Effect of preoperative risk group stratification on oncologic outcomes of patients with adverse pathologic findings at radical prostatectomy

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Effect of preoperative risk group stratification on oncologic outcomes of patients with adverse pathologic findings at radical prostatectomy

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ABSTRACT

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Purpose

Current National Comprehensive Cancer Network (NCCN) guideline recommends initial therapy for non-metastatic prostate cancer (PC) according to the preoperative risk groups. But adjuvant therapy after radical prostatectomy (RP) is recommended only based on the adverse pathologic findings (APFs) irrespective of these risk groups. We assessed whether the model incorporates preoperative risk group and APFs can predict the long-term oncologic outcomes better than that only based on APFs.

Patients and Method

We retrospectively reviewed the clinical data of 4,404 men who underwent RP at our institution between 1992 and 2014. After exclusion of patients who received neoadjuvant therapy or those with incomplete pathological and follow-up data, 3,092 men were included in the final analysis. All patients were stratified into low-, intermediate-, and high-risk groups according to the NCCN guideline and APFs were defined as extraprostatic extension (EPE), seminal vesicle invasion (SVI), or positive surgical margin (PSM). Baseline characteristics of men and pathologic outcomes were compared using $\chi 2$-tests for categorical data, and Student's t-test or analysis of variance (ANOVA) test for continuous data. The adequacy of model fit

to the data was compared between the models of APFs with and without risk groups using the likelihood-ratio test and model discrimination was compared with the concordance index (c-index) for predicting biochemical recurrence (BCR) and PC-specific mortality (PCSM). Kaplan-Meier estimates of BCR-free survival (BCRFS) and cumulative incidence estimates of PCSM were compared between the models using log-rank test for BCRFS and Gray's modified log-rank test for PCSM. A multivariate Cox regression analysis was used to identify factors predictive of BCR, whereas a multivariate competing risk regression analysis was performed for PCSM with death from other causes as the competing event.

Results

There were significant differences in age, preoperative prostate-specific antigen (PSA) level, biopsy Gleason score (GS), clinical stage, and APFs across the risk groups ($p < 0.001$ for all). Of 3,092 patients, 899 men experienced BCR and 85 men died due to PC at a median follow-up of 66 months (interquartile ranges [IQR] 65-96). Adding risk groups to the model only with APFs significantly improved the fit to the data (likelihood ratio test, $p < 0.001$) and the c-index increased from 0.693 to 0.732 for BCR and from 0.707 to 0.747 for PCSM. The BCRFS rate for men with APFs was worse than those without APFs in not only overall patients but also each risk groups (overall: $p < 0.001$, low: $p = 0.027$, intermediate: $p < 0.001$, and high: $p < 0.001$), but there was no difference in the cumulative incidence estimates of PCSM between men with and without APFs in low and intermediate risk groups ($p = 0.903$ and $p = 0.253$, respectively). Although RP GS ≥8 and PSM were independently associated with BCR in not only overall patients but also each risk groups (overall: GS ≥8 [HR 4.66, $p < 0.001$], PSM [HR 1.93, $p < 0.001$], low: GS ≥8 [HR 2.94, $p = 0.007$], PSM [HR 1.87, $p = 0.010$], intermediate: GS ≥8 [HR 1.85, $p = 0.022$], PSM [HR 2.42, $p < 0.001$], and high: GS ≥8 [HR 4.63, $p < 0.001$], PSM [HR 1.71, $p < 0.001$]), only RP GS ≥8 and SVI

were associated with PCSM in overall patients (GS ≥8: HR 5.39, p <0.001, SVI: HR 3.36, p <0.001) and high risk group (GS ≥8: HR 6.31, p = 0.010, SVI: HR 4.05, p = 0.001). The major limitation was that we did not perform the competing risk analysis for PCSM in low and intermediate risk groups because of small number of events.

Conclusion

Our results show that the postoperative estimation of oncologic outcomes in men with APFs at RP is improved by considering preoperative risk group stratification. Although PSM was independent predictor for BCR, only RP GS ≥8 and SVI were associated with PCSM in overall patients and high risk group.

Key words : prostate cancer, radical prostatectomy, preoperative risk group

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I. INTRODUCTION

Since widespread prostate-specific antigen (PSA) screening was introduced in the early 1990s, the incidence of prostate cancer (PC) has increased dramatically.[1] PC is now the most common non-dermatologic cancer among Western men.[2] Due to screening efforts, PC is increasingly being diagnosed when the tumor is confined to the prostate.[3] The prolonged natural history of the disease as well as a potential risk of progression into metastasis and death need to be taken into consideration in the initial management of men with newly diagnosed PC. The initial evaluation including serum PSA level, biopsy Gleason score (GS), and clinical T staging determines risk stratification and assists in treatment decision making. Several risk group stratifications, such as D'Amico and National Comprehensive Cancer Network (NCCN).[4,5] have been constructed to predict the oncologic outcome in patients with PC.

