufactured by Roche Diagnostics (Basel, Switzerland). BCR was defined as a serum PSA level elevated > 0.2 ng/mL postoperatively and subsequently confirmed a second time [22]. If PSA levels did not decrease below 0.2 ng/mL postoperatively, the date of RARP was defined as the time when BCR developed.

Pathological analysis

All prostatectomy specimens were evaluated using whole-mount staining in accordance with ISUP guidelines [2]. Pathological evaluation of the prostatic apex was performed by cutting it perpendicular to the prostatic urethra. Pathological assessment of the bladder neck was performed by cutting the end of the bladder neck from the resected specimen into a conical shape and further cutting it vertically. The remaining prostatic tissue was sectioned perpendicular to the urethral axis, at 3–5 mm intervals for pathologic diagnosis.

Statistical analysis

The primary endpoint of this study was BRFS after RARP. The secondary endpoint was to identify the relationship between BCR and covariates. Data were analyzed using JMP Pro 16 software (SAS Institute Inc., Cary, NC, USA). We used the Kaplan–Meier method to analyze BRFS after RARP and the log-rank test to analyze the association between BCR and subgroup classification. The Cox proportional hazards model was adopted for multivariate analysis. All P values were two-tailed, and P values < 0.05 were considered statistically significant.

Results

Patients and characteristics

The demographic data of the enrolled patients are presented in Table 1. A total of 14 patients with preoperative lymph node or distant metastasis, those who underwent surgery for castration-resistant PCa (CRPC), and those who were followed up for ≤ 3 months, were excluded from the study. Additionally, 48 patients who had already received NHT were excluded from the study. All patients had a median age of 71 years [inter quartile range (IQR) 67–74 years], median body mass index of 23.2 kg/m^2 (IQR 21.6–25.0 kg/m^2), median initial PSA of 7.35 ng/mL (IQR 5.36–11.49 ng/mL), and median prostate volume of 31 mL (IQR 24–42 mL).

Surgical and pathological outcomes

The surgical and pathological results are shown in Table 2. In all patients, the median console time was 119 min (IQR 97–150 min) and the median EBL was 25 mL (IQR 5–75 mL). There was no significant difference in the PSM rates between the low-/intermediate-risk group and the high-/very-high-risk group undergoing NCHT (23.5% and 24.5%, respectively; $P = 0.454$).

Oncological outcome

For all enrolled patients, the median follow-up was 17.0 months (IQR 7.0–35.0 months). During the follow-up period, none of the enrolled patients died of PCa, while four patients (1.8%) died of other causes (details unknown). Nineteen patients (8.3%) developed BCR with a median time from RARP to BCR of 12.2 months (IQR: 8.4–12.0) when the follow-up period ended. The 1 and 2 years BRFS rates in the entire study population were 95.4% and 90.9%, respectively.

The 1 and 2 years BRFS in patients with low-/intermediate-risk PCa was 97.1% and 94.3%, respectively, and 93.7% and 87.5%, respectively, in high-/very-high-risk group ($P = 0.419$; Fig. 1A). The 1 and 2 years BRFS rates were 100% and 100%, respectively, in patients with high-risk PCa and 83.4% and 68.3%, respectively, in the very-high-risk PCa group ($P = 0.0028$; Fig. 1B). In high-/very-high-risk PCa groups, patients diagnosed with PSM after RARP tended to have lower BRFS rates; however, there was no significant difference between the two groups ($P = 0.112$; Fig. 2).

Multivariate analysis revealed that PSM was a statistically independent factor for predicting BCR in patients with PCa undergoing RARP (Table 3).

Discussion

Since several guidelines do not recommend an optimal treatment strategy for patients with high-/very-high-risk PCa, the established therapeutic modalities for these PCa categories have remained inconclusive [1, 3]. The BRFS for patients with PCa who underwent RP was reported to be 70% for those with low-risk, 36% for those with intermediate-risk, 31% for those with high-risk, and 26% for those with very-high-risk at 10 years after surgery, with BCR increasing as the risk category became higher [23]. Compared to patients with high-risk PCa, the risk of distant metastasis [hazard

