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Stratification based on adverse laboratory/pathological features for predicting overall survival in patients undergoing radical prostatectomy

A K-CaP registry-based analysis

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Abstract

When making clinical decisions concerning additional treatment for patients who have undergone radical prostatectomy (RP), adverse laboratory/pathological features are considered major factors. We investigated and compared the prognostic efficacy of adverse laboratory/pathological features in predicting overall survival (OS) and biochemical failure (BCF) in these patients.

The Korean Prostate Cancer Database was used to identify patients undergoing RP between May 2001 and April 2013. Patients with incomplete clinicopathological data or positive lymphadenectomy results were excluded. Finally, 4486 patients included in the final analysis were categorized based on their adverse laboratory/pathological features.

Adverse pathological features and detectable prostate-specific antigen (PSA) levels 6 weeks after surgery were observed in 1977 (44.1%) and 634 (14.1%) patients, respectively. PSA levels, pathological Gleason score ≥8, adverse pathological features [positive surgical margin (PSM), seminal vesicle invasion (SVI), and extracapsular extension (ECE)], and adverse laboratory features (detectable PSA levels after 6 weeks) together were significant predictors of BCF-free survival (BCFFS). SVI was identified as a predictor of OS. Additionally, patients with ECE, PSM, and detectable PSA levels after 6 weeks, but without SVI, showed similar OS to those without ECE, PSM, and detectable PSA levels after 6 weeks and with SVI (log-rank test, $P = .976$).

We successfully stratified patients based on adverse laboratory/pathological features after RP and demonstrated that these are important prognostic factors for OS and BCFFS. Additionally, we identified the criteria for selecting appropriate patients for undergoing additional treatment based on OS and BCFFS.

Abbreviations: ADT = androgen deprivation therapy, ART = adjuvant radiotherapy, BCF = biochemical failure, BCFFS = BCF-free survival, BMI = body mass index, CCI = Charlson comorbidity index, CI = confidence interval, ECE = extracapsular extension, HR = hazard ratio, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, OS = overall survival, PCa = prostate cancer, PSA = prostate-specific antigen, PSM = positive surgical margin, PV = prostate volume, RP = radical prostatectomy, RT = radiotherapy, SRT = salvage radiotherapy, SVI = seminal vesicle invasion, TV = tumor volume.

Keywords: prostatectomy, prostatic neoplasm, risk assessment, survival

1. Introduction

Radical prostatectomy (RP) is a widely chosen treatment option for patients with localized prostate cancer (PCa) worldwide.[1,2] However, some patients undergoing RP experience biochemical failure (BCF) or show adverse pathological features such as positive surgical margin (PSM), seminal vesicle invasion (SVI), and extracapsular extension (ECE). For these patients,

Editor: Giuseppe Lucarelli.

The authors have no conflicts of interests to disclose.

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How to cite this article: Park JS, Koo KC, Choi IY, Lee JY, Hong JH, Kim CS, Lee HM, Hong SK, Byun SS, Rha KH, Chung BH, Lee KS. Stratification based on adverse laboratory/pathological features for predicting overall survival in patients undergoing radical prostatectomy. Medicine 2019;98:45(e17931).

Received: 10 May 2019 / Received in final form: 26 September 2019 / Accepted: 14 October 2019

http://dx.doi.org/10.1097/MD.0000000000017931

postoperative radiotherapy (RT) including adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) is recommended as an additional treatment.[3–6] Based on high-level evidence from large randomized clinical trials, the National Comprehensive Cancer Network (NCCN), American, and European guidelines have recommended ART for patients with adverse laboratory/pathological features after RP.[6–8]

According to recent studies, clinical practices demonstrated that frequency of radiotherapy use has not increased or declined, although ART can improve oncological outcomes.[9–11] Moreover, ART was not considered to be a significant prognostic factor for overall survival (OS).[12] These findings suggest that more precise criteria, based on the survival of PCa patients, are required to select patients for postoperative radiotherapy.

Although PSM, SVI, ECE, and BCF are known to be predictors for poor oncological outcomes, we do not know which factors might be more significantly involved with the oncological outcomes. By investigating the most significant predictors for oncological outcomes, we could develop nomograms to predict poor oncological outcomes thereby help clinicians decide on postoperative RT. Therefore, we classified a large cohort of patients who had undergone RP depending on their adverse laboratory/pathological features. Moreover, we investigated and compared the prognostic efficacy of adverse laboratory and pathological features in predicting OS and BCF.