Of several therapeutic modalities for PC, radical prostatectomy (RP) is one of the most commonly used treatments for patients with localized PC and ≥10-years life-expectancy. In a randomized trial, RP reduced distant metastasis and

disease-specific death among patients with clinically localized PC.[6] However, approximately 30% of patients treated with RP have adverse pathologic findings (APFs)[7]. Recurrence rates in post-RP patients with APFs may be greater than 60% at 5 years.[8] In these patients with APFs at RP, the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) recommend that adjuvant radiotherapy (ART) should be offered because of demonstrated reductions in biochemical recurrence (BCR), local recurrence, and clinical progression.[9] However, such decision-making for ART is only based on the presence of APFs at RP irrespective of preoperative risk group stratification.[10] We hypothesized that oncologic risk associated with APFs is highly influenced by preoperative risk group constructed to predict the oncologic outcome. Therefore, we assessed whether the model incorporates preoperative risk group and APFs can predict the long-term oncologic outcomes better than that only based on APFs.

II. MATERIALS AND METHODS

1. Patient Population

After Institutional Review Board approval was obtained, we performed a retrospective review of data collected from our PC database on 4,404 patients who had undergone RP at our institution between 1992 and 2014. After exclusion of patients who received neoadjuvant therapy or those with incomplete pathological and follow-up data, 3,092 men with were included in the final analysis. Men with lymph node invasion at RP were excluded because they are candidates for adjuvant androgen deprivation therapy rather than ART. Although secondary therapy was delivered according to individual surgeon's preference, it was uncommonly administered in the absence of BCR in most men.

2. Patient Characteristics

Clinical characteristics of patients, including age, preoperative PSA level, clinical stage, and biopsy GS were obtained through a review of our institutional medical records. TNM stage was determined according to the American Joint Committee on Cancer 7th edition TNM staging system.[11] All patients were stratified into low-, intermediate-, and high-risk groups according to the NCCN Guidelines Version 1. 2015 Prostate Cancer (Table 1).[4] APFs were defined as extraprostatic extension (EPE), seminal vesicle invasion (SVI), or positive surgical margin (PSM).[9]

3. Pathological Analysis

Pathological analysis of RP specimens was performed by experienced uropathologists in our institute as described previously.[12] Briefly, the entire surface of the resected prostate specimens was coated with India ink, fixed in neutral buffered formalin, and embedded in paraffin blocks. Whole mount step sections were cut transversely at regular intervals from the apex of the prostate to

the tips of the seminal vesicles. Each section was examined for SVI, EPE, and PSM.

4. Follow-Up

Postoperative PSA follow-up was undertaken at 3 months interval for the first 2 years and at 6 months interval for the next 3 years, and annual PSA follow-up was recommended thereafter. BCR was defined as any two consecutive increase in serum PSA $\geq$0.2 ng/ml after RP. Data regarding mortality and cause of death were obtained from medical records in the Cancer Registry Center database at our institution.[13] The follow-up period was calculated from the time of RP to the date of the last known contact with the patient or the date of death. PC-specific mortality (PCSM) was defined as the time from initial RP to death due to PC or complications of this disease.

5. Statistical Analysis

Baseline characteristics of men and pathologic outcomes were compared using χ2-tests for categorical data, and Student's t-test or analysis of variance (ANOVA) test for continuous data. The adequacy of model fit to the data was compared between the models of APFs with and without risk groups using the likelihood-ratio test and model discrimination was compared with the concordance index (c-index) for predicting BCR and PCSM.[14] Kaplan-Meier method with a log-rank test was used to estimate and compare the probabilities of BCR between groups. Cox proportional hazards models were used to investigate associations between variables and the risk of BCR. Significant variables on univariate analysis were included in the multivariate model. The cumulative incidence estimates of PCSM were compared between groups using Gray's modified log-rank test for PCSM. Multivariate competing risk regression was also used to evaluate for a possible association between covariates and the risk of PCSM.[15]

The statistical analysis was conducted using Stata v.12.0 (StataCorp, College Station, TX, USA) and R (R version 3.0.1, R Foundation for Statistical Computing, Vienna, Austria). Comparisons with p values <0.05 were considered to be statistically significant.

6. Good Clinical Practice Protocols

The study was performed in accordance with all applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. The Institutional Review Board of our hospital approved the study protocol (approval number: 4-2015-0978).

