Characteristics and Oncological Outcome of Clinical T3a Prostate Cancer Patients Undergoing Radical Prostatectomy in the Multi-Parametric MRI Era

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Abstract

We aimed to reveal the association between the method of diagnosis (multi-parametric magnetic resonance imaging [mpMRI] and digital rectal examination [DRE]) and oncological outcomes of patients with clinical T3a (cT3a) prostate cancer after radical prostatectomy (RP) and stratify them according to oncological risk.

We included 132 cT3a prostate cancer patients who underwent RP between 2008 and 2018. The biochemical recurrence (BCR)-free survival rate was evaluated according to the method of diagnosis (mpMRI alone; mpMRI group vs. DRE [with or without mpMRI]; DRE group). Several preoperative factors were evaluated in the multivariate analysis. Patients were divided into risk groups by our prediction model.

The mpMRI group had significantly longer BCR-free survival than the DRE group (p<0.0001). The method of diagnosis (hazard ratio [HR]=2.69; 95% confidence interval [CI] 1.45-5.06; p=0.0017) and % positive cores (HR=4.36; 95% CI 1.14-16.5; p=0.031) were independent prognostic factors. Patients were divided into three risk groups based on these factors. There was a significant difference in BCR-free survival rate among the groups (p=0.0002).

The method of diagnosis of cT3a prostate cancer was associated with BCR-free survival, and we categorized patients into risk groups. These assessments were attributable to the appropriate therapeutic strategy for patients with cT3a prostate cancer.

Introduction

Clinical T3a (cT3a) prostate cancer is present in 10–40% of all newly diagnosed prostate cancer, and they are heterogenous in terms of pathological T (pT) stage, biopsy Gleason score (GS), and initial prostate specific antigen (PSA) level.[1-4] The oncological outcomes of patients with cT3a prostate cancer are also variable.[1-4] Available treatment strategies for cT3a prostate cancer are selected based on clinical characteristics as well as personal preference. Several studies have compared oncological outcomes and complications after treatment, but there is no clarified protocol for a multimodal treatment strategy for cT3a prostate cancer.[5-7] As some patients with cT3a prostate cancer are at high risk of symptomatic progression, patients with cT3a prostate cancer should be divided into multiple oncological risk groups and undergo appropriate management. Establishing an oncological risk classification system for cT3a prostate cancer is one of the most significant challenges in prostate cancer treatment at present.

Although the diagnosis of cT stage in prostate cancer was conventionally based on the results of digital rectal examination (DRE), multiparametric magnetic resonance imaging (mpMRI) is currently being used for more accurate preoperative diagnosis. The diagnostic accuracy of DRE to detect local invasion and predict patients' prognosis is limited because locally invasive tumors are often under-staged.[8] In contrast, the positive predictive value (PPV) of mpMRI for extracapsular extension and the negative predictive

value of mpMRI for seminal vesicle invasion are relatively high.[9] Advancements in mpMRI and development of the Prostate Imaging Reporting and Data System have improved the accuracy of prostate cancer detection and cT staging.[10-12] However, whether the method of diagnosis can be used to predict oncological outcomes remains unclear.

The aim of this study was to divide patients with cT3a prostate cancer into several risk groups and predict their oncological outcomes accurately in order to identify appropriate therapeutic strategies. We evaluated some preoperative characteristics, such as the method of diagnosis and mpMRI findings, made a clear distinction between this study and previous studies which focused on pathological findings.

Results

Patients characteristics

The preoperative characteristics of the patients in this study are shown in Table 1. Out of the 132 eligible patients with cT3a prostate cancer, 38 (28.8%) patients had anterior cancer, 28 (21.2%) had lateral cancer, and 66 (50%) had posterior cancer. There were 89 patients diagnosed using mpMRI alone (mpMRI group) and 43 patients diagnosed using DRE with or without mpMRI (DRE group). There was no significant difference in age, GS, initial PSA, or follow-up period between the two groups; however, there were significant differences in the site of the tumors and % positive cores. Out of the 66 patients with cT3a posterior cancer, 31 (47%) patients were diagnosed with cT3a on mpMRI in whom DRE did not show cT3a prostate cancer. The remaining 35 (53%) patients were diagnosed with cT3a prostate cancer based on the results of DRE. There was no significant difference in age, initial PSA, follow-up period, or % positive cores between the two groups.

