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Predictors of Progression to Castration-resistant Prostate Cancer After Radical Prostatectomy in High-risk Prostate Cancer Patients

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Abstract. *Background/Aim: To examine the specific time frame and identify associated risk factors from commencement of hormonal therapy to the onset of castration-resistant prostate cancer among patients who have developed biochemical recurrence following radical prostatectomy. Patients and Methods: We retrospectively reviewed the records of 92 patients who developed biochemical recurrence and received hormonal therapy as initial salvage treatment after radical prostatectomy for high-risk localized prostate cancer from 2005 to 2021. The castration-resistant prostate cancer-free survival rates from the commencement of salvage hormonal therapy were analyzed using log-rank methods. Cox proportional hazard regression was performed to analyze the risk factors associated with acquiring castration resistance. The patients were stratified based on those risk factors. Results: During a median follow-up duration of 57 months, 24 (26.1%) patients developed castration-resistant prostate cancer. The 5- and 10-year castration-resistant prostate cancer-free survival rates were 73.6% and 54.5%, respectively. A multivariate analysis showed that Grade Group of 5 and prostate-specific antigen doubling time at biochemical recurrence of ≤3 months were independent predictors of castration-resistant prostate cancer. The 5-year castration-resistant prostate cancer-free survival rates in the low- and high-risk groups, stratified according to the aforementioned factors, were 85.4% and 47.6%, respectively. Conclusion: Patients in high Grade Group and short prostate-specific antigen doubling time after radical prostatectomy are more likely to develop resistance to salvage hormonal therapy.*

Although radical prostatectomy (RP) generally achieves good control of localized prostate cancer (PCA), 15% to 30% of patients develop biochemical recurrence (BCR) (1). Radiation therapy (RT) and hormonal therapy (HT) are commonly employed as salvage treatments. However, while some patients quickly progress to castration-resistant prostate cancer (CRPC), others maintain easily manageable prostate-specific antigen (PSA) control even after PSA recurrence. The mechanisms underlying the development of castration resistance are incompletely understood. CRPC is characterized by over-expression or hyperactivation of androgen receptors despite the availability of only castration levels of androgens (2). For patients with *de novo* metastatic PCA, multiple reports have suggested that pathological severity indices, such as Grade Group (GG) and the responsiveness to HT (post-treatment PSA level or rate of decline), may be valuable predictive factors for future acquisition of castration resistance in tumors (3). However, few reports have focused on the development of CRPC after RP. With respect to the occurrence of BCR following RP, clinicians should have a thorough understanding of the timing and risk of acquiring castration resistance for subsequent treatment decisions. The present study was performed to determine the effective duration of salvage HT after RP and identify clinical risk factors associated with the acquisition of castration resistance.

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Key Words: Biochemical recurrence, castration-resistant prostate cancer, hormonal therapy, prostate cancer, radical prostatectomy.