Table 1. Risk-group assessment according to NCCN criteria[5]

Risk group	Description	Treatment option	
Very low	T1c GS ≤6 PSA <10 ng/mL PSA density <0.15 Fewer than 3 cores positive; ≤50% cancer in each core	LE ≥20 yrs	AS EBRT or BTx RP ± PLND
		LE 10–20 yrs	AS
		LE <10 yrs	Observation
Low	T1–T2a GS ≤6 PSA <10 ng/mL	LE ≥10 yrs	AS EBRT or BTx RP ± PLND
		LE <10 yrs	Observation
Intermediate	T2b–T2c or GS 7 or PSA 10–20 ng/mL	LE ≥10 yrs	RP ± PLND EBRT ± ADT (4–6 mo) ± BTx BTx alone
		LE <10 yrs	EBRT ± ADT (4–6 mo) ± BTx BTx alone Observation
High	T3a or GS 8–10 or PSA >20 ng/mL		EBRT + ADT (2–3 yrs) EBRT + BTx ± ADT (2–3 yrs) RP + PLND
Very high	T3b-T4 Primary Gleason pattern 5 or >4 cores with GS 8–10		EBRT + ADT (2–3 yrs) EBRT + BTx ± ADT (2–3 yrs) RP + PLND (in select patients) ADT (in select patients)

T-stage based on TNM system; GS = Gleason score; PSA = prostate specific antigen; LE = life expectancy; AS = active surveillance; EBRT = external beam radiation therapy; BTx = brachytherapy; RP = radical prostatectomy; PLND = pelvic lymph node dissection; ADT = androgen deprivation therapy.

III. RESULTS

1. Descriptive Statistics

Of 3,092 patients in the final cohort, 603 (19.5%), 1,031 (33.3%), and 1,458 (47.2%) patients were classified as low risk-, intermediate risk-, and high risk-group, respectively according to the NCCN risk stratification. The median age and PSA were 66 (interquartile ranges [IQR] 61-70) years and 8.0 (IQR 5.3-13.9) ng/ml, respectively. Clinical and pathological features of overall patients, stratified by preoperative risk group, are detailed in Table 2. There were significant differences in age, preoperative PSA level, biopsy GS, clinical stage, and APFs across the risk groups ($p < 0.001$ for all). When overall patients were divided by the presence or the absence of APFs, two groups showed significant difference in all clinical and pathological parameters including age ($p = 0.003$), year of surgery ($p < 0.001$), preoperative PSA level ($p < 0.001$), biopsy GS ($p < 0.001$), clinical stage ($p < 0.001$), preoperative risk group ($p < 0.001$), and APFs ($p < 0.001$) (Table 3).

2. Comparison of the performance of survival models

2-1. Goodness of fit test (likelihood ratio test)

We assessed the goodness of fit between two models of APFs with and without preoperative risk group for BCR and PCSM. Adding preoperative risk groups to the model only with APFs significantly improved the fit to the data for BCR and PCSM (likelihood ratio test $p < 0.001$ for both).

2-2. Discriminatory power of risk model (c-index)

C-index showed that the predictive value for BCR and PCSM was considerably increased when preoperative risk classification was incorporated to the model with APFs (c-index for BCR from 0.693 to 0.732 and for PCSM from 0.707 to 0.747, respectively).

Table 2. Comparison of clinical and pathological characteristics according to preoperative risk group

Variable	Overall	Low	Intermediate	High	p value*
	3,092 (100)	603 (19.5)	1,031 (33.3)	1,458 (47.2)	
Age, years	66	64	65	66	<0.001
IQR	61-70	59-69	61-70	62-71	
Year of surgery	2009	2009	2009	2010	0.050
IQR	2007-2011	2007-2011	2007-2011	2008-2011	
PSA, ng/ml	8.0	5.6	8.1	11.3	<0.001
IQR	5.3-13.9	4.4-7.0	5.3-12.0	6.5-23.4	
Biopsy GS					<0.001
≤6	1,386 (44.8)	603 (100)	444 (43.1)	339 (23.3)	
7	980 (31.7)	0	587 (56.9)	393 (27.0)	
≥8	726 (23.5)	0	0	726 (49.7)	
Clinical T stage					<0.001
≤T2	2,145 (69.4)	603 (100)	1031 (100)	555 (38.1)	
≥T3	947 (30.6)	0	0	903 (61.9)	
RP GS					<0.001
≤6	865 (28.0)	371 (61.5)	297 (28.8)	197 (13.5)	
7	1,533 (49.6)	208 (34.5)	643 (62.4)	682 (46.8)	
≥8	694 (22.4)	24 (4.0)	91 (8.8)	579 (39.7)	
RP T stage					<0.001
OC	1,343 (43.4)	380 (63.0)	505 (49.0)	458 (31.4)	
EPE	1,448 (46.8)	211 (35.0)	485 (47.0)	752 (51.6)	
SVI	301 (9.7)	12 (2.0)	41 (4.0)	248 (17.0)	
PSM					<0.001
No	1,604 (51.9)	400 (66.3)	546 (53.0)	658 (45.1)	
Yes	1,488 (48.1)	203 (33.7)	485 (47.0)	800 (54.9)	

PSA = prostate specific antigen; GS = Gleason score; RP = radical prostatectomy; OC = organ confined; EPE = extraprostatic extension; SVI = seminal vesicle invasion; PSM = positive surgical margin.

