Pathology & Oncology Research (2020) 26:2115–2121
https://doi.org/10.1007/s12253-019-00762-6

ORIGINAL ARTICLE

Impact of the Proportion of Biopsy Positive Core in Predicting Biochemical Recurrence in Patients with Pathological Pt2 and Negative Resection Margin Status after Radical Prostatectomy

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Received: 11 July 2019 / Accepted: 10 October 2019 / Published online: 8 January 2020

Abstract

This study aimed to determine the prognostic factors associated with biochemical recurrence (BCR) after radical prostatectomy (RP) in patients with pathological T2 (pT2) prostate cancer (PCa) and negative resection margin (RM) status at a single institution. In this retrospective study, we examined 386 patients who were diagnosed with pT2 PCa with negative RM after RP. The length of the tumor was provided for each biopsy core and the overall percentage of PCa was calculated by a pathologist at our institution. We estimated the BCR-free survival (BRFS) in these patients. Univariate and multivariate analyses were performed using the Cox proportional hazard model to determine the risk factors of BCR. The median age of the participants was 68 years, and their initial prostate-specific antigen level was 6.55 ng/mL. The median follow-up period was 85.7 months. The 5-year BRFS rate of the participants was 89.0%. The 5-year BRFS rates were 89.8% in patients with a biopsy Gleason score of 6, 90.4% in those with 7, and 64.1% in those with ≥8 ($P = 0.007$). The BRFS rate was 93.3% in patients who had a biopsy positive core ≤20% and 82.0% in those who had ≥21% ($P = 0.001$). Based on the multivariate analysis, the proportion of biopsy positive core was significantly associated with BCR. The proportion of biopsy positive core may predict preoperative covariates in patients with pT2 PCa and negative RM status after RP.

Keywords Organ-confined prostate cancer · Negative surgical margin · Radical prostatectomy · Biochemical recurrence · Proportion of biopsy positive core · Biopsy Gleason score

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Introduction

The incidence of prostate cancer (PCa) is the highest in men worldwide [1]. In Japan, PCa is the fourth commonest malignancy in men, and the Japanese National Cancer Institute revealed that approximately 78,400 men were newly diagnosed with PCa in 2018 [2]. Radical prostatectomy (RP) provides a favorable curative outcome, particularly in patients with pathologically organ-confined disease (pT2) and a life expectancy >10 years [1]. The oncological goal of RP is the complete removal of the prostate and seminal vesicles without positive resection margin (PRM) [3]. Despite excellent surgical treatment, up to 40% of patients will have biochemical recurrence (BCR) after RP [3]. Several studies have identified the independent predictors of BCR in patients with PCa who underwent RP, which include preoperative serum prostate-specific antigen (PSA) levels, Gleason score (GS), pathological stage (pT), resection margin (RM) status, perineural invasion (PNI), lymphovascular invasion (LVI), and percent tumor

involvement [3–9]. Although patients with pT2 and negative RMs (NRMs) may have excellent prognosis after RP, 4%–32% of patients with pT2 PCa develop BCR within 10 years after RP [8, 10, 11].

The present study aimed to determine the prognostic factors associated with BCR after RP in Japanese patients who were diagnosed with pT2 PCa with NRMs at a single institution.

Patients and Methods

Patient Characteristics

In this retrospective study, we reviewed the clinical and pathological records of 1503 patients with PCa who underwent RP and bilateral pelvic lymphadenectomy (PLND) between July 1996 and March 2018 at Hirosaki University. Of these patients, 386 who had pT2 PCa with NSM status were examined. Patients with histologically confirmed clinical stage (cT)T1a–T3 PCa without lymph node (LN) involvement or distant metastasis were considered eligible. The exclusion criteria were patients with PRM status, those with pathological LN involvement, those receiving neoadjuvant or adjuvant therapy, those who previously received radiation therapy to the prostate or pelvis, and those treated with finasteride or dutasteride before surgery. In this analysis, the following patient characteristics were collected: age, body mass index, initial serum PSA level, cT, biopsy GS, prostate volume, and number of prostate biopsy and biopsy positive core. The postoperative variables included pathological T stage, pathological GS, PNI status, and tumor volume (TV). Information about the patients and the characteristics of the tumor was obtained from medical charts. The patients were divided into two groups according to BCR: patients without BCR group and patients with BCR group.