Table 1 Clinical covariates of the enrolled patients

Variables	Low/Intermediate-risk group N = 132	High-risk-group N = 64	Very-High-risk-group N = 34	P value
Age (year, median, IQR)	71 (67.0–73.0)	71 (67.0–74.0)	71 (69.0–74.0)	0.582
Body mass index (kg/m^2,median, IQR)	23.1 (21.3–24.7)	23.4 (21.7–25.6)	23.7 (22.1–25.3)	0.410
Initial PSA (ng/mL, median, IQR)	6.50 (4.90–9.11)	8.65 (5.57–11.75)	14.06 (9.44–32.70)	< 0.001
Prostate volume (cc, median, IQR)	34.8 (27.0–45.0)	30.0 (22.5–39.0)	25.5 (17.2–47.5)	0.001
Biopsy Gleason Group (number, %)				< 0.001
1	35 (26.5)	1 (1.6)	0 (0.0)	
2	50 (37.9)	4 (6.2)	1 (2.9)	
3	45 (34.1)	4 (6.2)	0 (0.0)	
4	1 (0.8)	39 (60.9)	13 (38.2)	
5	1 (0.8)	16 (25.0)	20 (58.8)	
Clinical T stage (number, %)				< 0.001
T1c	19 (14.4)	4 (6.2)	1 (2.9)	
T2a	87 (65.9)	38 (59.4)	3 (8.8)	
T2b	4 (3.0)	8 (12.5)	4 (11.8)	
T2c	22 (16.7)	10 (15.6)	5 (14.7)	
T3a	0 (0.0)	4 (6.2)	12 (35.3)	
T3b	0 (0.0)	0 (0.0)	6 (17.6)	
T4	0 (0.0)	0 (0.0)	3 (8.8)	
NCCN risk classification (number, %)				< 0.001
Very Low	4 (3.0)	0 (0.0)	0 (0.0)	
Low	21 (15.9)	0 (0.0)	0 (0.0)	
Intermediate	107 (81.1)	0 (0.0)	0 (0.0)	
High	0 (0.0)	64 (100.0)	0 (0.0)	
Very High	0 (0.0)	0 (0.0)	34 (100.0)	
Neoadjuvant therapy (number, %)				< 0.001
None	132 (100.0)	0 (0.0)	0 (0.0)	
Chemohormonal therapy	0 (0.0)	64 (100.0)	34 (100.0)	
Follow-up period (months, median, IQR)	16.0 (6.0–36.0)	16.5 (5.7–29.2)	21.0 (13.0–31.7)	0.390

ratio (HR) 2.75] and cancer-specific mortality (HR 3.44) was significantly higher in those with very-high-risk PCa ($P < 0.001$ and $P < 0.001$, respectively), as well as statistically significantly worse 10 years MFS and CSS [24]. In a multicenter cohort of 266 very-high-risk PCa patients treated with RP, 34 (13%) had PCa and 73 (28%) died of other causes; the 10 years CSM and other-caused mortality rates ranged from 5.6 to 12.9% and 10 to 38%, respectively [25]. Conversely, according to a multicenter cohort study with 164 enrolled patients, 77% of patients with high-risk PCa at a median follow-up of 31.1 months and 58% of patients with very-high-risk PCa at 36.1 months follow-up did not have a BCR [26]. The differences in oncologic outcomes for patients with very-high-risk PCa may be due to the fact that very-high-risk PCa is a heterogeneous population, and age and comorbidities may have a significant influence on clinical outcomes in this cohort [25].

There are several reports on the efficacy of RT in patients with very-high-risk PCa. The 5 years BRFS of patients with very-high-risk PCa having GG5 and T3b/T4 who underwent EBRT and BT boost was 49.1%, with no benefit from the BT boost compared to the other groups [27]. Patients with very-high-risk PCa who received intensity-modulated RT and 1.5–3 years of ADT had a significantly higher risk of BCR than those who received RP ($P < 0.001$); however, there was no significantly increased risk for all-cause mortality, local recurrence, or distant metastasis ($P = 0.564$, $P = 0.352$, and $P = 0.918$, respectively) [28]. In patients with very-high-risk PCa who received ADT for ≥ 2 years, the 8 years CSM rate was 7.6% for those receiving EBRT and 11.9% for those receiving EBRT with BT, and the MFS rate was 18.3% for those receiving EBRT and 14.8% for those receiving EBRT with BT [29]. Compared to EBRT, EBRT with BT showed no significant difference in the risk of CSM ($P = 0.53$) or MFS ($P = 0.54$) [29]. Many reports have shown no significant difference in oncological outcomes, including CSS and MFS, between RP and RT for very-high-risk PCa [27–29]. However, because many patients treated with RT were also