* p values are for comparison of low, intermediate, and high risk group.

Table 3. Comparison of clinical and pathological characteristics according to adverse pathological findings

variable	negative APFs	positive APFs	p value
	n = 985 (31.9)	n = 2,107 (68.1)	
Age, years	65	66	0.003
IQR	60-70	61-70	
Year of surgery	2010	2009	<0.001
IQR	2008-2012	2008-2011	
PSA, ng/ml	6.3	9.2	<0.001
IQR	4.5-9.8	5.9-15.9	
Biopsy GS			<0.001
≤6	563 (57.1)	823 (39.1)	
7	256 (26.0)	724 (34.4)	
≥8	166 (16.9)	560 (26.6)	
Clinical T stage			<0.001
≤T2	798 (81.0)	1,391 (66.0)	
≥T3	187 (19.0)	716 (34.0)	
Preoperative risk			<0.001
Low	298 (30.3)	305 (14.5)	
Intermediate	354 (35.9)	677 (32.1)	
High	333 (33.8)	1,125 (53.4)	
RP GS			<0.001
≤6	463 (47.0)	402 (19.1)	
7	412 (41.8)	1,121 (53.2)	
≥8	110 (11.2)	584 (27.7)	
RP T stage			<0.001
OC	985 (100)	358 (17.0)	
EPE	0	1,448 (68.7)	
SVI	0	301 (14.3)	
PSM			<0.001
No	985 (100)	619 (29.4)	
Yes	0	1,488 (70.6)	

PSA = prostate specific antigen; GS = Gleason score; RP = radical prostatectomy; OC = organ confined; EPE = extraprostatic extension; SVI = seminal vesicle invasion; PSM = positive surgical margin; APFs = adverse pathologic findings.

3. Cox regression analysis of biochemical recurrence

Of 3,092 patients, 899 men experienced BCR at a median follow-up of 66 months (IQR 65-96). Five-year BCRFS for men with low-, intermediate-, and high-preoperative risk was 86.6%, 75.5%, and 52.0%, respectively.

The BCRFS rate for men with APFs was worse than those without APFs in not only overall patients but also each risk groups (overall: $p < 0.001$, low: $p = 0.027$, intermediate: $p < 0.001$, and high: $p < 0.001$) (Fig. 1A, B, C and D, respectively).

Table 4 shows results of multivariate Cox regression analyses predicting BCR following RP in the overall and stratified cohort according to preoperative risk category. For the overall population, year of surgery (HR 0.97, $p < 0.001$), PSA (HR 1.00, $p = 0.012$), RP GS (GS 7: HR 2.18, $p < 0.001$, GS $\geq$8: HR 4.66, $p < 0.001$) and APFs (EPE: HR 1.36, $p < 0.001$, SVI: HR 2.45, $p < 0.001$, and PSM: HR 1.93, $p < 0.001$) were significantly associated with BCR. In the low-risk group age (HR 1.04, $p = 0.029$), year of surgery (HR 0.85, $p < 0.001$), RP GS $\geq$8 (HR 2.94, $p = 0.007$), and PSM (HR 1.87, $p < 0.010$) were independent prognostic factors for BCR while in the intermediate-risk group, BCR was significantly associated with PSA (HR 1.08, $p < 0.001$), RP GS (7: HR 1.73, $p = 0.004$, $\geq$8: HR 1.85, $p = 0.022$) and APFs (SVI: HR 2.16, $p = 0.002$, and PSM: HR 2.42, $p < 0.001$). For the high-risk group, year of surgery (HR 0.98, $p = 0.022$), PSA (HR 1.00, $p < 0.001$), RP GS (7: HR 2.35, $p < 0.001$, $\geq$8: HR 4.63, $p < 0.001$), and APFs (EPE: HR 1.51, $p < 0.001$, SVI: HR 2.34 $p < 0.001$, and PSM: HR 1.71, $p < 0.001$) were significant predictors for BCR. EPE was not an independent prognostic factor of BCR for low- and intermediate-risk group ($p = 0.910$ and $p = 0.923$, respectively). Also there was no association between SVI and BCR in the low-risk group ($p = 0.118$).