2. Materials and methods

2.1. Study population and data collection

This study was approved by our institutional review board (2016-0493-001). The Korean Prostate Cancer Database (K-CaP), which was the first registry to comprehensively collect data regarding Korean patients with PCa undergoing RP, was used to identify patients.[13] A total of 6735 consecutive patients with PCa who underwent RP between 2001 and 2012 were selected from 5 Korean tertiary referral hospitals (Asan Medical Center, Samsung Medical Center, Seoul National University Bundang Hospital, Seoul St. Mary's Hospital, and Yonsei University Severance Hospital). Patient records were anonymized and de-identified before analysis.

2.2. Assessments of clinicopathological variables

Clinicopathological data, including age at diagnosis, body mass index (BMI), Charlson comorbidity index (CCI), PSA level at diagnosis, prostate volume (PV) in preoperative imaging studies, pathological outcomes [pathological stage, Gleason score, tumor volume (TV), and adverse pathological features (ECE, SVI, and PSM)], and follow-up PSA levels, were extracted from the K-CaP registry. Patients with incomplete clinicopathological data, those undergoing neoadjuvant androgen deprivation therapy (ADT), or those with positive lymphadenectomy results were excluded. Finally, 4486 patients were included in the final analysis.

The magnetic resonance imaging (MRI) data of all patients were interpreted by radiologists from the urology department at each participating hospital. The final pathology was determined using RP specimens and reported by the pathologists from the urology department of each institution. The clinicopathological stage was assigned according to the tumor/node/metastasis staging system.

To analyze the preoperative risk, we categorized patients into 3 risk categories, including low (PSA <10 ng/ml, biopsy Gleason score ≤ 6, clinical stage $<$T2a), high (PSA >20 ng/ml, biopsy Gleason score ≥ 8, clinical stage $\geq$T3a), and intermediate (patients who did not meet the criteria for the high- or low-risk groups).

2.3. Pathological finding assessments

We analyzed pathological factors including the final pathological stage, Gleason score, TV, ECE, SVI, and PSM. Adverse pathological features were defined as ECE, SVI and PSM.

2.4. Follow-up PSA assessments

PSA was considered undetectable at a level of <0.01 ng/ml, as seen on an ultrasensitive assay. The time to PSA nadir was defined as the duration from the day of surgery to the time when the PSA level reached its nadir. For patients who showed detectable PSA levels at the PSA nadir, the time to PSA nadir was considered to be that at 6 weeks after RP. All patients were classified depending on the presence of detectable PSA levels after 6 weeks.

BCF was characterized by a confirmed increase of more than 0.2 ng/ml (threshold) in the PSA level; failure of the PSA level to decrease to undetectable levels; or the existence of additional therapy, including radiotherapy, ADT, or both for consecutive PSA increases, even if they did not reach the threshold of 0.2 ng/ml.

2.5. Statistical analyses

Continuous variables are expressed as medians (interquartile ranges). Categorical variables are reported as numbers and frequencies. Student t test was used to compare continuous variables, and Chi-Squared test was used to compare categorical variables. Simple and multiple logistic regressions with forward selection were used. Survival curves were established using the Kaplan–Meier method and compared using the log-rank test. Prognostic factors were established using univariate analysis, and the factors significant in univariate analysis were entered into multivariate analysis using the Cox stepwise regression method. No harmful collinearity among prognostic factors identified in multivariate analysis was confirmed using coefficients of variance inflation below 10. All statistical comparisons were conducted using IBM SPSS Statistics, version 23 (IBM Corporation, Armonk, NY, USA). P values $<.05$ indicated statistically significant differences.

3. Results

3.1. Patient characteristics

Table 1 summarizes the clinicopathological characteristics of the study patients. Among 4486 patients, the mean age and PSA levels were 72.0 years and 6.70 ng/ml, respectively. These parameters were significantly higher in the high-risk PCa group than in the low- and intermediate-risk PCa groups. The mean PV and TV were 32.2 cc and 2.6 cc, respectively, and both volumes significantly increased as the risk of PCa increased.

With regard to adverse pathological features, PSM was the most feature reported in 1379 patients (30.7%), followed by ECE, which was reported in 1207 patients (26.9%). SVI was observed in 334 patients (7.4%). Each adverse pathological feature increased as the risk of PCa increased. All 3 adverse pathological features were found in 176 patients (3.9%).