The study protocol was approved by the institutional review board of Hirosaki University (no. 2013–349) and Gifu University (no. 2019–062), and informed consent was obtained from the participants.

Treatment

All patients underwent a 10- to 12-core transrectal ultrasound-guided prostate biopsies [12]. In this study, the participants did not undergo multi-parametric magnetic resonance imaging (mpMRI) before prostate biopsy. In addition, all patients were not evaluated to predict biopsy outcomes using the Prostate Imaging Reporting and Data System version 2.0 (PI-RADS v2) [13].

The participants in the present study underwent RP and PLND. Our surgical technique for open RP has been previously described in detail [14]. Robot-assisted laparoscopic RP was performed from July 2011 to March 2018 [15]. All patients in the present study underwent the same lymphadenectomy procedure, which included the removal of pelvic LNs in both sides [16].

Pathological Analysis

The following baseline information was obtained from each patient: complete history and physical examination findings, Eastern Cooperative Oncology Group Performance Status score, and abdominal and pelvic computed tomography (CT) scan and MRI, chest radiography and CT, and bone scintigraphy findings.

At our institution, a single pathologist evaluated the GSs of prostate biopsies and prostatectomy specimens according to the International Society of Urological Pathology 2005 guidelines [17]. The percentage of PCa was given for each biopsy core. The overall percentage of PCa defined was calculated by a pathologist at our institution. All prostatectomy specimens were sectioned using the whole-mount technique. The apex of the prostate was shaved perpendicular to the prostatic urethra. The bladder neck margin was coned from the specimen and sectioned perpendicularly. The remaining prostate was completely sectioned at 3-mm intervals along a plane perpendicular to the urethral axis. Immunohistochemical staining was not performed in this study.

Tumor staging was performed according to the staging system defined in the American Joint Committee on Cancer Staging Manual [18].

Follow-Up Schedule

All patients were followed up by assessing serum PSA and testosterone levels every 3 months for 5 years and every 6 months thereafter. BCR was defined as serum PSA levels >0.2 ng/mL. If the PSA levels did not decrease to <0.2 ng/mL after surgery, the date of RP was defined as the date of disease recurrence.

Endpoints and Statistical Analysis

The primary endpoint was BRFS. Data were analyzed using the Statistical Package for the Social Sciences software version 24.0 (IBM Corp., Armonk, NY, the USA). Survival after RP was analyzed using the Kaplan–Meier method. The relationship between survival and subgroup classification was analyzed using the log-rank test. The date of surgery was used as the starting point for the estimates of BRFS after RP. Differences between patients without BCR and patients with BCR groups were compared using the Student's t test or Mann–Whitney$U$ test for categorical variables. Multivariate analysis was performed using the Cox proportional hazard model. All P values were two-sided, and the significance level was set at <0.05.

Results

Patient Characteristics

A total of 386 patients who had pT2 PCa with NRM were enrolled in this study. The demographic data of the participants, according to BCR, are listed in Table 1. All patients were diagnosed with PCa based on the histological examination findings of the specimens obtained during prostate biopsy. The median age of the participants was 68 (interquartile range [IQR]: 63–71) years, and the initial PSA level was 6.55 (IQR: 5.00–9.04) ng/mL. The median follow-up period was 85.7 (IQR: 46.0–118.9) months. The initial PSA levels were relatively higher in patients with BCR group than in patients without BCR group; however, no significant difference was observed in both groups.

Pathological Outcomes

The pathological evaluation data of the participants are listed in Table 2. PNI and TV were relatively higher in patients with BCR group than in patients without BCR group. However, all covariates were not significantly different in both groups. Additionally, it was found that the prostate and tumor volumes were not mutually associated. ($P = 0.199$).