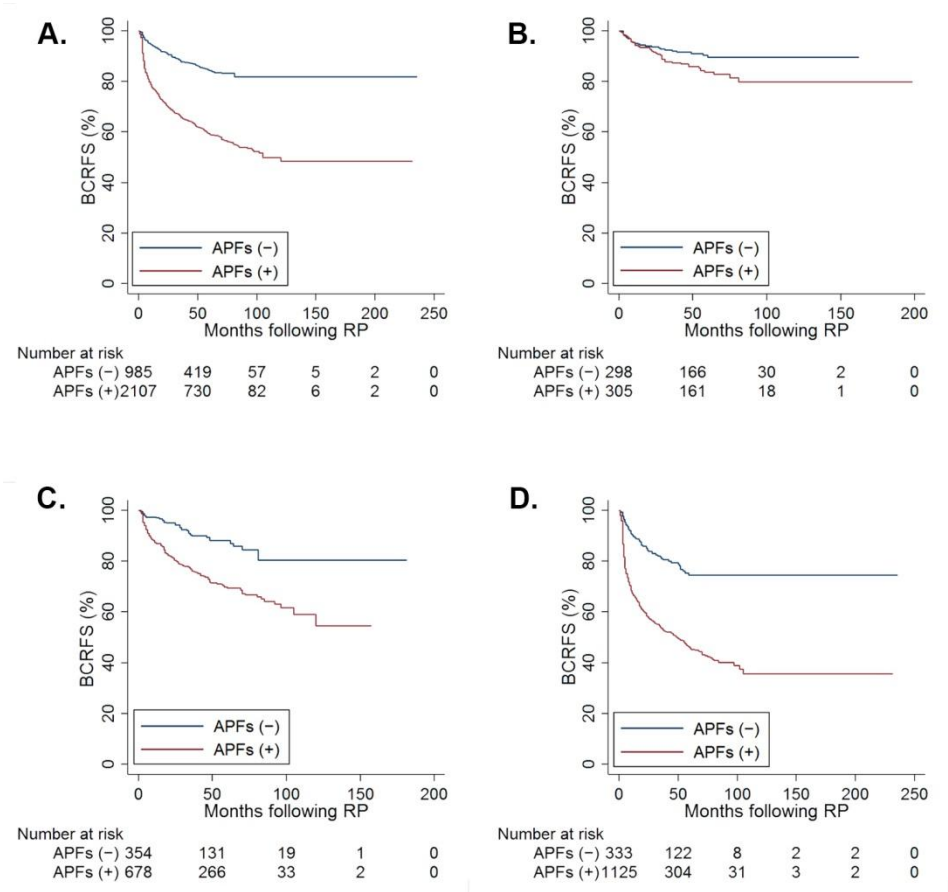

Fig. 1 Kaplan-Meier estimates of biochemical recurrence–free survival (BCRFS) after radical prostatectomy (RP) by the presence of adverse pathological findings (APFs) for (A) overall patients (log-rank test, $p < 0.001$), (B) low-risk patients ($p = 0.027$) (C) intermediate-risk patients ($p < 0.001$), and (D) high-risk patients ($p < 0.001$)

Table 4. Multivariate Cox regression analysis of biochemical recurrence according to the preoperative risk group

variable	Overall		Low		Intermediate		High	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.01 (0.99-1.02)	0.093	1.04 (1.00-1.08)	0.029				
Year of surgery	0.97 (0.95-0.98)	<0.001	0.85 (0.79-0.91)	<0.001	0.97 (0.94-1.02)	0.305	0.98 (0.95-0.99)	0.022
PSA	1.00 (1.00-1.00)	0.012	1.09 (0.96-1.24)	0.170	1.08 (1.05-1.11)	<0.001	1.00 (1.00-1.01)	<0.001
RP GS								
≤6	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
7	2.18 (1.74-2.72)	<0.001	1.60 (0.97-2.68)	0.067	1.73 (1.20-2.50)	0.004	2.35 (1.59-3.48)	<0.001
≥8	4.66 (3.70-5.88)	<0.001	2.94 (1.34-6.48)	0.007	1.85 (1.09-3.12)	0.022	4.63 (3.15-6.82)	<0.001
RP T stage								
OC	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
EPE	1.36 (1.14-1.61)	<0.001	0.97 (0.57-1.65)	0.910	1.02 (0.75-1.37)	0.923	1.51 (1.20-1.91)	<0.001
SVI	2.45 (1.97-3.04)	<0.001	2.23 (0.82-6.10)	0.118	2.16 (1.32-3.53)	0.002	2.34 (1.79-3.06)	<0.001
PSM								
No	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Yes	1.93 (1.66-2.24)	<0.001	1.87 (1.16-3.03)	0.010	2.42 (1.79-3.28)	<0.001	1.71 (1.42-2.06)	<0.001

PSA = prostate specific antigen; RP = radical prostatectomy; GS = Gleason score; OC = organ confined; EPE = extraprostatic extension; SVI = seminal vesicle invasion; PSM = positive surgical margin; HR = hazard ratio; CI = confidence interval; Ref = reference.
Significant variables on univariate analysis were included in the multivariate model.

4. Competing risk regression analysis of prostate cancer-specific mortality

Of 3,092 patients, 85 men (low: 8, intermediate: 13, and high: 63) died due to PC at a median follow-up of 66 months (IQR 65-96). Five-year PC-specific survival rates for men with low-, intermediate-, and high-preoperative risk were 99.6%, 99.4%, and 97.1%, respectively. Ten year PC-specific survival rates for patients with low-, intermediate-, and high- preoperative risk were 97.3%, 96.6%, and 87.5%, respectively.