Pathological findings

In the entire cohort, 60.6% of patients in the mpMRI group and 69.8% of patients in the DRE group had pT3 stage cancer. There was no significant difference between these two groups ($p = 0.21$). However, the percentage of pT3 patients was significantly higher in patients diagnosed using both mpMRI and DRE (80.7 %; $p = 0.03$). Out of the 66 patients with cT3a posterior cancer, the percentages of pT3 patients in the mpMRI group and the DRE group were 83.9 % and 68.6 %, respectively. There was no significant difference between the two groups. Pathological findings from radical prostatectomy (RP) specimens are shown in Table 2.

Oncological outcomes

In the entire cohort, the 5- and 10-year BCR-free-survival rates of the mpMRI and DRE groups were 74.7% and 65.6%, respectively, in the mpMRI group, and 63.3% and 27.5%, respectively, in the DRE group. The BCR-free survival of the mpMRI group was significantly higher than that of the DRE group (Figure1 (a), $p < 0.0001$). Among the patients with posterior prostate cancer, the 5- and 10-year BCR-free-survival rates of the mpMRI and DRE groups were 67.4% and 57.8%, respectively, in the mpMRI group, and 36.0% and

25.7%, respectively respectively, in the DRE group. The BCR-free survival of the mpMRI group was significantly higher than that of the DRE group (Figure 1(b), $p = 0.013$).

Multivariate analysis for BCR-free survival

First, multivariate analysis for BCR-free survival was performed using the entire cohort. In the full model, the method of diagnosis (HR = 2.69; 95% CI 1.45-5.06; $p = 0.0017$) and % positive cores (HR = 4.36; 95% CI 1.14–16.5; $p = 0.031$) were independent prognostic factors for BCR. In the reduced model, the method of diagnosis (HR = 2.87; 95% CI 1.57–5.34; $p = 0.0007$) and % positive cores (HR = 3.62; 95% CI 0.97–13.0; $p = 0.056$) remained independent prognostic factors for BCR. Second, multivariate analysis for BCR-free survival was performed for patients with cT3a posterior cancer. In the full model, the method of diagnosis (HR = 2.68; 95% CI 1.45-5.06; $p = 0.0017$) was an independent prognostic factor for BCR (Table 3). In the reduced model, the method of diagnosis (HR = 2.87; 95% CI 1.85–6.10; $p < 0.0001$) remained the only independent prognostic factor for BCR (Table 4).

Prediction models for BCR

In the receiver operating characteristic (ROC) curve analysis, estimation of the area under the curve (AUC) determined the cut-off point for % positive cores as 25%. The sensitivity, specificity, and PPV were 89.1%, 23.3%, and 38.3%, respectively. The patients were divided into three groups based on the method of diagnosis and % positive cores according to the results of the multivariate analysis. The low-risk group included patients diagnosed by mpMRI alone and whose % positive cores were less than 25%. The intermediate-risk group included patients diagnosed by mpMRI alone and whose % positive cores was more than 25% and patients diagnosed by DRE (with/without mpMRI) and whose % positive cores was less than 25%. The high-risk group included patients diagnosed by DRE (with/without mpMRI) and whose % positive cores was more than 25%. The 5- and 10-year BCR-free-survival rates of the low-, intermediate-, and high-risk groups were 86.4% and 86.4%, 68.2% and 57.7%, and 38.1% and 28.6%, respectively. There was a significant difference in the BCR-free survival rates among the three groups (Figure 1(c), $p = 0.0002$).

Discussion

First, patients with cT3a prostate cancer had heterogenous oncological outcomes after RP and can be divided into several oncological risk groups. Heterogeneity of high-risk prostate cancer has been revealed, and the previous study presents a stratification of patients with high-risk prostate cancer into oncological risk subgroups based on biopsy GS and initial PSA as well as cT stage.[13] The management of cT3a prostate cancer, including RP, should be determined appropriately depending on their prognostic factors because of their risk of BCR and metastasis.[1] RP with extended pelvic lymph node dissection as part of a multimodal treatment strategy for cT3 prostate cancer is strongly recommended in the EAU prostate cancer guidelines.[14] A previous study reported that RP as a primary treatment for cT3-4 prostate cancer improved cancer-specific survival and overall survival compared to upfront radiation therapy with

androgen deprivation therapy.[15] Furthermore, salvage radiation therapy after RP as a primary treatment strategy decreases the risk of urinary incontinence and erectile dysfunction compared to salvage RP after radiation therapy as a primary treatment.[7] With the recently expanded indication for RP, preoperatively predicting a patient's risk of BCR and metastasis is essential for the treatment strategy. We successfully divided patients into three oncological risk groups, using % positive cores and the method of diagnosis, and observed that the BCR-free survival rates were significantly different among these three groups. Thus, the identified risk classification can be used as a criterion to inform the therapeutic strategy.

