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Long-Term Oncological Outcomes for Histologically Confirmed High-Risk Prostate Cancer

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Background: The optimal treatment modality for locally advanced prostate cancer has not been established. Radiotherapy, hormonal therapy, and combination treatments are the main strategies, although the feasibility of radical prostatectomy as a first-line therapy needs to be considered. This retrospective analysis of pathological results of extracted specimens evaluated long-term oncological outcomes for high-risk prostate cancer treated surgically. The association of number of risk factors with long-term outcome was specifically analyzed.

Methods: We identified patients with high-risk prostate cancer who underwent laparoscopic radical prostatectomy, without neoadjuvant therapy, at Nippon Medical School from 2000 to 2012. Risk factors were a prostate-specific antigen (PSA) concentration ≥20 ng/mL, pathological ≥T3, and pathological Gleason Score ≥8. Biological failure was defined as a PSA concentration ≥0.2 ng/mL.

Results: 222 men were identified. One patient had a positive lymph node status, and there was a significant difference in surgical margin positivity (52 men, 68.4% vs 56 men 38.4%) between patients with and without biochemical failure. Among patients meeting the high-risk criteria with a follow-up of up to 133 months, the biochemical recurrence (BCR)-free survival rates at 5 and 10 years were 62.8% and 58.4%, respectively, and mean time to BCR was 14.0 months. BCR-free survival rates at 5 and 10 years were 73.6% and 71.4%, respectively, for 1 risk factor, 48.7% and 34.6% for 2 factors, and 34.5% and 34.5% for 3 factors. Patients with a single risk factor had a significantly better outcome than those with multiple risk factors. The overall survival rates at 5 and 10 years were 94.6% and 93.7%, and the cancer-specific survival rate was 100% at both 5 and 10 years.

Conclusions: Reasonable long-term oncological outcomes can be achieved by surgical treatment for high-risk prostate cancer. Patients with 1 risk factor had a significantly better BCR-free rate than those with multiple risk factors. (J Nippon Med Sch 2023; 90: 202–209)

Key words: prostate cancer, high risk, prostatectomy

Introduction

Widespread prostate-specific antigen (PSA) screening and an extensive biopsy strategy have increased identification of men with low-risk and intermediate-risk prostate cancer (PCa)[1]. Studies show a reduction in prostate cancer mortality with PSA screening[2]. However, 15-30% of patients are diagnosed with high-risk prostate cancer (HPCa), which is relevant to cancer death, and mortality has increased over the past decade in Asian countries. It is likely that more Japanese men will be diagnosed with HPCa in the future.

Although radical prostatectomy (RP), external beam ra-

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Table 1 Preoperative characteristics of patients

	N (%)
	562
Age, mean (y)	68 (range 49-81)
Preoperative PSA, mean (ng/mL)	9.9 (range 3.7-150)
<4.0	20 (3.6%)
4.0-9.9	353 (62.8%)
10.0-19.9	139 (24.7%)
≥20.0	50 (8.9%)
Clinical T stage	
T1c	139 (24.7%)
T2a	219 (39.0%)
T2b	117 (20.8%)
T2c	45 (8.0%)
T3a	35 (6.2%)
T3b	6 (1.1%)
T4	1 (0.2%)
Biopsy Gleason Score, N (%)	
6	185 (32.9%)
7	250 (44.4%)
8	61 (10.9%)
9	64 (11.4%)
10	2 (0.4%)
Neoadjuvant therapy	
yes	60 (10.7%)
no	502 (89.3%)

diation therapy (EBRT), brachytherapy, hormonal therapy, and combined treatments are the main strategies, there is no consensus on the optimal treatment modality for HPCa, since no randomized study has compared treatments. Androgen-deprivation therapy (ADT) plus EBRT is chosen as a first-line therapy, despite the lack of data to support its use or the use of other treatment modalities. Only about 36% of patients are initially treated by RP[3], although recent studies support the feasibility of RP as first-line therapy[4].

According to the National Comprehensive Cancer Network (NCCN) guideline[5], RP is considered an appropriate therapy for any clinically localized PCa that can be completely resected surgically in patients with a life expectancy of more than a decade who have no serious comorbidities that would contraindicate elective surgery. Laparoscopic RP (LRP) and robot-assisted RP (RARP) are commonly used, and in experienced hands, the results of these approaches appear comparable to those of open surgical approaches[6]. LRP was associated with technical difficulties and a long learning-curve, whereas a short learning curve without any experience in LRP has enabled RARP to spread widely and quickly as a surgical treatment option after it was introduced in 2000. RARP was approved by the medical insurance system in 2012, and almost all candidates for surgical treatment at Nippon Medical School underwent RARP. LRP and RARP were both performed by the transperitoneal approach, and most of the surgical procedures are similar. Thus, the long-term follow-up results of LRP can be used as an indicator for patients treated with RARP. Therefore, this study evaluated the long-term oncological outcomes for HPCa treated surgically at our center.