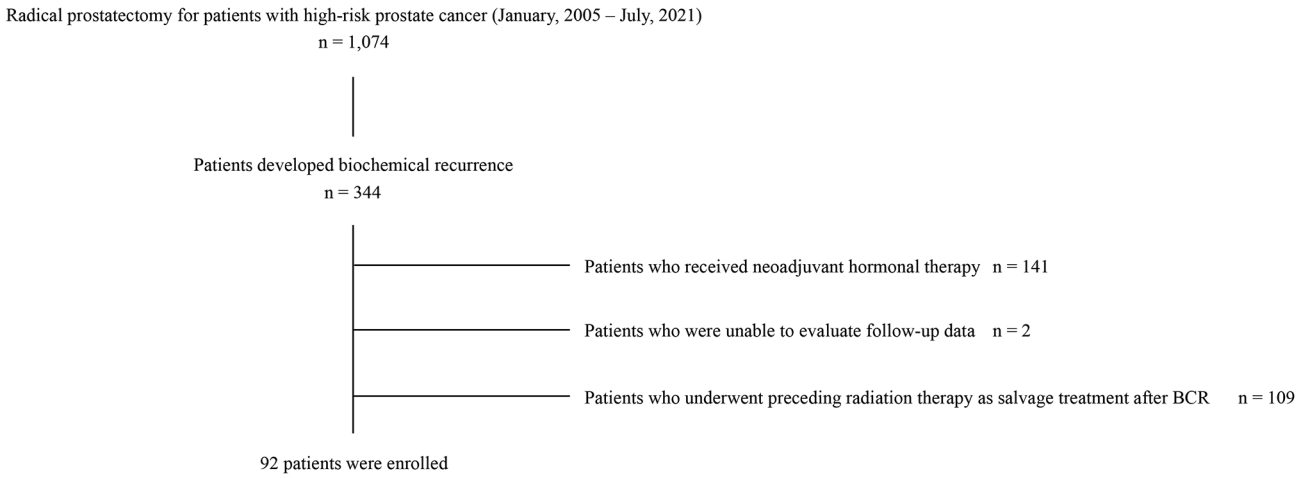

Figure 1. *Study design and inclusion criteria. BCR: Biochemical recurrence.*

Patients and Methods

Study population. We retrospectively reviewed the medical records of Japanese patients with clinically localized high-risk PCA who underwent RP from January 2005 to July 2021 at the Cancer Institute Hospital (Tokyo, Japan). The present study protocol was approved by the institutional review board of the hospital (approval no: 2020-GA-1198) and informed consents were obtained from all subjects. In total, 1,074 patients with high-risk PCA underwent RP during the study period. High-risk PCA was defined as PCA that met any of the following criteria: PSA level at diagnosis exceeding 20 ng/ml, GG of 4 or higher, or clinical T stage 3a or above (4). Among the 1,074 patients, we focused on those who developed BCR and underwent HT as the initial salvage treatment. Patients who received neoadjuvant HT, those with insufficient medical records, and those who underwent preceding salvage RT were excluded, resulting in a final study population of 92 patients. Figure 1 shows the study inclusion criteria.

Treatment. RP was performed *via* an open approach (5-11) or a robot-assisted approach (12, 13). During RP, standard (obturator and external iliac regions) pelvic lymph node (LN) resection and extended (obturator, external, and internal common iliac regions) pelvic LN resection were performed until 2010 and thereafter, respectively. The indications for salvage treatment after BCR were determined at the discretion of the attending physician. HT was mainly administered thorough androgen deprivation therapy or combined androgen blockade. In some cases, intermittent androgen suppression was carried out.

Statistical analysis. To evaluate the duration of efficacy of salvage HT after RP, the starting point of the study was initiation of salvage HT, and the primary endpoint was the development of CRPC. CRPC was defined as a post-castration serum testosterone level of <50 ng/dl plus biochemical progression (characterized by three consecutive increasing PSA levels ≥1 week apart, resulting in two 50% increases over the nadir and PSA level of >2 ng/ml) or radiological progression evident on a bone scan or indicated by enlargement of soft tissue lesions (14). The CRPC-free survival rates were analyzed using log-rank methods, and clinical risk factors for the acquisition of castration resistance were assessed through Cox proportional hazards regression analysis. The following clinical parameters were assessed through univariate and multivariate analyses: age at surgery, PSA level at diagnosis, pathological GG, seminal vesicle invasion, LN metastasis, lymphovascular invasion, surgical margin status, time to BCR from RP, prostate-specific antigen doubling time (PSADT) at BCR, persistent PSA after RP, utilization of salvage RT, time to initiation of HT from BCR, and PSA level at the onset of HT and 1 to 3 months after its initiation. The patients were stratified according to their risk factors, and their actuarial probabilities were evaluated. BCR was defined as PSA level of >0.2 ng/ml after RP, and persistent PSA was defined as postoperative nadir PSA level of ≥0.1 ng/ml. PSADT was calculated as log (2) divided by the slope of the linear regression of log (PSA) over time. For convenience, we used two consecutive PSA levels: immediately before and at the time of BCR diagnosis. For patients who developed BCR immediately after RP, the PSADT was assigned a value of 0. All *p*-values of <0.05 were considered statistically significant. Data analyses were performed using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Table I shows the patients' clinical characteristics and pathological findings. Their median age at the time of surgery was 67 years [interquartile range (IQR)=61-71 years), and their median PSA level at diagnosis was 10.8 ng/ml (IQR=6.7-18.5 ng/ml). The median time from RP to BCR was 11 months (IQR=1-24 months). The median PSADT at BCR was 2.5 months (IQR=0.0-5.3 months). The median follow-up duration after initiation of salvage HT was 57 months (IQR=29-92 months). Pathologically, GG of 5 accounted for 52% of cases. Extraprostatic extension was

Table I. *Patient characteristics*.