The cumulative incidence estimates of PCSM for men with APFs was higher than those without APFs in not only overall patients but also high risk group (Gray's modified log rank, $p = 0.001$ and $p = 0.010$, respectively), while it was not in the low and intermediate risk groups ($p = 0.903$ and $p = 0.253$, respectively) (Fig. 2A, B, C and D, respectively).

In the multivariate competing risk regression analysis, RP GS $\geq$8 and SVI were independent predictors for PCSM in overall patients (GS $\geq$8: HR 5.39, $p < 0.001$, SVI: HR 3.36, $p < 0.001$) and high risk group (GS $\geq$8: HR 6.31, $p = 0.010$, SVI: HR 4.05, $p = 0.001$), while EPE and PSM were not (Table 5).

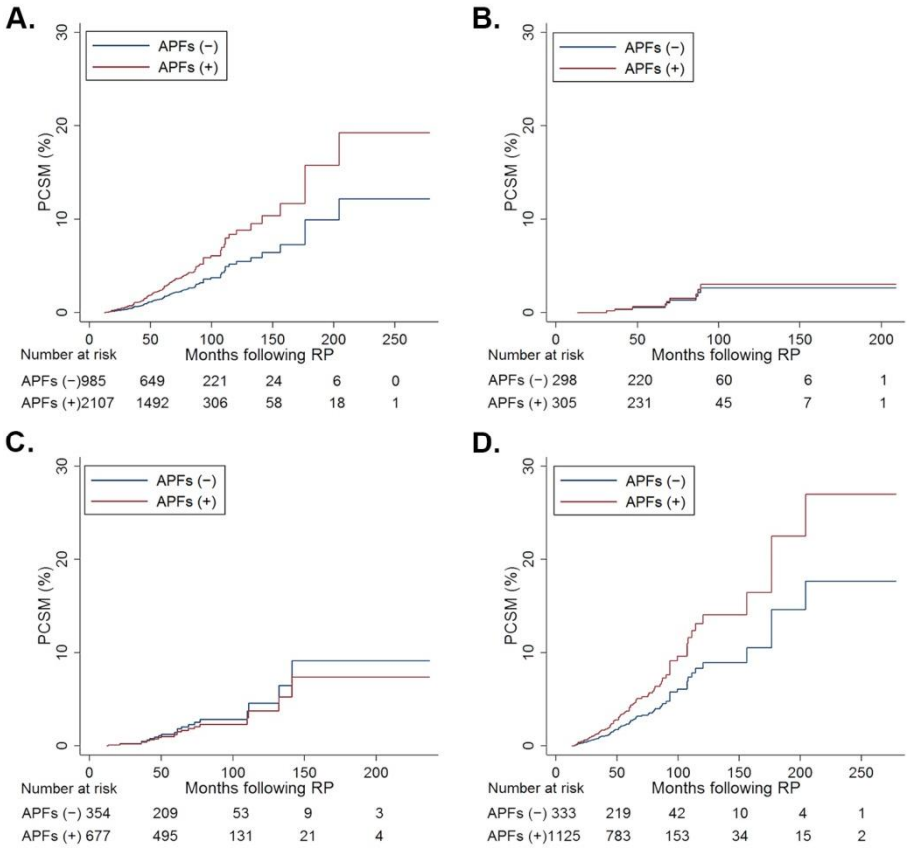

Fig. 2 Cumulative incidence estimates of prostate cancer-specific mortality (PCSM) after radical prostatectomy (RP) using competing risk analysis by adverse pathological findings (APFs) for (A) overall patients (Gray's modified log rank, p = 0.001), (B) low-risk patients (p = 0.903) (C) intermediate-risk patients (p = 0.253), and (D) high-risk patients (p = 0.010).

Table 5. Multivariate competing risk regression analysis of prostate cancer-specific mortality in overall patients and high risk group

variable	Overall*		High risk*	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.03 (0.99-1.07)	0.076	1.04 (0.99-1.09)	0.081
RP GS				
≤6	1 (Ref)		1 (Ref)	
7	1.30 (0.59-2.84)	0.517	1.88 (0.43-8.15)	0.398
≥8	5.39 (2.56-11.32)	<0.001	6.31 (1.54-25.8)	0.010
RP T stage				
OC	1 (Ref)		1 (Ref)	
EPE	1.46 (0.82-2.60)	0.201	1.97 (0.88-4.43)	0.099
SVI	3.36 (1.77-6.38)	<0.001	4.05 (1.74-9.40)	0.001

RP = radical prostatectomy; GS = Gleason score; OC = organ confined; EPE = extraprostatic extension; SVI = seminal vesicle invasion; HR = hazard ratio; CI = confidence interval.