Second, the method of diagnosis was the independent prognostic factors of oncological outcomes. We cannot detect anterior cancers by DRE, and patients with posterior cancer accounted for 81.4% of the DRE group in this study. It has been reported that transitional zone/anterior cancers diagnosed by RP specimens are commonly seen in Japanese cohorts; however, anterior cancers are less aggressive.[16] Additionally, the mpMRI has improved the chances of detecting local invasion whose prognosis are better. Previous studies reported that the maximum joint sensitivity and specificity for detecting local invasion using mpMRI reached 71%.[9] In clinical fields, mpMRI is usually used in combination with DRE for higher diagnostic accuracy. In this study, the PPV of both mpMRI and DRE when used to diagnose local invasion was significantly higher than using either modality alone. Therefore, the method of diagnosis reflects cancer locations and local invasion which affect oncological outcomes. This is the first study to reveal that the method of diagnosis is associated with oncological outcomes after RP, and to establish a prediction model composed of preoperative factors only.

Our study has some limitations and sources of bias. First, this was a retrospective, non-randomized study. Therefore, the patient groups have differed in several baseline characteristics that were associated with differences in BCR. Second, multiple urologists performed DRE, which may have led to inconsistencies in examination findings. Finally, we used BCR as the endpoint because the median follow-up period was 4.9 years, which was too short to estimate prostate cancer metastatic-free survival, cancer specific survival, or overall survival.

In conclusion, the method of diagnosis of cT3a prostate cancer was a strong prognostic factor for BCR-free survival, and we established a prediction model for BCR-free survival including the methods of diagnosis and %positive cores. Using this model, we successfully divided patients with cT3a prostate cancer into three oncological risk groups. Therefore, the prediction model and the risk classification have potential in therapeutic decision-making. Future studies should evaluate the accuracy of this oncological risk classification and reveal the optimal therapeutic strategy for each oncological risk group.

Materials And Methods

Patients

Cancer Institute Hospital of Japanese Foundation for Cancer Research ethics committee review board approved this retrospective single-institution study (study number: 0994) and waived informed consent

requirements and all methods were performed in accordance with the relevant guidelines and regulations. All patients provided written informed consent. A total of 1771 consecutive Japanese patients with localized prostate cancer underwent RP at the Cancer Institute Hospital, Tokyo, Japan between September 2008 and December 2018. Out of these 1771 patients, we reviewed the medical records of 328 patients diagnosed with cT3aN0M0. Out of these 328 patients, 158 patients who received neoadjuvant hormonal therapy before surgery and 78 patients who did not undergo mpMRI to determine the cT stage were excluded from this study. Finally, 132 patients with cT3a prostate cancer who underwent preoperative mpMRI before RP were included in this study. The cT stage of all 132 patients was estimated by experienced urologists using mpMRI and DRE findings. After RP, 118 patients (89.4 %) were prospectively observed without any adjuvant treatment until PSA failure was confirmed, and 14 patients (10.6%) received salvage hormonal therapy for persistently elevated PSA following RP. The clinical stage was determined according to the 2010 TNM classification.[17]

Surgery

Of the 132 patients in this study, 90 (68.2%) and 42 (31.8%) patients underwent open RP and robot-assisted RP, respectively. Open RP was performed as reported previously.[18-20] All patients underwent pelvic lymph node dissection. Thirty-seven (28.0 %) patients underwent unilateral or bilateral nerve-sparing procedures.

mpMRI image analysis

Patients that underwent identical imaging procedures using 3-Tesla or 1.5-Tesla MRI were included into the image analysis. All MRI examinations were performed on four scanners at 3-Tesla (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany; Discovery MR750w, GE Healthcare, Waukesha, WI, USA; and Vantage Titan, Canon Medical Systems, Otawara, Tochigi, Japan), and 1.5-Tesla (Vantage Excelart; Canon Medical Systems). Following routine T1- and T2-weighted imaging, Axial diffusion-weighted single-shot spin-echo echo planar sequences were acquired using the following parameters: MAGNETOM Skyra, b value = 0 and 2000 s/mm2; Repetition time (TR)/ Echo time (TE) = 6400/70 ms; section thickness/gap = 3.6 mm/0 mm; field of view (FOV) = 300 × 240 mm; acquisition matrix = 120 × 96; number of excitation (NEX)=7; Discovery MR750w, b value = 0 and 2000 s/mm2; TR/TE = 5300/95 ms; section thickness/gap = 3.6 mm/0 mm; FOV = 280 × 280 mm; acquisition matrix = 96 × 160; NEX = 13; Vantage Titan, b value = 0 and 2000 s/mm2; TR/TE = 4741/95 ms; section thickness/gap = 3.6 mm/0 mm; FOV = 300 × 260 mm; acquisition matrix = 112 × 80; NEX = 10; Vantage Excelart, b value = 0 and 1500 s/mm2; TR/TE = 3000/100 ms; section thickness/gap=4.2 mm/0 mm; FOV = 280 × 280 mm; matrix size = 112 × 112; NEX = 8. ADC maps were automatically generated. All eligible patients underwent mpMRI with the above settings and imaging protocols.