Table 2 Surgical and pathological outcomes in the enrolled patients

Variables	Low/Intermediate-risk group N = 132	High-risk-group N = 64	Very-high-risk-group N = 32	P value
Console time (minutes, median, IQR)	128 (106–167)	114 (91–140)	106 (85–138)	0.001
Estimated blood loss (mL, median, IQR)	30.0 (5.0–92.5)	20.0 (5.0–62.5)	22.5 (5.0–50.0)	0.617
Pathological Gleason Group (number, %)				< 0.001
pT0	2 (1.5)	1 (1.6)	1 (2.9)	
1	8 (6.1)	0 (0.0)	2 (5.9)	
2	65 (49.2)	15 (23.4)	6 (17.6)	
3	46 (34.8)	8 (12.5)	6 (17.6)	
4	4 (3.0)	20 (31.2)	3 (8.8)	
5	7 (5.3)	20 (31.2)	16 (47.1)	
Pathological T stage (number, %)				< 0.001
pT0	2 (1.5)	1 (1.6)	1 (2.9)	
pT2	109 (82.5)	51 (76.6)	16 (50.0)	
pT3	21 (15.9)	12 (18.8)	10 (29.4)	
pT4	0 (0.0)	0 (0.0)	5 (14.7)	
Positive lymphatic invasion (number, %)	18 (13.6)	6 (9.4)	6 (17.6)	0.488
Positive venous invasion (number, %)	15 (11.4)	13 (20.3)	7 (20.6)	0.044
Positive perineural invasion (number, %)	73 (55.3)	35 (54.7)	25 (73.5)	0.133
Positive surgical margin (number, %)	31 (23.5)	13 (20.3)	11 (32.4)	0.253

administered ADT for a relatively long period, it is necessary to consider the risk of complications resulting from this treatment. In contrast, although RP is often performed for curative resection of localized PCa, enhanced local control by cytoreductive surgery has been suggested for patients with very-high-risk PCa [25]. Therefore, it may be necessary to establish alternative treatment strategies, including surgery, for patients with very-high-risk PCa, despite the possibility of higher PSM rates and BCRs.

Currently, it has been reported that RARP can be an oncologically effective procedure, especially for high-risk PCa [30], and it has been suggested that it may decrease the risk of PSM and BCR [31]. PSM and BCR after RARP for locally advanced PCa have been found in 20 to 60% and 18.5 to 28.6%, respectively [31]. In addition, multivariate Cox regression analysis revealed that PSM was an independent predictor of BCR in locally advanced PCa who underwent RARP (HR 6.28; $P = 0.010$) [30]. On the other hand, it has been reported that PSM is not correlated with BCR in patients with locally advanced PCa after RARP even though PSM may be a significant negative predictor of BCR (relative risk: 0.163, 9, $P < 0.001$), [32]. In this study, multivariate analysis suggested that PSM may be a significant predictor of BCR in patients with very-high-risk PCa receiving RARP. However, because it would be difficult to reduce PSM and BCR using RARP alone in patients with very-high-risk PCa, we reasoned that some additional therapy may be necessary to improve oncologic outcomes.

Neoadjuvant therapy for high-/very-high-risk PCa remains controversial. NHT before RP is not recommended by various guidelines because it has been shown to reduce the PSM rate but not to affect oncologic outcomes [1, 3, 17, 18]. In a recent report on the efficacy of NHT with second-generation antiandrogens before RP in patients with high-risk PCa, the time to BCR (HR = 0.25) and metastasis-free survival (HR = 0.26) were also significantly different in patients who received neoadjuvant second-generation antiandrogens compared with those who received only RP [33]. In contrast, the 3 years BRFS and MFS rates were 59% and 95%, respectively, in the group receiving NHT with second-generation antiandrogens and 15% and 68%, respectively, in the group receiving RP alone [33]. Although NHT with second-generation antiandrogens significantly improved oncological outcomes, such as BCR and MFS, compared with RP alone ($P < 0.001$ and $P < 0.001$, respectively), in high-risk PCa, NHT using second-generation antiandrogens appears to be ineffective in controlling cancer [33]. Therefore, NCHT in combination with cytotoxic anticancer agents has been attempted for high- and very-high-risk PCa [13–17]. Narita et al. [13] compared patients who underwent NCHT with ADT, docetaxel, and estramustine (EMP) followed by RP with those who underwent RP alone