Table 1

Characteristics of patients in the low-, intermediate-, and high-risk prostate cancer groups.

	Total	Low risk	Intermediate risk	High risk	*P* value
Number of patients (n, (%))	4486	1483 (33.1)	2,014 (44.9)	989 (22.0)	
Age (years)	72.0 (67.0–76.0)	71.0 (66.0–75.0)	72.0 (67.0–77.0)	73.0 (67.0–77.0)	<.001
CCI (≥3)	26 (0.6)	3 (0.2)	14 (0.7)	9 (0.9)	.050
BMI (kg/cm^2)	24.3 (22.6–26.1)	24.3 (22.6–26.0)	24.4 (22.6–26.1)	24.3 (22.5–26.1)	.708
PSA (ng/mL)	6.70 (4.72–10.78)	5.17 (4.01–6.78)	7.32 (5.05–11.27)	13.0 (6.76–25.32)	<.001
Prostate volume (cc)	32.2 (25.2–42.0)	34.4 (27.0–45.0)	31.0 (24.7–40.0)	32.0 (26.0–41.0)	<.001
Tumor volume (cc)	2.6 (1.1–5.6)	1.5 (0.6–3.0)	2.8 (1.4–5.4)	5.4 (2.4–10.8)	<.001
Pathological Gleason score (n, (%))					<.001
≤7	3954 (88.1)	1459 (98.4)	1899 (94.3)	596 (60.3)	
≥8	532 (11.9)	24 (1.6)	115 (5.7)	393 (39.7)	
Pathological stage (n, (%))					<.001
≤T2	3180 (70.9)	1482 (99.9)	1237 (61.4)	461 (46.6)	
T3	1306 (29.1)	1 (0.1)	777 (38.6)	528 (53.4)	
Adverse pathological features (n, (%))					
Extracapsular extension	1207 (26.9)	1 (0.1)	724 (35.9)	482 (48.7)	<.001
Seminal vesicle invasion	334 (7.4)	0 (0.0)	137 (6.8)	197 (19.9)	<.001
Positive surgical margins	1379 (30.7)	264 (17.8)	676 (33.6)	439 (44.4)	<.001
Number of adverse pathological features (n, (%))					<0001
0	2509 (55.9)	1218 (82.1)	952 (47.3)	339 (34.3)	
1	1210 (27.0)	265 (17.9)	647 (32.1)	298 (30.1)	
2	591 (13.2)	0 (0.0)	355 (17.6)	236 (23.9)	
3	176 (3.9)	0 (0.0)	60 (3.0)	116 (11.7)	
Detectable PSA levels after 6 weeks (n, (%))	634 (14.1)	177 (11.9)	272 (13.5)	185 (18.7)	<0001
BCF [n, (%)]	915 (20.4)	142 (15.5)	397 (19.7)	376 (38.0)	
Time to BCF (months)	23.0 (10.1–40.6)	27.7 (16.0–50.5)	24.1 (10.5–41.0)	20.2 (8.1–36.8)	<.001
5-year BCFFS (%)	63.3	80.7	63.8	37.7	<0001
BCF within 1 year (n, (%))	266 (5.9)	23 (1.6)	108 (5.4)	135 (13.7)	<.001
Follow-up (years)	43.1 (21.6–67.2)	42.9 (23.3–67.7)	44.1 (21.2–67.5)	41.0 (19.8–65.8)	.417

Values are presented as the number (%) or median (interquartile range).

BCF = biochemical failure, BCFFS = BCF-free survival, BMI = body mass index, CCI = Charlson comorbidity index, PSA = prostate-specific antigen.

With regard to adverse laboratory features, 634 patients (14.1%) showed detectable PSA levels after 6 weeks. BCF was noted in 915 patients and the mean time to BCF and 5-year BCF-free survival (BCFFS) rate were 23.0 months and 63.3%, respectively. Detectable PSA levels after 6 weeks and the proportion of patients with BCF significantly increased with the risk of PCa.