Clinical characteristics	Median (IQR)
Age at surgery, years	67 (61-71)
PSA at diagnosis, ng/ml	10.8 (6.7-18.5)
Time to BCR from RP, months	11 (1-24)
PSADT at BCR, months	2.5 (0.0-5.3)
Time to starting SHT from BCR, months	1 (0-6)
Follow-up period after starting SHT, months	57 (29-92)
Nadir PSA after RP, ng/ml	0.03 (0.01-0.25)
PSA at starting SHT, ng/ml	0.58 (0.29-1.76)
PSA after starting SHT, ng/ml	0.10 (0.03-0.31)
	n (%)
Operation	
Open	70 (76.1)
Robot-assisted	22 (23.9)
Salvage treatment	
Only hormonal	70 (76.1)
Hormonal+radiation	22 (23.9)
Persistent PSA	
Yes	31 (33.7)
No	61 (66.3)
Number of CRPC	24 (26.1)
Number of distant metastases	21 (22.8)
Number of cancer-specific deaths	4 (4.4)
Pathological findings	n (%)
Gleason Grade Group	
1	0 (0.0)
2	4 (4.4)
3	32 (34.8)
4	8 (8.7)
5	48 (52.2)
Pathological T stage	
≤2	17 (18.5)
3a	35 (38.0)
≥3b	40 (43.5)
Lymph node metastasis	
Positive	35 (28.0)
Negative	57 (62.0)
Lymphovascular invasion	
Positive	47 (51.1)
Negative	45 (48.9)
Perineural invasion	
Positive	87 (94.6)
Negative	5 (5.4)
Surgical margin status	
Positive	37 (40.2)
Negative	55 (59.8)

BCR: Biochemical recurrence; CRPC: castration-resistant prostate cancer; IQR: interquartile range; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; RP: radical prostatectomy; SHT: salvage hormonal therapy.

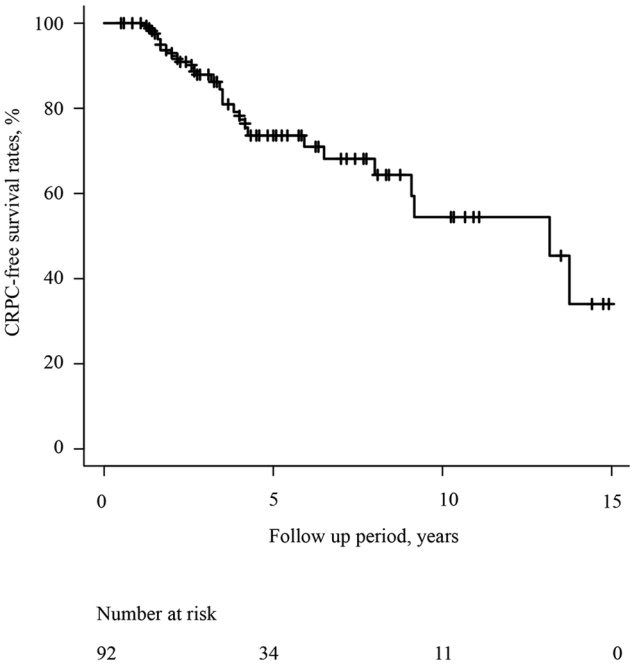

Figure 2. *Kaplan-Meier curves showing castration-resistant prostate cancer (CRPC)-free survival rates. The starting point is the initiation of salvage hormonal treatment.*

observed in 38% of patients, seminal vesicle invasion in 43%, and LN metastasis in 38%. The median postoperative nadir PSA level was 0.03 ng/ml (IQR=0.01-0.25 ng/ml), and persistent PSA was present in 31/92 (34%) patients. Among the salvage treatments after BCR, HT alone was administered in 70/92 (76%) patients, whereas 22/92 (24%) patients received a combination of HT and subsequent RT. The median PSA level at HT initiation was 0.58 ng/ml (IQR=0.29-1.76 ng/ml); at 1 to 3 months post-initiation, the median PSA level had dropped to 0.10 ng/ml (IQR=0.03-0.31 ng/mI).