Materials and Methods

1. Patient Population

Between March 2000 and December 2012, a total of 562 patients with clinically localized or locally advanced PCa underwent LRP at Nippon Medical School. The patients' clinical characteristics are shown in **Table 1**. The minimum duration of follow-up was 5 years, and patients with missing data on postoperative PSA values, biopsy results, or clinical stage, and those who received neoadjuvant therapy of any kind, were excluded from the analysis. Biopsy specimens were re-evaluated before LRP by a single pathologist.

This study was approved by the Ethics Committees of Nippon Medical School (approval no. M-2022-037).

2. Operative Technique

LRP was performed by the Montsouris technique re-

Table 2 Postoperative characteristics of high-risk patients

	No. of Patients	Percentage (%)
Overall	222	100
Gleason Score ≥8	141	63.5
PSA ≥20 ng/mL	41	18.5
Stage ≥pT3a	146	65.8
Patients with 1 factor	136	61.3
Gleason Score ≥8	64	28.8
PSA ≥20 ng/mL	10	4.5
Stage ≥pT3a	62	27.9
Patients with 2 factors	67	30.2
Gleason Score ≥8 + PSA ≥20 ng/mL	3	1.3
Gleason Score ≥8 + ≥pT3a	55	24.8
PSA ≥20 ng/mL + ≥pT3a	19	8.6
Patients with 3 factors	19	8.6
Gleason Score ≥8 + PSA ≥20 ng/mL + ≥ pT3a	19	8.6

ported by Guillonneau and Vallancien[7]. Pelvic lymph node dissection (PLND) was performed only if the probability of lymph node metastasis was ≥3% according to the Japanese Partin nomogram.

3. Pathological Findings

LRP specimens were examined according to the classification criteria of the International Society of Urological Pathologists (ISUP). Two board-certified pathologists independently reviewed the specimens, and the results were confirmed by an expert genitourinary pathologist. Pathologic variables evaluated included pathological T stage (pT), Gleason Score (GS), tumor volume, prostate weight, lymph node status, perineural invasion, angiolymphatic invasion, and surgical margin status. Extraprostatic extension was defined as spread of cancer to soft tissue or skeletal muscle, and positive surgical margin (PSM) was defined as extension of cancer to the inked surface. The included patients were classified as having high-risk prostate cancer on final pathology. Factors indicating highrisk were defined as a PSA concentration ≥20 ng/mL, a pathological T stage ≥T3, and a pathological GS (pGS) ≥8.

4. Oncological Outcomes

PSA was monitored every 3 months. Biochemical recurrence (BCR) was defined as a PSA concentration >0.2 ng/mL. BCR-free survival (BCRFS), overall survival (OS), and cancer-specific survival were evaluated. The cause of death was identified from death certificates or physician correspondence.

5. Statistical Analysis

Statistical analysis was performed using the SAS software package, JMP version (SAS Institute Inc.). BCRFS, OS, and cancer-specific survival were estimated using the Kaplan-Meier method.

Results

1. Patient Preoperative Characteristics

A total of 562 men underwent LRP (**Table 1**). The mean age was 68 years (range 49-81 years), and the mean preoperative PSA was 9.9 ng/mL (range 3.7-150 ng/mL). Overall, 520 patients had organ-confined disease, and 42 patients had a pathological T stage ≥cT3. Biopsy GS was 6 in 185 patients, 7 in 250 patients, and ≥8 in 127 patients. The 60 patients who received hormonal therapy were excluded from the analysis.

2. Patient Postoperative Characteristics

Of the 502 men who underwent LRP without hormonal therapy, 222 had HPCa on pathological examination of the resected specimens (**Table 2**). The pGS was ≥8 in 141 patients (63.5%), PSA was ≥20 in 41 patients (18.5%), and T stage was ≥pT3a in 146 patients (65.8%). Overall, 136 patients (61.3%) had 1 risk factor, 67 patients (30.2%) had 2 risk factors, and 19 patients (8.6%) had 3 risk factors.