3.2. Prognostic significance of adverse laboratory/ pathological features in BCF

The Cox proportional hazards regression analyses of BCF are presented in Table 2. In univariate analysis, preoperative PSA levels, pathological Gleason score ≥8, ECE, SVI, PSM, and detectable PSA levels after 6 weeks were associated with BCF. In multivariate analysis, preoperative PSA levels [hazard ratio (HR): 1.01; 95% confidence interval (CI) 1.001–1.011, $P < .001$], pathological Gleason score ≥8 (HR: 1.99; 95% CI 1.569–2.502, $P < .001$), ECE (HR: 1.44; 95% CI 1.152–1.802, $P = .001$), SVI (HR: 2.24; 95% CI 1.696–2.944, $P < .001$), PSM (HR: 2.07; 95% CI 1.694–2.531, $P < .001$), and detectable PSA levels after 6 weeks (HR: 2.06; 95% CI 1.703–2.488, $P < .001$) remained independent predictors of BCF.

3.3. Determination of BCFFS by stratifying the combination of adverse pathological features

We compared the BCFFS based on the combination of adverse pathological features (Table 3). Incidence of BCF was highest in the group with SVI and PSM, but without ECE (60.7%). Patients

Table 2

Univariate and multivariate analyses to identify the significant predictors of postoperative biochemical failure.

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	1.00 (0.989–1.008)	.818		
PSA levels	1.01 (1.010–1.013)	<.001	1.01 (1.001–1.011)	<.001
Pathological Gleason score (≥8)	3.23 (2.778–3.759)	<.001	1.99 (1.569–2.502)	<.001
Extracapsular extension	2.71 (2.377–3.088)	<.001	1.44 (1.152–1.802)	.001
Seminal vesicle invasion	4.34 (3.75–5.130)	<.001	2.24 (1.696–2.944)	<.001
Positive surgical margins	2.73 (2.397–3.108)	<.001	2.07 (1.694–2.531)	<.001
Detectable PSA levels after 6 weeks	2.42 (2.005–2.913)	<.001	2.06 (1.703–2.488)	<.001

CI = confidence interval, LVI = lymphovascular invasion, PNI = perineural invasion, PSA = prostate-specific antigen.

Table 3

Biochemical failure outcomes of prostate cancer patients who were treated with radical prostatectomy, stratified by the number of adverse pathological features.

	ECE	SVI	PSM	ECE+SVI	ECE+PSM	SVI+PSM	ECE+PSM+SVI	*P* value
BCF (n, (%))	98 (20.9)	20 (43.5)	192 (27.6)	42 (50.0)	173 (36.1)	17 (60.7)	93 (52.8)	<.001
Time to BCF (months)	20.7	18.0	24.6	18.2	20.6	21.4	9.3	<.001
5-year BCFFS (%)	62.0	22.8	52.4	24.0	47.2	7.9	25.4	<.001
OS (n, (%))	42 (1.7)	14 (3.0)	19 (2.7)	1 (1.2)	16 (3.3)	0 (0.0)	13 (7.4)	.028
Time to OS (months)	53.0	N/A	45.0	61.2	47.8	N/A	29.9	.809
5-year OS (%)	88.6	100.0	93.3	91.0	91.2	100.0	85.5	<.001

The values are presented as a number (%) or median (interquartile range).
BCF = biochemical failure, BCFFS = BCF-free survival, PSA = prostate-specific antigen.

with all pathological features showed slightly lower rates of BCF (52.8%). On comparing each adverse pathological feature, SVI was the most significant factor for the prediction of BCF. Time to BCF significantly decreased with every pathological feature.

3.4. Prognostic significance of adverse laboratory/pathological features in overall survival

Cox proportional hazards regression analyses were performed for the determining the prognostic factors for OS (Table 4). The 5-year OS rate was 97.8%. In univariate analysis, age, CCI (≥3), pathological Gleason score ≥8, ECE, SVI, PSM, and detectable PSA levels after 6 weeks were associated with OS. In multivariate analysis, age (HR: 1.01; 95% CI: 1.049–1.122, $P < .001$) and SVI (HR: 1.99; 95% CI 1.078–3.686, $P = .028$) were the only significant predictors of OS. Detectable PSA levels after 6 weeks was not identified as a predictor of OS in multivariate analysis.