An experienced urological radiologist (T.Y.) examined the preoperative mpMRI of eligible patients. The diagnostic criteria of cT3a prostate cancer on mpMRI were asymmetry or invasion of the neurovascular bundles, a bulging prostatic contour, an irregular or spiculated margin, obliteration of the rectoprostatic

angle, and a tumor-capsule interface greater than 12mm.[21] The site of the extracapsular lesion on mpMRI was divided into three locations (anterior, lateral, and posterior).

Oncological outcomes

The biochemical recurrence (BCR)-free survival rate was evaluated according to the method of diagnosis (mpMRI alone vs. DRE [with or without mpMRI]). The BCR-free survival rate was also evaluated based on the method of diagnosis for patients with posterior extracapsular lesions on mpMRI. After RP, postoperative PSA levels were measured every 3 months during first 2 years of follow-up, every 6 months during years 3-5, and annually thereafter. BCR was defined as a postoperative PSA level ≥ 0.2 ng/mL.[22, 23]

Statistical analysis

The differences in clinicopathological variables based on the method of diagnosis were analyzed by Fisher's exact test, the Mann-Whitney U test, and the Wilcoxon signed-rank test. GS was compared using the Wilcoxon two sample test. The proportion of risk category and pT classification were compared using the Mann-Whitney U test. Age and PSA were compared using the Wilcoxon signed-rank test. The BCR-free survival rates, based on the method of diagnosis, were estimated using the Kaplan-Meier method, and differences were assessed with the log-rank test. Multivariate analysis was assessed by a Cox proportion hazard model. In multivariate analysis, the method of diagnosis (mpMRI alone vs. DRE [with or without mpMRI]), % positive cores (continuous), initial PSA (continuous), and GS (<8 vs. ≥8) were evaluated as possible prognostic factors. Estimates from receiver operating characteristics (ROC) curve analysis-derived area under the curve (AUC) determined the cut-off points of % positive cores (defined as the ratio of positive cores in a systematic biopsy specimen). All p-values were two-sided. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed with JMP version 13.2.1 software (SAS Institute Inc., Cary, NC, USA)

Declarations

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Not applicable

Additional information

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Availability of data and material

The data that support the findings of this study are available on request from the corresponding author, [S.Y.]. The data are not publicly available due to their containing information that could compromise the privacy of patients.

Author contributions statement

Conceptualization: [Shinya Yamamoto]; Methodology: [Shinya Yamamoto]; Formal analysis and investigation: [Shinya Yamamoto]; Writing - original draft preparation: [Kasumi Kaneko Yoshitomi]; Writing - review and editing: [Shinya Yamamoto],[Tatsuya Yamamoto], [Eri Fukagawa], [Kosuke Hamada], [Yusuke Yoneoka], [Motohiro Fujiwara], [Ryo Fujiwara], [Tomohiko Oguchi], [Yoshinobu Komai], [Noboru Numao], [Takeshi Yuasa], [Iwao Fukui]; Funding acquisition: [Shinya Yamamoto]; Resources: [Shinya Yamamoto]; Supervision: [Junji Yonese].

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Tables

Table 1: Patient characteristics

Method of diagnosis	MRI alone	DRE (with/without MRI)	p value
	(n = 89)	(n = 43)	
Median age	68	67	0.68
Biopsy GS			0.084
5-7, n (%)	67 (75.3)	26 (60.5)	
8-10, n (%)	22 (24.7)	17 (39.5)	
Median PSA (ng/mL)	10.0	9.9	0.97
Median follow-up period (year)	5.1	4.7	0.44
Cancer location			< 0.0001
Anterior	37 (41.6)	1 (2.3)	
Lateral	21 (23.6)	7 (16.3)	
Posterior	31 (34.8)	35 (81.4)	
Median % positive core (%)	33.3	50.0	0.0095
DRE, digital rectal examination; PSA, prostate-specific antigen; MRI, magnetic resonance imaging; pT, pathological tumor stage; pN, pathological node stage; GS, Gleason score.			