During a median follow-up of 82 months (range 60-133 months), BCR was observed in 96 patients overall. Among patients meeting criteria indicating highrisk, 76 experienced BCR (**Table 3**). Age, prostate volume, and preoperative PSA were comparable between the groups. Pathologically, 108 patients had a PSM, and 52 men had BCR. Among HPCa patients with BCR, 68.4% had a PSM, and 38.4% with a PSM were BCR-free. Similarly, 121 patients had extracapsular extension, with 47 men (61.8%) having BCR, whereas 74 men (50.7%) were BCR-free. Only 1 patient had positive lymph nodes.

Table 3 Characteristics of patients with biochemical recurrence

	Total		Recurrence	No recurrence
Number of subjects	222		76	146
Age, mean (y)		range 49-76	67	69
Prostate volume (g)		range 14-111	44.0	39.0
Preoperative PSA, mean (ng/mL)	9.9	range 4.2-165	10.1	9.8
Positive surgical margin, N (%)	108 (48.6)		52 (68.4%)	56 (38.4%)
Extracapsular extension, N (%)	121 (54.5)		47 (61.8%)	74 (50.7%)
Lymph node-positive, N (%)	1 (0.5%)		1 (0.5%)	0 (0.0%)

3. Oncological Outcomes

The 5-year BCRFS rate was 80.3%. **Figure 1a～c** shows BCRFS rates in relation to each risk classification factor. When analyzing GS as a risk factor, the BCRFS rates for men with a GS of ≥8 and ≥7 were 56.9% and 89.1%, respectively (**Fig. 1a**). Similarly, when comparing PSA as a risk factor, the BCRFS rates for PSA concentrations of ≥20 and <20 ng/mL were 43.1% and 83.5%, respectively (**Fig. 1b**). When T stage was considered as a risk factor, the BCR-free rates for a pathological T stage of ≥pT3 and ≤pT2c were 60.1% and 88.3%, respectively (**Fig. 1c**). Each risk factor meeting the high-risk criteria was associated with a significantly higher BCR rate.

4. Number of Risk Factors

The BCRFS rates for patients meeting the high-risk criteria at 5 and 10 years were 62.8% and 58.4%, respectively. The OS rates at 5 and 10 years were 94.6% and 93.7%, respectively. Two patients died of progressive prostate cancer, 11 developed new disease, and 1 was lost to follow-up. The 5-year and 10-year BCRFS rates were 73.6% and 71.4%, respectively, for 1 risk factor, 48.7% and 34.6% for 2 factors, and 34.5% and 34.5% for 3 factors (**Fig. 2**). Men with a single risk factor had a significantly better outcome than those with multiple risk factors ($p < 0.001$)

Discussion

Because of the lack of evidence, there is no consensus on the optimal treatment for locally advanced prostate cancer; no well-designed randomized study has compared treatments. The NCCN and European Association of Urology (EAU) guidelines support RP + PLND as a first-line therapy for selected high-risk patients. D'Amico et al defined high-risk prostate cancer as ≥cT2c, GS ≥8, and PSA >20 ng/mL, although the NCCN and EAU guidelines use ≥cT3 as the criterion. The 5-year OS and prostate cancer-specific survival (PCSS) rates for T1-4N0M0 Japanese patients were 93.3% and 98.4%, respectively, according to a report from the Cancer Registration Committee of the Japanese Urological Association (JUA)[8]. In a high-risk setting, 5-year and 10-year PCSS rates were 45-62% and 43-51%, respectively[9,10]. In the present study, the overall BCRFS rates at 5 and 10 years-62.8% and 58.4%, respectively-were comparable to previous findings. Several studies identified GS as an independent predictor of BCR after RP[11–13], indicating that GS is the most powerful prognostic factor. Kishan et al reported that 5-year and 10-year OS and BCRFS rates of pathological GS 9-10 PCa patients treated with RP were 90.3% and 72.1%, respectively, for OS, and 26.4% and 16.2% for BCRFS[14]. They concluded that GS was an extremely strong predictor in a very high-risk setting. In the present study, GS was a predictive factor, but all 3 factors were risk factors significantly associated with BCR. The distribution of the 3 risk factors was not equal in the present study: only 18.5% of patients had high serum PSA levels, which is lower than in previous studies. Widespread PSA screening and an extensive biopsy strategy have improved early detection of PCa, thereby decreasing the population of high-risk patients. The JUA Cancer Registration Committee reported that the trend in choosing initial treatment for Japanese men differs somewhat from that in western countries: the most frequent treatment for non-metastatic PCa in men younger than 70 years was RP (62.5%); men older than 70 years were more likely to choose hormonal therapy. A relatively high age at diagnosis, a high rate of health insurance coverage, and indifference regarding erectile dysfunction might be reasons for choosing hormonal therapy[8].