CRPC developed in 24/92 (26.1%) patients during follow-up. The 5- and 10-year CRPC-free survival rates, indicating the efficacy of HT in this cohort, were 73.6% [95% confidence interval (CI)=60.7-82.9] and 54.5% (95%CI=35.9-69.7), respectively (Figure 2). Table II shows the results of the univariate and multivariate analyses of predictors of progression to CRPC. GG of 5 [hazard ratio (HR)=3.05, 95%CI=1.23-7.58, p=0.02] and a PSADT at BCR of ≤3 months (HR=2.85, 95%CI=1.05-7.73, p=0.04) were risk factors for HT resistance. Patients with neither or one of these risk factors were categorized as low risk (n=65), whereas those with both risk factors were categorized as high risk (n=27). The duration until the acquisition of castration resistance was analyzed using Kaplan-Meier curves (Figure 3). The probabilities of

Table II. *Univariate and multivariate analyses of risk factors for progression to castration-resistant prostate cancer (CRPC) (n=92).*

	Univariate			Multivariate		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age at surgery, <65 *vs.* ≥65 years	1.22	0.54-2.75	0.63			
PSA at diagnosis, ≤10 *vs.* >10 ng/ml	1.02	0.44-2.38	0.96			
Gleason Grade Group, 5 *vs.* ≤4	3.16	1.28-7.83	0.01	3.05	1.23-7.58	0.02
Seminal vesicle invasion, yes *vs.* no	0.96	0.42-2.20	0.92			
Lymph node metastasis, positive *vs.* negative	1.30	0.58-2.90	0.53			
Lymphovascular invasion, positive *vs.* negative	1.72	0.73-4.02	0.21			
Surgical margin, positive *vs.* negative	0.81	0.35-1.91	0.64			
Time to BCR from RP, ≤6 *vs.* >6 months	1.23	0.54-2.82	0.62			
PSADT at BCR, ≤3 *vs.* >3 months	2.99	1.10-8.12	0.03	2.85	1.05-7.73	0.04
Persistent PSA, yes *vs.* no	1.54	0.68-3.46	0.30			
Salvage RT, yes *vs.* no	0.64	0.19-2.16	0.47			
Time to starting SHT from BCR, <3 *vs.* ≥3 months	1.05	0.43-2.57	0.92			
PSA at starting SHT, <1 *vs.* ≥1 month	1.83	0.82-4.11	0.14			
PSA after starting SHT, <0.05 *vs.* ≥0.05 ng/ml	1.55	0.65-3.70	0.32			

BCR: Biochemical recurrence; CI: confidence interval; IQR: interquartile range; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; RT: radiation therapy; SHT: salvage hormonal therapy.

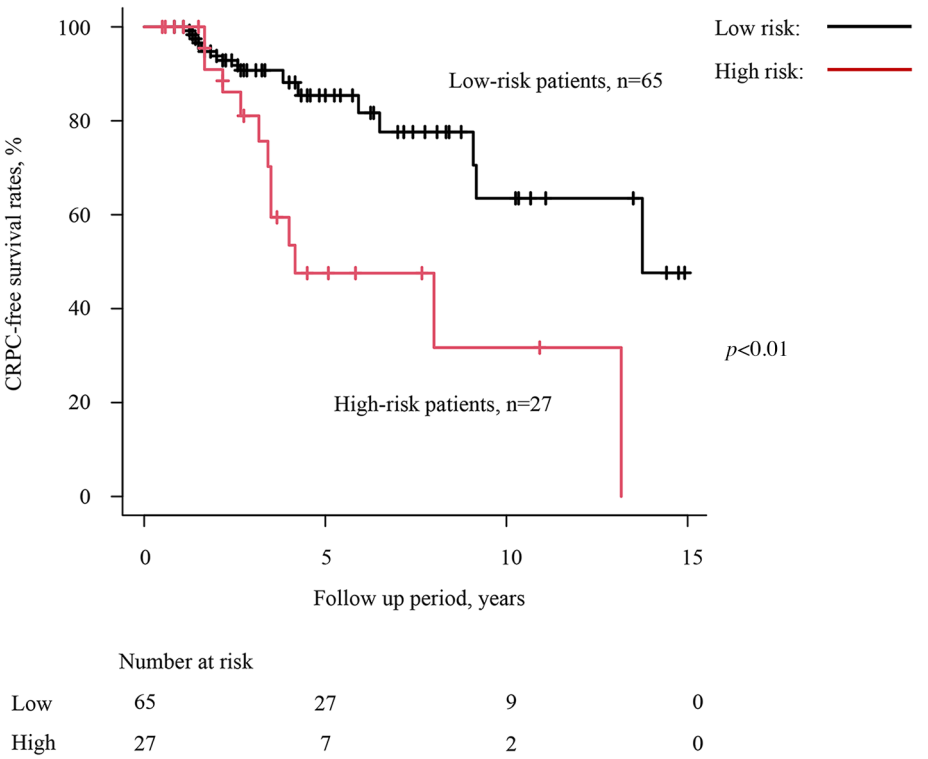

Figure 3. *Kaplan-Meier curves showing castration-resistant prostate cancer (CRPC)-free survival rates according to risk stratification. The starting point is the initiation of salvage hormonal treatment.*