Oncological Outcomes

The 5- and 10-year BRFS rates of the participants were 89.0% and 87.8%, respectively. The 5- and 10-year overall survival rates of the participants were 98.9% and 96.0%, respectively. At the end of the follow-up period, 40 (10.4%) patients developed BCR and 10 (2.6%) died after RP. One patient died of PCa and nine of other causes, including other types of cancer in seven patients, chronic kidney disease in one patient, and an unknown cause in one patient. The biopsy of the patient who died of PCa had a GS of 9 and GS percentage of 40%. The patient developed BCR at 37.7 months and castration-resistant PCa at 72.1 months after RP.

According to biopsy GS, the 5-year BRFS rates were 89.8% in patients with a biopsy GS of 6, 90.4% in those with 7, and 64.1% in those with ≥8 (Fig. 1). BRFS in patients with a

Table 1 Preoperative patients' characteristics

	Patients without BCR ($N = 346$)	Patients with BCR ($N = 40$)	*P*
Age (year, median, IQR)	67 (63–71)	68 (65–69)	0.583
Body mass index (kg/m^2, median, IQR)	23.9 (22.1–25.4)	24.2 (23.2–25.9)	0.221
Initial PSA (ng/mL, median, IQR)	6.44 (5.00–8.88)	7.56 (5.35–10.54)	0.075
Clinical T stage, number (%)			0.884
T1c	250 (72.3)	27 (67.5)	
T2a/b	80 (23.1)	12 (30.0)	
T2c	4 (1.2)	1 (2.5)	
T3	12 (3.5)	0	
Biopsy Gleason score, number (%)			0.400
6	58 (16.8)	0	
7	275 (79.4)	34 (85)	
≥8	13 (3.8)	6 (15)	
D'Amico risk classification, number (%)			0.09
Low	39 (11.3)	4 (10)	
Intermediate	278 (80.3)	28 (70)	
High	29 (8.4)	8 (20)	
Proportion of biopsy positive core (%, median, IQR)	20 (10–30)	30 (18.2–40)	0.001
Prostate volume (mL, median, IQR)	36.4 (26.5–48.0)	33.6 (29.2–46.3)	0.786
PSA density ($ng/mL/cm^3$, median, IQR)	0.18 (0.13–0.26)	0.2 (0.15–0.35)	0.109
Follow-up period (months, median, IQR)	80.8 (41.2–114.3)	108.2 (93.7–142.2)	<0.001

BCR biochemical recurrence; *IQR* interquartile range; *PSA* prostate-specific antigen

Table 2 Pathological outcomes

	Patients without BCR (N = 346)	Patients with BCR (N = 40)	*P*
Pathological T stage, number (%)			0.754
T2a	92 (26.0)	10 (25.0)	
T2b	25 (7.2)	6 (15.0)	
T2c	229 (66.2)	24 (60.0)	
Pathological Gleason score, number (%)			0.143
≤6	25 (7.2)	1 (2.5)	
7	262 (75.7)	30 (75.0)	
≥8	59 (17.1)	9 (22.5)	
Perineural invasion, number (%)			0.073
Negative	143 (41.3)	10 (25.0)	
Positive	203 (58.7)	30 (75.0)	
Tumor volume (cm^3, median, IQR)	0.93 (0.39–2.10)	1.22 (0.52–2.29)	0.188

BCR biochemical recurrence; *IQR* interquartile range

biopsy GS ≥8 was significantly lower than that with a biopsy GS of 6 or 7 ($P = 0.007$ and 0.001, respectively). Regarding D'Amico risk stratification, the 5-year BRFS rates in the low-, intermediate-, and high-risk groups were 86.5%, 90.7%, and 76.9%, respectively (Fig. 2). BRFS in the high-risk group was significantly lower than that in the intermediate group ($P = 0.018$). According to the proportion of biopsy positive core, the BRFS rate was 93.3% in patients with a biopsy positive core ≤20% and 82.0% in those with ≥21% (Fig. 3). BRFS in patients with a biopsy positive core ≤20% was significantly higher than that in counterparts ($P = 0.001$). Based on the multivariate analysis, the proportion of biopsy positive core was significantly associated with BCR (Table 3).