Table 2: Pathological findings on radical prostatectomy specimens

Method of diagnosis	MRI alone	DRE (with/without MRI)	p value
	(n = 89)	(n = 43)	
pT			0.21
2a	7 (7.9)	2 (4.7)	
2c	28 (31.5)	11 (25.6)	
3a	44 (49.4)	19 (44.2)	
3b	10 (11.2)	11 (25.6)	
Surgical margin status			0.70
positive	57 (64.0)	29 (67.4)	
negative	32 (36.0)	14 (32.6)	
pN status			0.90
0	78 (87.6%)	38 (88.4%)	
1	11 (12.4%)	5 (11.6%)	
Pathological GS			0.53
5-7	68 (76.4%)	28 (65.1%)	
8-10	21 (23.6%)	15 (34.9%)	
DRE, digital rectal examination; PSA, prostate-specific antigen; MRI, magnetic resonance imaging; pT, pathological tumor stage; pN, pathological node stage; GS, Gleason score.			

Table 3: Multivariant analysis of predictors for BCR in the entire cohort

	Full model			Reduced model		
Variables	HR	95%CI	p value	HR	95%CI	p value
Method of diagnosis			0.0017			0.0007
MRI only	0.37	0.20-0.69		0.35	0.19-0.64	
DRE (with/without MRI)	2.69	1.45-5.06		2.87	1.57-5.34	
% Positive cores	4.36	1.14-16.5	0.031	3.62	0.97-13.0	0.056
PSA (ng/mL)	1.84	0.22-10.4	0.55			
Biopsy GS			0.076			
5-7	0.57	0.31-1.06				
8-10	1.77	0.94-3.25				
BCR, biochemical recurrence; GS, Gleason score; DRE, digital rectal examination; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval						

Table 4: Multivariant analysis of predictors of BCR in patients with clinical T3a prostate cancer at posterior site

	Full model			Reduced model		
Variables	HR	95%CI	p value	HR	95%CI	p value
Method of diagnosis			0.0017			< 0.0001
MRI only	0.57	0.31-1.06		0.30	0.16-0.54	
DRE (with/without MRI)	2.68	1.45-5.06		2.87	1.85-6.10	
% Positive cores	4.36	1.14-16.5	0.16			
PSA (ng/mL)	1.84	0.22-10.4	0.55			
Biopsy GS			0.076			
5-7	0.57	0.31-1.06				
8-10	1.77	0.94-3.25				
BCR, biochemical recurrence; GS, Gleason score; DRE, digital rectal examination; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval						