effectiveness of salvage HT at 5 years for the low- and high-risk groups were 85.4% (95%CI=71.3-92.9) and 47.6 % (95%CI=24.1-67.8), respectively, and those at 10 years were 63.5% (95%CI=39.0-80.3) and 31.7% (95%CI=7.5-60.1), respectively. Significant differences were observed between the two groups ($p<0.05$).

Discussion

This study revealed the efficacy duration of salvage HT after RP for treatment of high-risk PCA and identified predictive factors for the acquisition of treatment resistance. After surgery, 26% of patients experienced HT failure during the follow-up period. The actuarial probability of HT effectiveness was 73.6% at 5 years and 54.5% at 10 years. The acquisition of castration resistance is suggested to involve a transformation in which androgen receptors undergo permanent activation or up-regulation, even in the absence of androgens (2). Several reports on metastatic PCA have suggested that GG and early response to HT are predictive factors for the development of CRPC (3). We investigated the efficacy of salvage HT in patients after RP. GG and PSADT at the time of BCR were identified as risk factors for the development of CRPC. Our findings regarding the GG align with previously reported findings in patients with metastatic PCA. Thus, HT presents limited effectiveness in pathologically high-grade PCA. After RP, however, the initial effectiveness of HT was suggested to be unsuitable as a predictive indicator for subsequent castration resistance. In cases of postoperative recurrence, HT presumably begins at a stage at which the tumor volume is relatively low. PSADT, reflecting the disease progression of tumors at the time of recurrence, may alternatively serve as a predictive factor for future early resistance to HT. GG and PSADT were previously reported as predictors of distant metastasis and cancer-specific mortality following RP (15, 16). After BCR, the acquisition of castration resistance is considered a crucial event directly affecting patient outcomes. The alignment between the identified risk factors for CRPC and other prognostic factors in the present study is a convincing outcome.

We stratified the risk of CRPC among patients based on PSADT and GG. In patients with high GG and short PSADT (categorized as high risk), the sustained efficacy of HT over 5 years was only 50%. For these high-risk patients, there might be an option to introduce androgen receptor-axis-targeted therapies or chemotherapy with docetaxel without waiting for progression to CRPC.

Study limitations. It was performed at a single institution and had a small sample size. The involvement of salvage treatments, such as androgen deprivation therapy, combined androgen blockade, and intermittent androgen suppression contributed to a lack of homogeneity among the patient cohorts. Combined use of RT with HT did not emerge as a risk factor for acquiring castration resistance. However, insufficient data hindered the evaluation of patients in whom RT preceded HT.

Conclusion

GG and PSADT predict the risk of castration resistance after RP. Both are assessable indicators at the time of BCR. For patients exhibiting high GG and short PSADT, careful monitoring and active treatment interventions should be considered even after the initiation of HT.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Conceptualization: T.N., S.Y.; Data curation: T.N., S.Y., N.N., Y.K., T.O., Y.Y., R.F., J.Y.; Formal analysis: T.N.; Funding acquisition: N/A.; Investigation: T.N., S.Y., J.Y.; Methodology: T.N., S.Y.; Project administration: S.Y., J.Y.; Resources: S.Y., J.Y.; Software: T.N., S.Y.; Supervision: J.Y.; Validation: S.Y., N.N., Y.K., T.O., Y.Y., R.F., T.Y., J.Y.; Visualization: T.N.; Writing – original draft: T.N.; Writing – review & editing: S.Y., T.Y., J.Y.