Discussion

Although several patients with organ-confined PCa achieve disease-free survival after RP, the complete removal of the prostate with NRMs does not guarantee the absence of disease progression [19]. Preoperative serum PSA levels, GS, pT, and PRM status are the widely accepted significant prognostic factors according to BCR after RP [20]. Of these factors, the PRM status was associated with a poor prognosis, including BCR and PCa-specific mortality [3, 5, 6]. Zhang et al. conducted a meta-analysis of high-quality retrospective cohort studies to assess the prognostic value of PRM in BCR [7]. Results showed that PRM was associated with a higher risk of BCR in the univariate (hazard ratio [HR] = 1.56; $P < 0.001$)

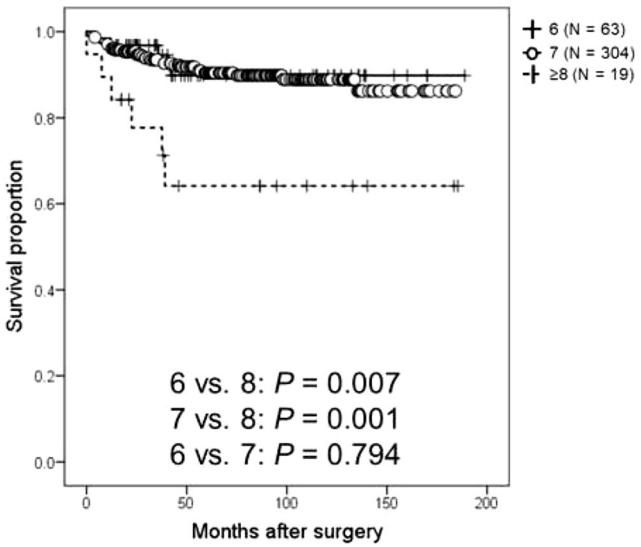

Fig. 1 According to biopsy Gleason score (GS), the 5-year biochemical recurrence-free survival (BRFS) rates were 89.8% in the patients with a biopsy GS of 6, 90.4% in those with 7, and 64.1% in those with ≥8. The BRFS in patients with a biopsy GS ≥8 was significantly lower than that in patients with a biopsy GS of 6 or 7 ($P = 0.007$ and 0.001, respectively)

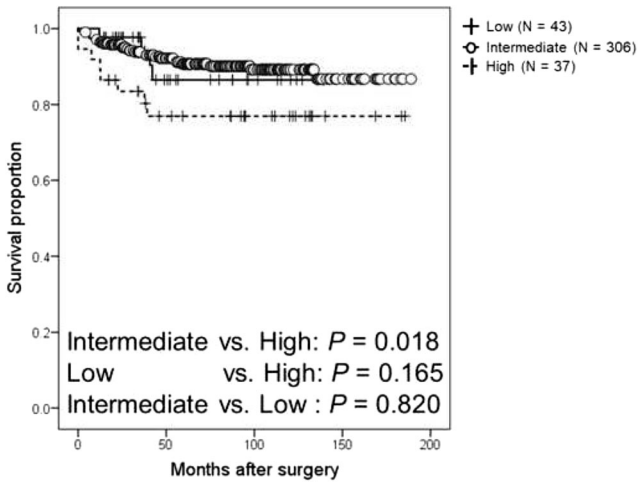

Fig. 2 With regard to D'Amico risk stratification, the 5-year biochemical recurrence-free survival (BRFS) rates in the low-, intermediate-, and high-risk groups were 86.5%, 90.7%, and 76.9%, respectively. The BRFS in the high-risk group was significantly lower than that in the intermediate group ($P = 0.018$)