*Year of surgery, PSA level, and positive surgical margin were not included in the multivariate model because they are not significant in the multivariate model, and we only have 85 PCSM (63 for high risk group), so including more variables will risk overfitting the model.

IV. DISCUSSION

Approximately 60% of patients with APFs after RP will experience BCR.[8] In this context, AUA/ASTRO guideline recommends ART, given soon after RP and in the absence of a rise in PSA, for patients with APFs in RP specimen. AUA/ASTRO guideline for ART is largely based on three randomized clinical trials (SWOG 8794, EORTC 22911 and ARO 96-02).[16-18] These three randomized clinical trials have shown that ART after RP for patients with APFs reduces the risk of BCR. In addition, SWOG 8794 reported improved overall survival with ART compared to observation.

Even though this guideline is in place, clinicians differ in their opinion and have a widely varied practice pattern with regards to the provision of ART.[19] This is partly due to perceived toxicity of radiotherapy potentially impairing quality of life as a result of functional complications such as incontinence and impotence while oncological benefit may not be clinically significant.[20] Moreover, SWOG 8794 trial reported that patients who underwent salvage radiotherapy (SRT) after BCR had similar overall survival rate compare to those who underwent ART with undetectable PSA level after RP.[21] In addition, Soloway et al. reported that patients with PSM who underwent ART and recurred had similar long-term outcomes compare to those who underwent SRT after BCR.[22] These results suggest that ART is not necessary for all patients with APFs after RP.

Kang et al subsequently evaluated patients with APFs who meet the current AUA/ ASTRO guideline for ART. They found that only 16.6% of patients ART developed BCR. In addition, in 87 patients with pre-operative PSA less than 6.35 ng/ml and GS <8 only three recurred (3.4%). Thus, they recommended more customized approach in selecting patients for ART to avoid significant overtreatment. They also demonstrated an association between preoperative PSA and oncological outcome. However, it was not revealed to be significant in the multivariate analysis ($p = 0.082$).[23] Swanson et al also concluded that the risk of

BCR in men with locally advanced disease varies widely depending on preoperative PSA value (<10 vs. ≥10 ng/ml) and RP GS (<7 vs. ≥7).[7]

As described above, current guideline only based on APFs could not predict oncologic outcomes accurately thus could not select optimal ART candidates after RP. To this end, we assessed whether the model incorporates preoperative risk and APFs can predict the long-term oncologic outcomes better than that only based on APFs.

NCCN preoperative risk group stratification has been widely adopted as the mainstay of treatment criteria prior to making a definitive treatment plan and patients are managed in a different manner accordingly. For instance, a low risk group can be considered for active surveillance and be monitored regularly while avoiding more definitive invasive treatment. It would be reasonable to extend its usefulness and significance of preoperative risk group stratification to post RP patients with APFs. Based on this hypothesis, we believed that preoperative risk group stratification may also influence oncologic risk associated with APFs and play an adjunctive role in selection optimal candidate for ART after RP.

Imnadze et al. recently reported that the risk of BCR in men with APFs is dramatically attenuated by low preoperative risk status that reduces the risk associated with findings such as ECE or high Gleason grade disease >50%. This suggests that preoperative risk group stratification is an important factor to consider when evaluating post-RP risk of BCR in the setting of APFs.[10] However, this study was limited by using BCR as an end-point.

In our present study, we validated the additive prognostic value of preoperative risk group stratification for patients undergoing RP on the oncologic outcomes in patients with APFs. By likelihood ratio testing, adding risk groups to the model only with APFs significantly improved the fit to the data for BCR and PCSM. Moreover, C-index showed that the predictive value for BCR and PCSM was increased when preoperative risk group was added to the model with APFs. In

order to confirm the effect of preoperative risk group stratification on oncologic outcomes of patients with APFs at RP, we performed survival analysis in terms of BCR and PCSM in cohort stratified according to preoperative risk group to find differential oncologic outcomes in each risk group. The BCRFS rate for men with APFs was worse than those without APFs in not only overall patients but also each risk groups, but there was no difference in the cumulative incidence estimates of PCSM between men with and without APFs in low and intermediate risk groups. Although RP GS ≥8 and PSM were independently associated with BCR in not only overall patients but also each risk groups, only RP GS ≥8 and SVI were associated with PCSM in overall patients and high risk group. In other words, PSM could not predict long-term oncologic outcome in overall patients and high risk group, therefore ART for men only with PSM can have significant risk of overtreatment.

Our study has important clinical implications. To the best of our knowledge, this is the first study reporting the additive prognostic value of preoperative risk group stratification on long-term oncologic outcome for patients with APFs at RP. We demonstrated that APFs at RP are associated with an increased risk of BCR and PCSM, this oncologic risk is highly influenced by preoperative risk group. These findings suggest that through the additional stratification with preoperative risk group, oncological outcomes of patients with APFs can be predicted more accurately. In other words, we could provide significantly enhanced APFs-based risk prediction model by concomitant use of preoperative risk group stratification. Therefore, we suggest that preoperative risk group should be considered in the selection of optimal ART candidates after RP although our present results need to be validated by future studies before making any recommendation.