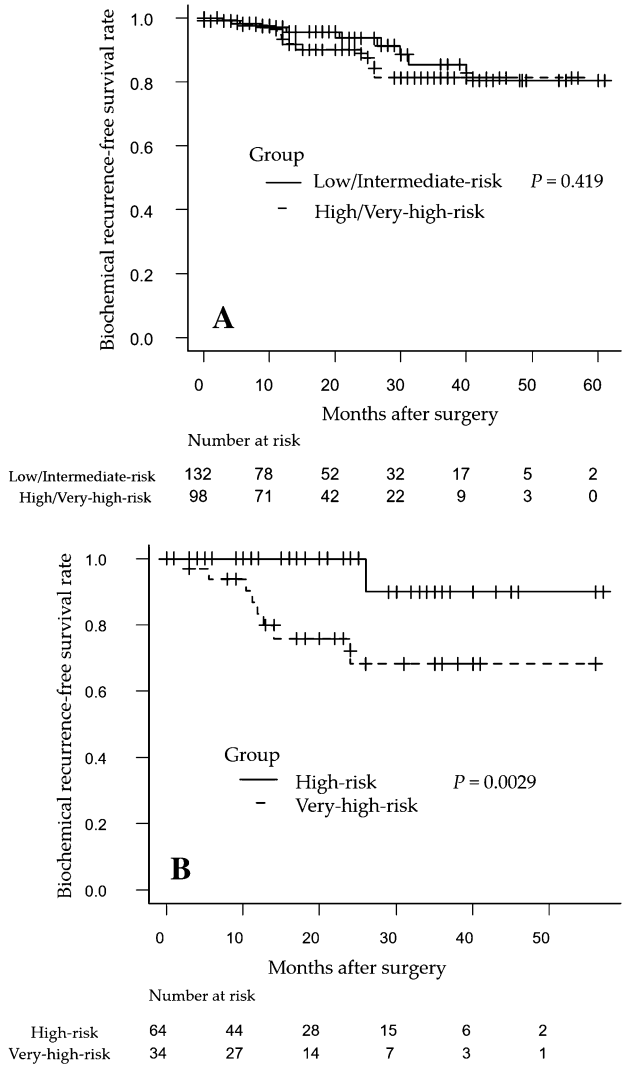

Fig. 1 Using the National Comprehensive Cancer Network risk criteria as well as the Kaplan–Meier estimate of the biochemical recurrence after robot-assisted radical cystectomy, enrolled patients were divided into two groups: those with low- and intermediate-risk prostate cancer (PCa; low/intermediate-risk group) and those with high- and very-high-risk PCa (high/very-high-risk group).The 2 years biochemical recurrence-free survival (BRFS) rates were 93.4% and 87.5% in the low/intermediate-risk group and the high/very-high-risk group, respectively ($P=0.419$; **A**). Regarding patients with high- and very-high-risk PCa, the 2 years BRFS rates were 100% in the high-risk group and 68.3% in the very-high-risk group ($P=0.0029$; **B**)

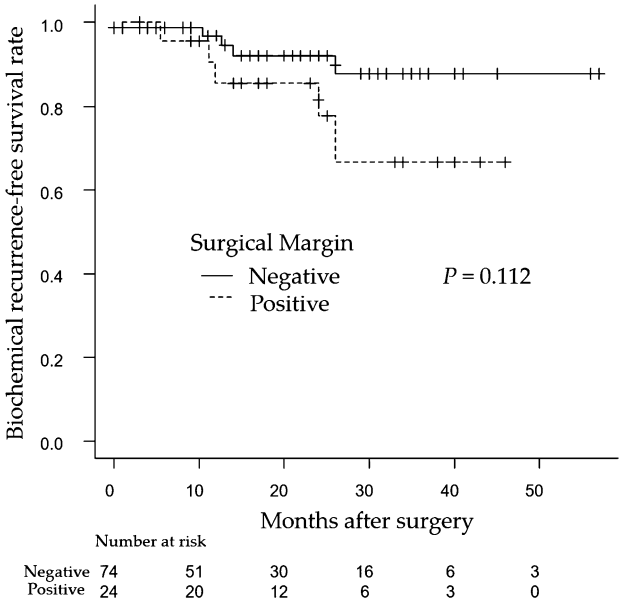

Fig. 2 The Kaplan–Meier estimates of biochemical recurrence-free survival (BRFS) in the patients of high-risk prostate cancer (PCa) group and very-high-risk PCa with surgical margin after robot-assisted radical prostatectomy. The 2 years BRFS rate was 92.0% in patients negative surgical margin and 77.6% in those with positive surgical margin ($P=0.112$; Fig. 2)