3.5. Determination of OS by stratifying adverse laboratory/pathological features

We tried to identify patients without SVI having similar OS rates to patients with only SVI as an adverse laboratory/pathological feature. For this subgroup analysis, patients were classified according to the presence of ECE, PSM, or detectable PSA after 6 weeks: [Group 1: SVI (+); Group 2: SVI/ECE/PSM/PSA (-/+/+/+); Group 3: SVI/ECE/PSM/PSA (-/+/+/-), or SVI/ECE/PSM/PSA (-/-/+/+), or SVI/ECE/PSM/PSA (-/+/-/+); Group 4: SVI/ECE/PSM/PSA (-/-/-/+), or SVI/ECE/PSM/PSA (-/-/+/-), or SVI/ECE/PSM/PSA (-/+/-/-); and Group 5: SVI/ECE/PSM/PSA (-/-/-/-)]. After adjustment for covariates, we found that the groups with a higher number of adverse laboratory/pathological features were associated with poor OS (log-rank test, $P < .001$). Notably, patients in Group 2 (with ECE, PSM, and detectable PSA levels after 6 weeks as risk factors) and Group 1 (with SVI) have poor OS compared with those in Groups 3 to 5; further, there were no differences in OS between Groups 1 and 2 (log-rank test, $P = .976$) (Fig. 1).

4. Discussion

We investigated BCFFS and OS based on adverse laboratory/pathological features. As expected, adverse laboratory/pathological features were significant prognostic factors for BCFFS. Additionally, SVI presented with the highest HR of predicting BCFFS, followed by PSM, detectable PSA levels after 6 weeks, pathological Gleason score, ECE, and PSA, in that order. Notably, of the adverse laboratory and pathological features, SVI was identified as the significant predictor for OS. Moreover, we found that patients without SVI and with ECE, PSM, and detectable PSA levels showed a similar OS to those with SVI and without ECE, PSM, and detectable PSA levels. Therefore, this study suggested that patients with SVI or those without SVI but with all ECE, PSM, and detectable PSA after 6 weeks should immediately be considered for multidisciplinary management (RT, RT + ADT, or ADT) postoperatively, and those not showing these features may undergo treatment based on the patient's and physician's preferences.

NCCN guidelines suggest that ART after recuperation from RP is likely beneficial in patients with 1 or more adverse laboratory or pathological features.[6] However, for adverse laboratory features, there was no definite time point for the measurement of postoperative PSA. In patients with a detectable PSA level, clinicians doubt the likelihood of cancer recurrence or residual cancer. Theoretically, PSA nadir, which decreases along with PSA's half-life, should be undetectable post-RP.[14] To determine the PSA nadir for prognosis, the exact follow-up time

Table 4

Univariate and multivariate analyses to identify the significant predictors of overall survival.

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	1.10 (1.059–1.131)	<.001	1.09 (1.051–1.125)	<.001
PSA	1.01 (0.999–1.016)	.094		
CCI (≥3)	4.17 (1.026–16.914)	.046	3.33 (0.807–13.763)	.096
Pathological Gleason score (≥8)	1.99 (1.234–3.212)	.005	1.66 (0.965–2.845)	.067
Extracapsular extension	2.01 (1.365–2.966)	<.001	1.27 (0.771–2.075)	.352
Seminal vesicle invasion	2.12 (1.210–3.729)	.009	1.99 (1.078–3.686)	.028
Positive surgical margins	1.72 (1.168–2.520)	.006	1.31 (0.832–2.061)	.244
Detectable PSA after 6 weeks	1.27 (0.816–1.969)	.290		

CCI = Charlson comorbidity index, CI = confidence interval, PSA = prostate-specific antigen.