In the present study, the BCRFS rate at 5 years significantly differed in relation to the number of risk factors (**Fig. 2**), and a long-term analysis showed that while a single risk factor was associated with good BCRFS, the presence of multiple risk factors was associated with worse outcomes. Walz reported that BCRFS rate differed according to the definition used for high risk. In a comparison of the 4 most commonly used definitions-cT3, biopsy GS ≥8, PSA ≥20 ng/mL, and the D'Amico high-risk

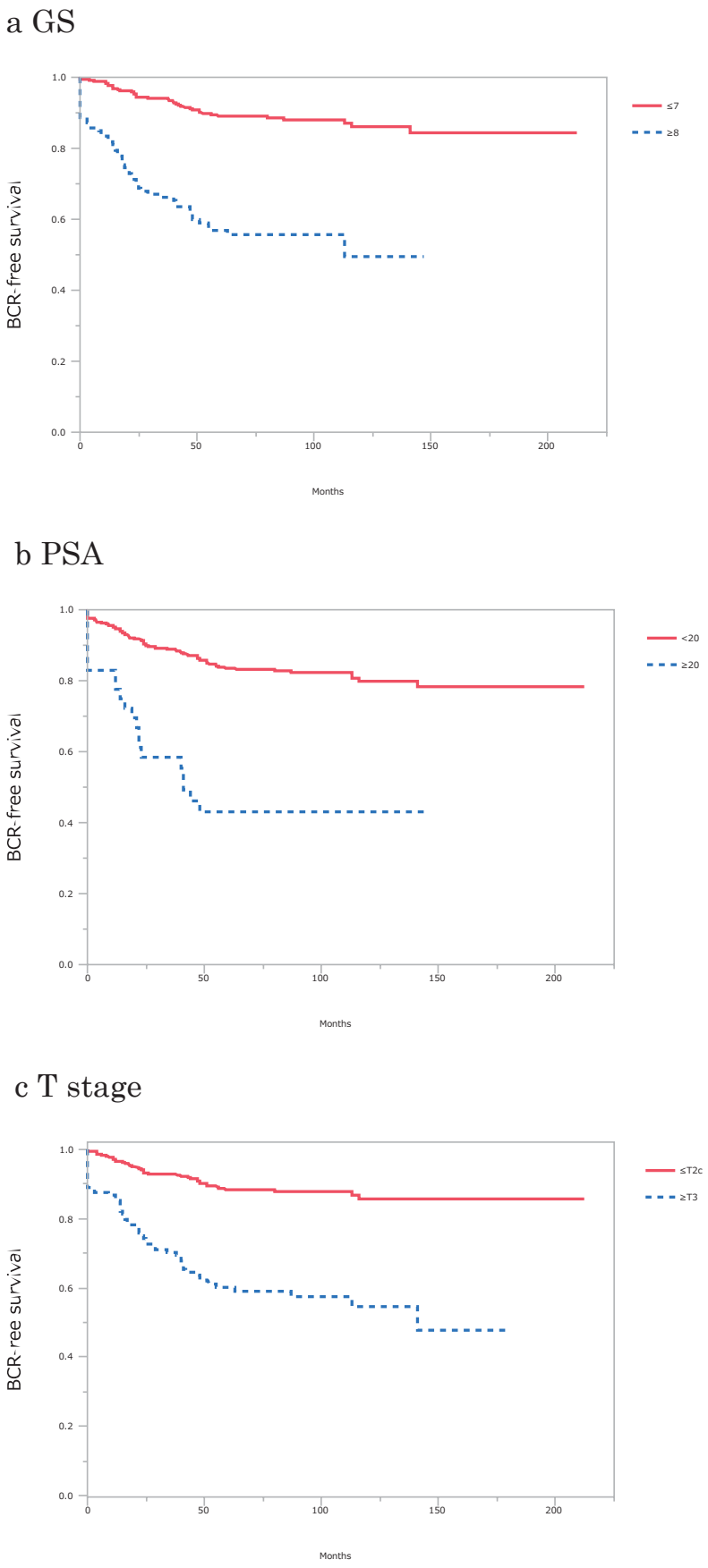

Fig. 1

Kaplan-Meier curves for biochemical recurrence (BCR)-free survival, according to risk classification factor. The effect of Gleason Score (a), prostate-specific antigen (PSA) concentration (b), and clinical stage (c) are shown.