and found that BCR was significantly lower in the former group ($P=0.02$) [13]. In our previous study, we showed that ADT + EMP before RP as NCHT significantly improved BRFS in patients with high-risk PCa ($P<0.001$) [15]. Furthermore, NCHT with ADT + EMP in patients with pT3 also revealed a BRFS almost equivalent to that in patients with localized PCa [15]. In contrast, when OS was investigated as the primary endpoint, patients with high-risk PCa who underwent NCHT followed by RP had significantly longer 5 and 10 years OS rates compared with those who underwent RP alone ($P=0.021$) [16]. In our present study, NCHT with a GnRH antagonist and UFT was administered to high-/very-high-risk PCa patients prior to RARP. The reason for using UFT as NCHT was selected based on the results of several clinical studies on CRPC [34–36]. According to a multicenter prospective randomized phase II trial, ADT plus UFT was significantly longer than ADT alone in terms of time to PSA progression, indicating that it is a more effective and better tolerated treatment for CRPC [34]. Hayakawa et al. [35] also showed that UFT as a fourth-line treatment in patients with CRPC who had already received ADT or alternative androgen therapy, and EMP was well-tolerated and had some inhibitory effects on disease progression. Furthermore, the combination of dexamethasone, UFT, and cyclophosphamide was reported to reduce PSA by ≥ 50% in 63% of patients with CRPC, with a median time to progression of 7.2 months [35]. Therefore, we hypothesized that the administration of a GnRH antagonist plus UFT as NCHT in the hormone-sensitive state could improve the prognosis of high-/very-high-risk PCa. However, the effect of NCHT combined with a GnRH antagonist and UFT on very-high-risk PCa was limited in this study. Therefore, it may be necessary to investigate NCHT options with more potent effects.

Several limitations exist with respect to this study. First, a potential selection bias might be present because of the single-center, retrospective nature of the study, with a relatively

Table 3 Multivariate analysis for predicting biochemical recurrence (BCR) in high-risk and very-high-risk prostate cancer (PCa) patients undergoing robot-assisted radical prostatectomy with neoadjuvant chemotherapy (RARP)

	n	Univariate analysis			Multivariate analysis		
		Hazard ratio	95% confidence interval	*P*	Hazard ratio	95% confidence interval	*P*
Positive surgical margin							
Positive	24	2.870	1.020–8.130	0.046	3.700	1.120–12.20	0.031
Negative	74	1 (ref.)	–	–	1 (ref.)	–	–
Clinical T stage							
≥ 3	25	2.530	0.894–12.90	0.072	3.380	0.960 – 16.30	0.087
< 3	73	1 (ref.)	–	–	1 (ref.)	–	–
Console time							
≥ 108 min	54	2.490	1.040–5.950	0.049	2.780	0.607–12.70	0.118
< 108 min	44	1 (ref.)	–	–	1 (ref.)	–	–

short follow-up period and a limited number of patients enrolled. Second, as NCHT for high-/very-high-risk PCa is not a well-established treatment, care must be taken when interpreting its efficacy. Third, RARP was not performed by a single surgeon, and this may have a significant impact on the surgical and pathological outcomes. Finally, we believe that multicenter prospective trials are needed to improve outcomes in very-high-risk PCa and that continued discussion is needed regarding treatment strategies for these patients.

Conclusion

In this study, we evaluated patient outcomes for high-/very-high-risk PCa cases who underwent NCHT with GnRH antagonists and UFT, followed by RARP. We found that it was difficult to control cancer progression in very-high-risk PCa, even though NCHT combined with RARP improved the BCR in high-risk PCa. To truly improve the oncological outcomes of very-high-risk PCa, a multicenter study should be designed to enroll a large number of patients for long-term follow-up and to fully investigate treatment strategies, including RARP.

Author contributions FS: Data analysis, manuscript writing/editing; data collection and management; MK: Data collection and management; SU: Data collection and management; MT: Data collection and management; YT: Data collection and management; TY: Data collection and management; SN: Data collection and management; NK: Data collection and management; KK: Data collection and management; DK: Data collection and management; MT: Data collection and management; KI: Protocol/project development and supervision; KN: Protocol/project development and supervision; YT: Data collection and management; TI: Data collection and management; TK: Protocol/project development, data management, manuscript writing/editing.

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Data availability Yes.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Received from the Japanese Ethics Committee and Ethics Guidelines.

Consent to participate Retrospective study, no consent required.

Consent for publication Taken from the Institute.

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