Our study has several limitations. First, data on all patients were reviewed retrospectively from a single institution thereby our results may not be generalizable. Second, patients receiving adjuvant or salvage treatment were

included in our analyses. We were only able to obtain information on radiotherapy in part of the cohort, mostly due to the retrospective nature of the current study. Lastly, the major limitation was that we did not perform the competing risk analysis for PCSM in low and intermediate risk groups because of small number of events. To better assess the effect of preoperative risk group on these groups, a larger sample size and longer follow-up are required.

V. CONCLUSION

Our results show that the postoperative estimation of oncologic outcomes in men with APFs at RP is improved by considering preoperative risk group stratification. Although PSM was independent predictor for BCR, only RP GS ≥8 and SVI were associated with PCSM in overall patients and high risk group. These findings suggest that preoperative risk group stratification should be considered in the selection of optimal ART candidates after RP.

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ABSTRACT (IN KOREAN)

근치적 전립선적출술 후 불량한 병리소견을 나타낸 환자의 종양학적인 예후에 대한 술 전 위험군의 영향

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장원식

근치적 전립선적출술 이후의 종양학적인 예후는 술 전 위험군에 따라 다르게 나타날 것으로 예상이 되나 현재의 술 후 보조 방사선치료에 관한 진료지침은 술 전 평가된 위험군을 고려하지 않고 술 후에 보고된 양성절제변연, 피막외침범, 정낭침범으로 정의되는 술 후 불량한 병리소견만을 토대로 대상자를 설정하고 있다. 따라서, 본 연구에서는 술 후 불량한 병리소견이 나타난 전립선암 환자의 종양학적인 예후에 대한 술 전 평가된 위험군의 영향을 분석해 보고자 하였다.

1992년부터 2014년 까지 근치적 전립선적출술을 시행 받은 환자 중 신보조요법 또는 보조요법을 받은 환자 및 림프절 전이 환자를 제외한 3092 명의 환자를 대상으로 후향적인 분석을 하였다. 전체 대상 환자는 NCCN 술 전 위험군에 따라 분류하여 각 위험군의 임상병리학적 특징을 분석하였으며 불량한 병리소견을 이용하여 예측한 모델에 술 전 위험군을 새로운 변수로 추가하였을 때 암특이사망을 예측하는 정확도에 어떠한 변화가 발생하는지를 분석하였다. 또한 경쟁위험분

석을 이용하여 불량한 병리소견에 따른 암특이사망을 각각의 위험군별로 분석하였다.

전체 추적관찰기간의 중간값은 66 개월이었으며 최대값은 278 개월이었다. NCCN 저위험군은 603명, 중간위험군은 1031명, 고위험군은 1458명이었으며 이들 중 불량한 병리소견이 보인 환자는 각각 305명 (50.6%), 677명 (65.7%), 1125명 (77.2%)이었다. 불량한 병리소견을 이용하여 생화학적 재발과 암특이사망을 예측한 모델에 비해 술 전 위험군을 새로운 변수로 추가하였을 때 더 데이터에 적합한 모델임을 확인하였으며 (likelihood ratio test, $p < 0.001$), c-index는 생화학적 재발에서 0.693 에서 0.732 로, 암특이사망에서는 0.707 에서 0.747로 유의하게 증가함을 알 수 있었다. 불량한 병리소견 여부에 따라 나눈 두 군간의 암특이사망율은 전체환자 ($p = 0.001$) 및 고위험군 ($p = 0.010$)에서는 통계적으로 유의한 차이를 보였으나, 저위험군 ($p = 0.903$)과 중간위험군 ($p = 0.253$)에서는 유의한 차이를 보이지 않았다. 또한 전체환자 및 고위험군의 암특이사망에 대한 다변량분석에서 병리글리슨점수 8점 이상 (전체환자 HR 5.39, $p < 0.001$; 고위험군 HR 6.31, $p = 0.010$)과 정낭침범 (전체환자 HR 3.36, $p < 0.001$; 고위험군 HR 4.05, $p = 0.001$) 만이 독립적으로 의미있는 인자였다.

결론적으로, 술 전 위험군의 분류는 근치적 전립선적출술 후 불량한 병리소견이 보고된 환자의 예후를 보다 정확하게 예측하는데 도움이 되었다. 근치적 전립선적출술 후 보조 방사선 치료를 결정할 때 불량한 병리소견과 함께 술 전 위험군을 고려해야 할 것으로 생각된다.

핵심되는 말 : 전립선 암, 근치적 전립선적출술, 술 전 위험군