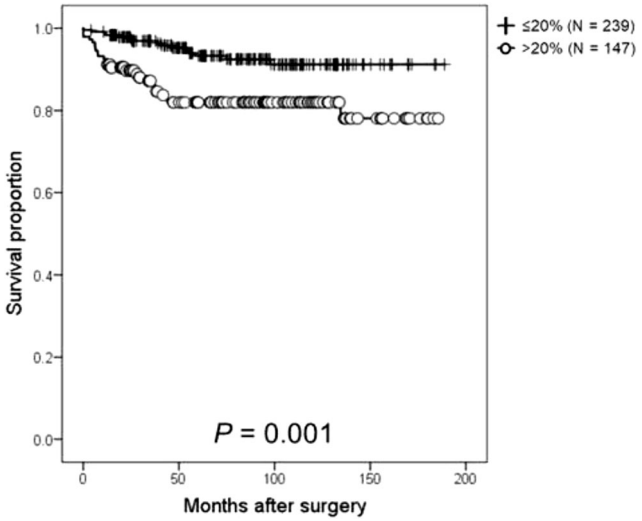

Fig. 3 According to the proportion of biopsy positive core, the biochemical recurrence-free survival (BRFS) rate was 93.3% in patients who had biopsy positive core ≤20% and 82.0% in those who had ≥21%. The BRFS in patients who had biopsy positive core ≤20% was significantly higher than that in counterparts ($P = 0.001$)

and multivariate analyses (HR = 1.35; $P < 0.001$) [7]. In a large multi-institutional study of almost 6000 patients who underwent RP, PRM was associated with a 3.7-fold risk of BCR [21]. Ploussard et al. reported that the 5-year BRFS rate was 84.4% in patients with NSMs and 57.5% in those with PSMs. The PRM status was significantly associated with BCR ($P < 0.001$) [5]. In addition, the RM status was a significant predictor of BCR in pT2 ($P < 0.001$) and pT3a ($P = 0.001$), whereas the impact of PRM was not significant in pT3b ($P = 0.196$) and pT4 ($P = 0.061$) [5]. Although PRM status was significantly associated with BCR, it may be necessary to pay careful attention at RP, particularly in patients with pT2.

Access to the systemic circulation by tumor cells is an important step in the dissemination of metastases to distant sites [22]. PNI and LVI are considered the major mechanism for the extraprostatic spread of PCa [7, 8]. Zhang et al. have evaluated whether the presence of PNI has a prognostic impact on BCR in patients after RP via a meta-analysis [7]. The pooled HR indicated that PNI was associated with a higher risk of BCR in patients with PCa after RP (HR = 1.23; $P < 0.001$) [7]. The phenomenon of PNI is recognized as a potential component of the cancer microenvironment [23]. PNI is also defined as cancer cell tracking along or around a nerve within the perineural space [24].

Table 3 Multivariate analysis for biochemical recurrence-free survival

	P	Hazard ratio	95% CI
Proportion of positive biopsy core	0.005	1.022	1.007–1.037
Biopsy Gleason score	0.112	0.272	0.055–1.353
D'Amico risk classification	0.998	0.998	0.239–4.175

CI confidence interval

Therefore, PCa patients with PNI may be at a risk of extraprostatic extension at the time of surgery [39]. In contrast, LVI was observed in the tumor cells that are directly observed within the lymphatic and/or vascular space and was associated with an increased risk of disease dissemination and recurrence [22]. Mitsuzuka et al. investigated about PCa patients with pT2 to determine whether LVI was associated with BCR [8]. With a median follow-up period of 50 months, the 5-year BRFS rates for LVI-negative and LVI-positive patients were 89.1% and 65.5%, respectively, in all patients ($P < 0.001$) and 98.7% and 85.3%, respectively, in patients with pT2 and NRM status ($P < 0.001$) [8]. Galiabovitch et al. reported that the BCRS rate in patients with LVI was significantly shorter than that in patients without LVI ($P < 0.001$) [22]. Undoubtedly, the RM status, PNI, and LVI were significantly associated with BCR in patients with PCa after RP. However, it may difficult to predict these pathologic features before surgery.

Preoperative risk stratification models are useful for patient counseling or evidence-based treatment decision-making in patients with PCa. Several authors have attempted to show the probability of positive extracapsular extension (EPE) or seminal vesicle involvement (SVI) using preoperative clinical parameters [13, 25]. In our previous study, 55% of the high-risk PCa patients who underwent RP alone had evidence of EPE or SVI in their surgical specimen [14]. Therefore, the accurate prediction of the localization of PCa and the occurrence of BCR after RP are crucial for determining the optimal treatment strategy [14].