Figures

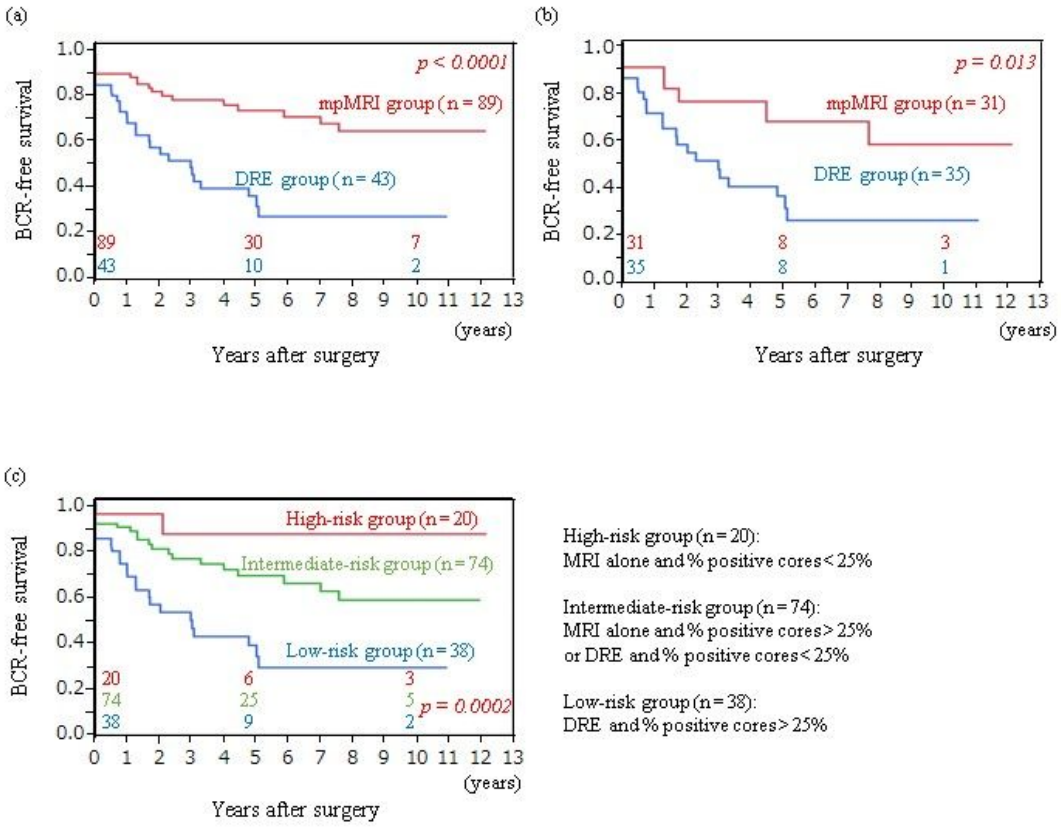
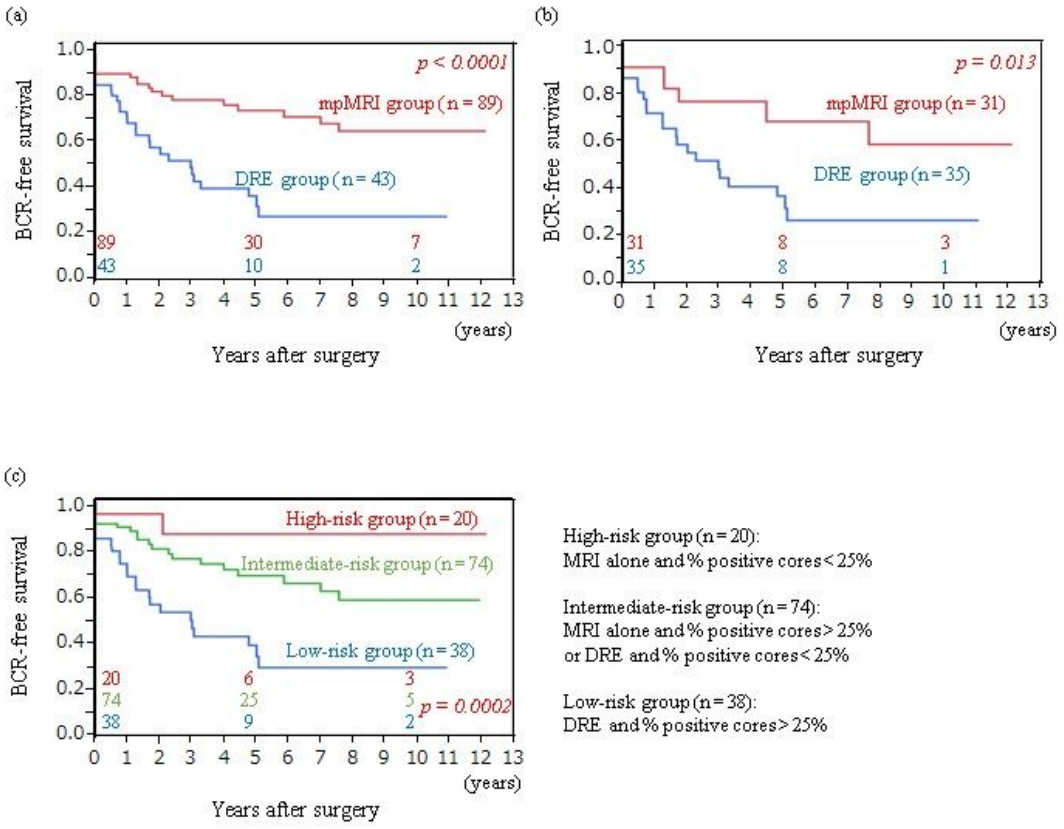


Figure 1

(a) Kaplan-Meier analysis of the biochemical recurrence (BCR)-free survival rate according to the method of diagnosis in the entire cohort. (b) Kaplan-Meier analysis of the BCR-free survival rate according to the method of diagnosis among patients with posterior prostate cancer (c) Kaplan-Meier analysis of the BCR-free survival rate of patients in the high-, intermediate-, and low-risk groups

Fig. 1



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