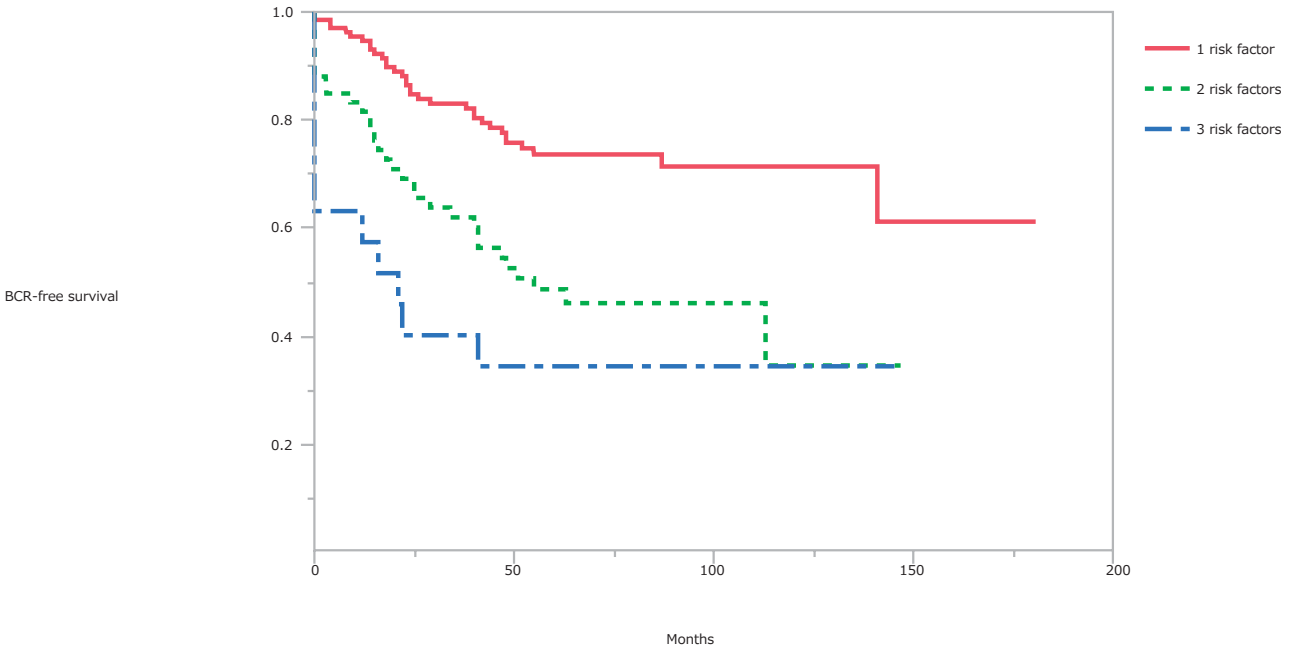

Fig. 2
Kaplan-Meier curves for BCR-free survival in relation to number of risk factors are shown.

criteria-the presence of 1 risk factor was associated with better 5-year BCRFS (50.3%) than the presence of ≥2 risk factors (27.5%). High-risk was defined as the presence of only 1 risk factor, although oncological outcomes differed in men with multiple risk factors. Patients with multiple risk factors need to be followed differently. Walz also concluded that the rate of a favorable pathological result increased in relation to risk factors. A regrading of up to 20% was seen after re-classification at the final pathological examination[15]. The present study categorized risk by using pathological T stage and GS, to exclude the effect of restaging. Previous studies have thoroughly discussed therapeutics in relation to biopsy GS and T stage, and satisfactory outcomes have been achieved. RP as primary treatment is considered appropriate for any patient with clinically localized PCa, and assessing the need for adjuvant therapy can substantially affect outcomes. Pathological data from extracted specimens provide precise staging and allow patients to be classified for follow-up as those with a single or multiple high-risk factors. Patients with multiple risk factors have at higher risk of BCR than those with 1 risk factor. If oncological outcomes differ according to number of risk factors, appropriate follow-up and need for adjuvant therapy should be individualized. A patient with 1 risk factor can be followed in the conventional way, but therapeutic intervention should be considered for patients with multiple factors. To our knowledge, the present study is the first to use pathological GS and T stage as factors indicating high risk, and the first to compare BCR in relation to number of risk factors.