Recently, mpMRI has been established to improve tumor detection and localization [26]. In 2012, the European Society of Urogenital Radiology proposed the PI-RADS to assess the risk of PCa in lesions detected using mpMRI [27]. Subsequently, the PI-RADS v2 was established in 2015, and it simplified rules for reporting, modifying imaging sequences, and defining clinically significant PCa [13]. Recently, Berney at al. reported the use of percentage of high-grade Gleason pattern in order to predict PCa-related deaths [28]. In this study, the participants did not undergo mpMRI before prostate biopsy. Therefore, whether PCa stage can be diagnosed accurately is not completely elucidated. In addition, the percentage of high GS was not calculated and immunohistochemical staining was not performed in this study. Although no correlation was observed between the proportion of positive biopsy core and tumor volume, the proportion of positive biopsy core was significantly associated with BCR in PCa patients with pT2 and NRM in this study.

The present study had several limitations. First, this was a retrospective study, and all variables were not controlled for selection bias and other unmeasurable confounding factors. Second, a relatively small number of patients were enrolled in this study, and the follow-up period was relatively short. Third, the participants did not undergo mpMRI before prostate biopsy. In addition, all patients were not evaluated for the prediction of biopsy outcomes using the PI-RADS v2.

Conclusion

Although patients with pT2 PCa and negative RM status had excellent oncological outcomes after RP, a low number of patients developed BCR. In this study, the proportion of biopsy positive core may predict preoperative covariates in patients with pT2 PCa and negative RM status after RP. A validation study of the combination of mpMRI or PI-RADS v2 and prostate biopsy may be conducted to assess whether the utility of the proportion of positive biopsy core can predict BCR in PCa patients who were diagnosed with pT2 with negative RMs after RP. In addition, several studies using immunohistochemical assays, including p53 [29] or LacdiNAc-glycosylated PSA [30] assays, will be required to prove the usefulness of the percentage of biopsy positive core as a clinical and pathological parameter for evaluating the prognosis in PCa patients.

Acknowledgements This work was supported by grants-in-aid for Scientific Research from the Japan Society for the Promotion of Science (15H02563 to C.O.), (15 K15579 to C.O.), and (17 K11118 to T.K.).

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

Informed Consent Informed consent was obtained from all individual participants included in the study.