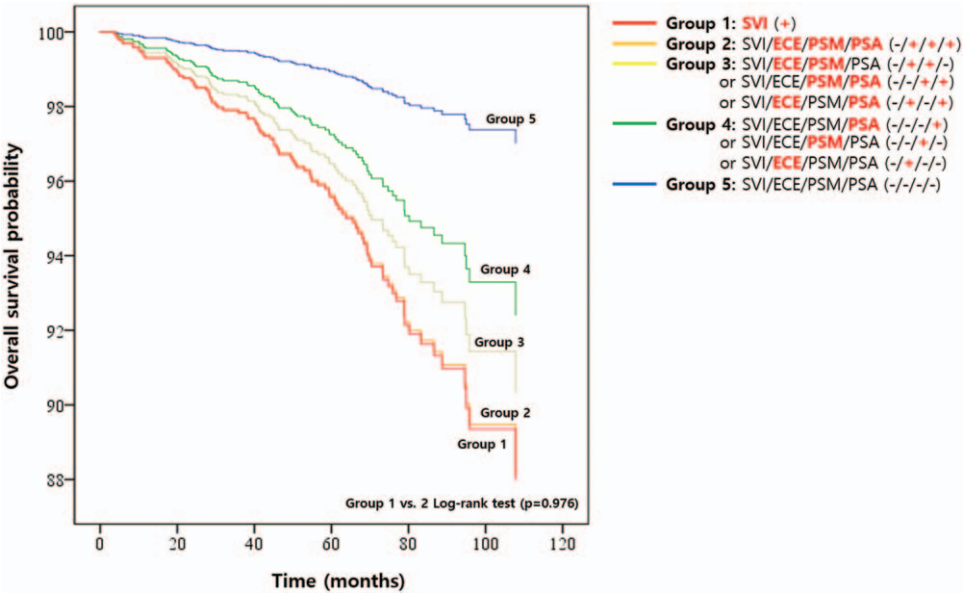

Figure 1. Overall survival in patients with seminal vesical invasion and the number of adverse laboratory/pathological features in patients without seminal vesical invasion after adjusting for covariates.

should be evaluated. Several studies have suggested that the 6-week period is the most useful for detecting PSA at its nadir.[15,16] Our results presenting the efficacy of detectable PSA after 6 weeks for predicting BCFFS supported the results of previous studies. No study has compared the prognostic significance of adverse laboratory feature vs adverse pathological features stated in NCCN guidelines.[6] Notably, to the best of our knowledge, this is the first study to demonstrate that an adverse laboratory feature, i.e., detectable PSA, has similar prognostic effects on disease progression as adverse pathological features. According to this study and previous studies that have emphasized on the importance of histopathological findings,[17] clinicians should not overlook patients who show undetectable PSA levels but have adverse pathological features.

Among adverse laboratory/pathological features, SVI was found to be the most significant factor for predicting BCFFS and OS. Previous studies have also demonstrated the importance of SVI; it was considered as negative prognostic factor of PCa and had a significantly worse prognosis than that with only ECE.[18,19] However, several studies reported that SVI is not associated with a uniformly poor prognosis and the prognosis could be dependent on the site of invasion.[20,21] We believe that the percentage of BCFFS and OS would increase if the exact location of SVI was evaluated.

Because the 5-year progression-free survival rates approach 100% in patients with localized PCa, survivors should be assessed for physical (urinary, sexual, and bowel) and psychosocial effects of PCa and should be treated for those.[22,23] Additional treatment after RP should be considered carefully and precisely. Although ART could reduce the risk of PSA relapse and disease recurrence, the period within 1 year after RP is crucial for the recovery of continence and sexual function. Without the precise indication for ART, some patients might not receive timely ART and some may undergo overtreatment.

High-level evidence concerning the efficacy of ART from several trials and the prognosis according to the patient's pathological features have been used to counsel patients who require additional treatment.[3–5] However, the use of postoperative radiotherapy for patients with PCa and adverse pathological features has not been commonly reported.[10,11] Moreover, the use of ART within 6 months after RP in patients with PCa and adverse pathological features is paradoxically declining.[9] This trend may be the result of multiple factors, including the patient's and physician's preferences, toxicity concerns, no consistent survival benefit in the updated randomized trials, or a growing preference for SRT at the time of PSA recurrence, rather than ART.[12,24,25] We believed that there was the need for a more precise criteria for selecting patients for postoperative radiotherapy in clinical practice. We identified the criteria for selecting patients who should receive ART on the basis of OS and BCFFS. Finally, we recommend that patients with SVI or without SVI but with ECE, PSM, detectable PSA levels after 6 weeks should immediately be considered for multidisciplinary management postoperatively.

There are several limitations of this study. First, this is the multi-center study that includes involvement of multiple physicians and a variety of postoperative management measures. Nevertheless, we believe that this effect is inherent in any retrospective study and may reflect real-world clinical practice. Second, although our study demonstrated the potential risk factors to stratify patients who were eligible for ART, we did not evaluate the efficacy of ART in patients with the identified risk factors. We are planning to perform randomized clinical trials to evaluate the impact of ART. Third, since we analyzed the database which started from 15 years ago, there could be some discrepancy in the pathological diagnosis criteria.

5. Conclusion

We successfully stratified patients according to the number of adverse laboratory/pathological features after RP, and demonstrated that these are important prognostic factors for OS and BCFFS. Additionally, we identified the criteria for selecting appropriate patients for undergoing additional treatment after RP based on OS and BCFFS.

Author contributions

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