Boorjar et al reported that the 10-year cancer-specific and overall survival rates for high-risk PCa patients treated with RP were 92% and 77%, respectively, during a median follow-up of 10.2 years. They concluded that RP and ADT plus EBRT for high-risk PCa patients yields similar long-term cancer control[16]. The primary goal of RP is removal of the entire prostate gland. Despite advances in surgical techniques, the prevalence of PSM is reported to range from 25% to 40%[17]. A randomized study found no difference in PSM between RARP and open RP (ORP) and concluded that outcome depends on the technical proficiency of the surgeon[18]. Other studies reported that the learning curve and PSM rate will decrease rapidly with RARP and that RARP will eventually yield lower rates than open RP and LRP. In the present study, the PSM rate was 48.6%, higher than in previous studies. Serial whole-mount sections were reviewed to determine the site of the tumor in the prostate gland, which may be a reason for the higher incidence of PSM in this study. The BCR rate in patients with PSM is approximately 50% (range, 42-64%). In the present study, 68.4% of patients with PSM developed BCR (**Table 3**), which is comparable to previous findings. Some studies used maximum diameter of the resection margin as a parameter and found that a margin of <1 mm of the speci-

men was associated with a satisfactory outcome. Cao et al reported that GS at the PSM and the linear length of the PSM may be predictive factors[19]. A wide resection may decrease the BCR rate for high-risk PCa in the future. The EAU guideline recommends an extended PLND (ePLND) rather than a limited PLND when a PLND is performed, but maintains that a PLND is not indicated for patients with a predicted probability of nodal metastasis of <2% on nomograms. Updated nomograms can be useful when performing ePLND[20], although the significance of PLND has not been verified by a randomized controlled trial. In the present study, limited PLND excluding the lymph nodes between the internal iliac artery and the obturator nerve was performed when the predicted probability of nodal metastasis was ≥3% on the Japanese Partin nomogram[21]. Of the 222 patients, only 1 patient had positive lymph nodes. Despite racial differences among the populations studied, this result is much lower than those of previous studies. Because of difficulties in surgical technique, ePLND is challenging in LRP, and limited LND is often performed. For patients with multiple risk factors, ePLND needs to be considered, and outcomes when performed by RARP should be evaluated in terms of disease control. RARP was approved by the Japanese medical insurance system in 2012, and almost all RPs were performed by RARP at our hospital. The BCR-free rate according to PSM and PLND performed by the laparoscopic technique is valuable information that can be applied to RARP. The shorter learning curve of surgical techniques for RARP, as compared with LRP, is beneficial and should decrease PSM and increase resected lymph node specimens.

Neoadjuvant therapy before radical prostatectomy does not improve OS or disease-free survival (DFS) but significantly reduces PSM rate and lymph node invasion and increases organ confinement[22]. Previous studies reported that adjuvant ADT improved local and systemic control after RP for high-risk PCa, although there was no difference in BCR[23]. PSM was not an independent risk for BCR in the present study, and immediate hormone therapy or salvage radiation was not performed at our center. Vesely reported that postoperative PSA kinetics could be useful to select candidates for immediate radiation, thus avoiding overtreatment[24]. The present definition of high-risk PCa differed from that of most previous reports. Biopsy GS and clinical T stage were used to classify risk and categorize outcomes, although the most valuable information-resected specimens, a benefit of surgical treatment-was not included in the classification. Downgrading was reported for 58% of cT1c and 51% of biopsy GS 8 cancers on whole-mount prostate sections[25], and restaging would likely affect outcomes. Many patients classified as high-risk on biopsy are treated surgically and have a good prognosis. In the present study, serial whole-mount sections of resected specimens were reviewed to determine histopathological features, to avoid restaging, and pathological GS and T stage were defined as risk factors for classification. Patients with multiple risk factors had a lower BCRFS rate than patients with a single risk factor. This finding suggests that patients with only 1 risk factor can be cured by RP alone, whereas patients with multiple risk factors need multidisciplinary treatment to prevent progression and achieve a satisfactory outcome. Precise pathological data are essential to determine the necessity of adjuvant hormonal and radiation therapy for patients with multiple risk factors. Widespread use of RARP and new devices and technologies, as well as improvements in surgical technique, have made RP a strategic option to cure patients with high-risk PCa. In the era of RARP as standard treatment, risk factors should be considered when selecting optimal treatments.

Conclusion

In conclusion, long-term outcomes for high-risk prostate cancer are satisfactory after RP. The BCR-free rate was significantly better for patients with a single risk factor than for those with multiple risk factors.

Conflict of Interest: None.

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