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References

1 Simmons MN, Stephenson AJ, Klein EA: Natural history of biochemical recurrence after radical prostatectomy: risk assessment for secondary therapy. Eur Urol 51(5): 1175-1184, 2007. DOI: 10.1016/j.eururo.2007.01.015

2 Nadiminty N, Gao AC: Mechanisms of persistent activation of the androgen receptor in CRPC: recent advances and future perspectives. World J Urol 30(3): 287-295, 2012. DOI: 10.1007/s00345-011-0771-3

3 Lin TT, Chen YH, Wu YP, Chen SZ, Li XD, Lin YZ, Chen SH, Zheng QS, Wei Y, Xu N, Xue XY: Risk factors for progression to castration-resistant prostate cancer in metastatic prostate cancer patients. J Cancer 10(22): 5608-5613, 2019. DOI:10.7150/jca.30731

4 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer. Version 4. 2018. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459 [Last accessed on May 23, 2024]

5 Kawakami S, Fukui I, Yonese J, Okubo Y, Yamamoto S, Tsukamoto T, Ishikawa Y: Antegrade radical retropubic prostatectomy with preliminary ligation of vascular pedicles in 614 consecutive patients. Jpn J Clin Oncol 37(7): 528-533, 2007. DOI: 10.1093/jjco/hym051

6 Yamamoto S, Yonese J, Kawakami S, Ohkubo Y, Tatokoro M, Komai Y, Takeshita H, Ishikawa Y, Fukui I: Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. Eur Urol 52(3): 696-701, 2007. DOI: 10.1016/j.eururo.2007.03.052

7 Yamamoto S, Kawakami S, Yonese J, Fujii Y, Ohkubo Y, Suyama T, Komai Y, Kijima T, Ishikawa Y, Fukui I: Lymphovascular invasion is an independent predictor of prostate-specific antigen failure after radical prostatectomy in patients with pT3aN0 prostate cancer. Int J Urol 15(10): 895-899, 2008. DOI: 10.1111/j.1442-2042.2008.02140.x

8 Yamamoto S, Kawakami S, Yonese J, Fujii Y, Tsukamoto T, Ohkubo Y, Komai Y, Ishikawa Y, Fukui I: Risk stratification of high-grade prostate cancer treated with antegrade radical prostatectomy with intended wide resection. Jpn J Clin Oncol 39(6): 387-393, 2009. DOI: 10.1093/jjco/hyp032

9 Yamamoto S, Kawakami S, Yonese J, Fujii Y, Urakami S, Masuda H, Numao N, Ishikawa Y, Kohno A, Fukui I: Long-term oncological outcome and risk stratification in men with high-risk prostate cancer treated with radical prostatectomy. Jpn J Clin Oncol 42(6): 541-547, 2012. DOI: 10.1093/jjco/hys043

10 Yamamoto S, Kawakami S, Yonese J, Fujii Y, Urakami S, Kitsukawa S, Masuda H, Ishikawa Y, Kozuka T, Oguchi M, Kohno A, Fukui I: Long-term oncological outcome in men with T3 prostate cancer: radical prostatectomy *versus* external-beam radiation therapy at a single institution. Int J Clin Oncol 19(6): 1085-1091, 2014. DOI: 10.1007/s10147-013-0654-2

11 Fukagawa E, Yamamoto S, Ohde S, Yoshitomi KK, Hamada K, Yoneoka Y, Fujiwara M, Fujiwara R, Oguchi T, Komai Y, Numao N, Yuasa T, Fukui I, Yonese J: External validation of the Briganti 2019 nomogram to identify candidates for extended pelvic lymph node dissection among patients with high-risk clinically localized prostate cancer. Int J Clin Oncol 26(9): 1736-1744, 2021. DOI: 10.1007/s10147-021-01954-4

12 Patel VR, Tully A, Holmes R, Lindsay J: Robotic radical prostatectomy in the community setting—the learning curve and beyond: initial 200 cases. Urol J 174(1): 269-272, 2005. DOI: 10.1097/01.ju.0000162082.12962.40

13 Patel VR, Thaly R, Shah K: Robotic radical prostatectomy: outcomes of 500 cases. BJU Int 99(5): 1109-1112, 2007. DOI: 10.1111/j.1464-410X.2007.06762.x

14 EAU Guidelines. edn. presented at the EAU Annual Congress Amsterdam, 2022. ISBN 978-94-92671-16-5. EAU Guidelines Office, Arnhem, The Netherlands. Available at: http://uroweb.org/guidelines/compilations-of-all-guidelines/ [Last accessed on May 23, 2024]

15 Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC: Natural history of progression after PSA elevation following radical prostatectomy. JAMA 281(17): 1591, 1999. DOI: 10.1001/jama.281.17.1591

16 Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, Partin AW: Risk of prostate cancer–specific mortality following biochemical recurrence after radical prostatectomy. JAMA 294(4): 433, 2005. DOI: 10.1001/jama.294.4.433

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