Author Contributions Protocol/project development: TK and YH. Dara collection or management: OM, TT, TN, DN, HI, HK, YH and TK. Data analysis: TY and YT. Manuscript writing/ editing: MO, TK and YH. Supervision: CO.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A et al (2015) The global burden of Cancer 2013. JAMA Oncol 1:505–527
2. Projected Cancer Statistics, 2018. Cancer Information Services. https://ganjoho.jp/en/public/statistics/short_pred.html Accessed 15 September 2018
3. Gettman MT, Blute ML (2010) Radical prostatectomy: does surgical technique influence margin control? Urol Oncol 28:219–225
4. Rampersaud EN, Sun L, Moul JW et al (2008) Percent tumor involvement and risk of biochemical progression after radical prostatectomy. J Urol 180:571–576
5. Ploussard G, Agamy MA, Alenda O et al (2011) Impact of positive surgical margins on prostate-specific antigen failure after radical prostatectomy in adjuvant treatment-naïve patients. BJU Int 107: 1748–1754
6. Chang SS, Cookson MS (2006) Impact of positive surgical margins after radical prostatectomy. Urology 68:249–252
7. Zhang LJ, Wu B, Zha ZL et al (2018) Perineural invasion as an independent predictor of biochemical recurrence in prostate cancer following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. BMC Urol 18:5
8. Mitsuzuka K, Narita S, Koie T et al (2015) Lymphovascular invasion is significantly associated with biochemical relapse after radical prostatectomy even in patients with pT2N0 negative resection margin. Prostate Cancer Prostatic Dis 18:25–30
9. Srougi V, Bessa J Jr, Baghdadi M et al (2017) Surgical method influences specimen margins and biochemical recurrence during radical prostatectomy for high-risk prostate cancer: a systematic review and meta-analysis. World J Urol 35:1481–1488
10. Hernandez DJ, Nielsen ME, Han M et al (2008) Natural history of pathologically organ-confined (pT2), Gleason score 6 or less, prostate cancer after radical prostatectomy. Urology 72:172–176
11. Budäus L, Isbarn H, Eichelberg C et al (2010) Biochemical recurrence after radical prostatectomy: multiplicative interaction between surgical margin status and pathological stage. J Urol 184:1341–1346
12. Hamano I, Hatakeyama S, Yoneyama T et al (2016) Safety of heparin bridging therapy for transrectal ultrasound-guided prostate biopsy in patients requiring temporary discontinuation of antithrombotic agents. Springerplus 5:1917
13. Weinreb JC, Barentsz JO, Choyke PL et al (2016)PI-RADS prostate imaging - reporting and data system: 2015, version 2. Eur Urol 69: 16–40
14. Koie T, Yamamoto H, Hatakeyama S et al (2011) Minimum incision endoscopic radical prostatectomy: clinical and oncological outcomes at a single institute. Eur J Surg Oncol 37:805–810
15. Fujita N, Koie T, Hashimoto Y et al (2018) Neoadjuvant chemohormonal therapy followed by robot-assisted and minimum incision endoscopic radical prostatectomy in patients with high-risk prostate cancer: comparison of perioperative and oncological outcomes at single institution. Int Urol Nephrol 50:1999–2005
16. Narita T, Koie T, Ookubo T et al (2017) The impact of extended lymph node dissection versus neoadjuvant therapy with limited lymph node dissection on biochemical recurrence in high-risk prostate cancer patients treated with radical prostatectomy: a multi-institutional analysis. Med Oncol 34:1
17. Epstein JI, Allsbrook WC Jr, Amin MB et al (2005) The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 29:1228–1242
18. American Joint Committee on Cancer (2010) Urinary bladder. In: Edge SB, Byrd DR, Compton CC et al (ed) AJCC Cancer staging manual, 7th Edition. Springer, New York, pp457–468
19. Isbarn H, Wanner M, Salomon G et al (2010)Long-term data on the survival of patients with prostate cancer treated with radical prostatectomy in the prostate-specific antigen era. BJU Int 106:37–43
20. Kotb AF, Elabbady AA (2011) Prognostic factors for the development of biochemical recurrence after radical prostatectomy. Prostate Cancer 2011:485189
21. Karakiewicz PI, Eastham JA, Graefen M et al (2005) Prognostic impact of positive surgical margins in surgically treated prostate cancer: multi-institutional assessment of 5831 patients. Urology 66:1245–1250
22. Galiabovitch E, Hovens CM, Peters JS et al (2017) Routinely reported 'equivocal' lymphovascular invasion in prostatectomy specimens is associated with adverse outcomes. BJU Int 119:567–572
23. Lee JT, Lee S, Yun CJ et al (2010) Prediction of perineural invasion and its prognostic value in patients with prostate cancer. Korean J Urol 51:745–751
24. Yu HH, Song DY, Tsai YY et al (2007) Perineural invasion affects biochemical recurrence-free survival in patients with prostate

cancer treated with definitive external beam radiotherapy. Urology 70:111–116
25. Ishida M, Nakashima J, Hashiguchi A et al (2009) Are predictive models for cancer volume clinically useful in localized prostate cancer? Int J Urol 16:936–940
26. Tan CH, Wei W, Johnson V, Kundra V (2012)Diffusion-weighted MRI in the detection of prostate cancer: meta-analysis. AJR Am J Roentgenol 199:822–829
27. Barentsz JO, Richenberg J, Clements R et al (2012) European Society of Urogenital Radiology. ESUR prostate MR guidelines 2012. Eur Radiol 22:746–757
28. Berney DM, Beltran L, Sandu H et al (2019) The percentage of high-grade prostatic adenocarcinoma in prostate biopsies significantly improves on grade groups in the prediction of prostate cancer death. Histopathology. 75:589–597
29. Guedes LB, Almutairi F, Haffner MC et al (2017) Analytic, preanalytic, and clinical validation of p53 IHC for detection of TP53 missense mutation in prostate cancer. Clin Cancer Res 23: 4693–4703
30. Yoneyama T, Tobisawa Y, Kaneko T et al (2019) Clinical significance of the LacdiNAc-glycosylated prostate-specific antigen assay for prostate cancer detection. Cancer Sci 110:2573–2589