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Research Article

Association between preradiation therapy prostate-specific antigen levels and radiation therapy failure after prostatectomy: a propensity score matched analysis

Younsoo Chung [a], Sang Hun Song [a], Hakmin Lee [a], Jong Ho Park [a], Sung Kyu Hong [a, b, *, ☆]

[a] Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea
[b] Department of Urology, Seoul National University College of Medicine, Seoul, Korea

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ABSTRACT

Purpose: We sought to determine the association between the pre-radiation therapy prostate-specific antigen (pre-RT PSA) 0.5 and RT failure in post-radical prostatectomy (post-RP) patients. Our study also investigated the prognostic factors for the failure of RT given concurrently with hormone therapy (HT) after RP.

Materials and methods: We retrospectively reviewed our institutional RP data from July 2004 to November 2021. Patients without concurrent hormone therapy were excluded. Propensity score matching was performed. Kaplan–Meier (KM) curve analysis was employed for RT failure-free survival, overall survival (OS), and cancer-specific survival (CSS). Cox regression analysis was used for the RT failure hazard ratio (HR).

Results: After propensity score matching, 193 patients were assigned to the pre-RT PSA ≥0.5 (high-P) arm, and 193 patients were assigned to the pre-RT PSA <0.5 (low-P) arm. There were no significant differences between the two arms after propensity score matching in terms of baseline characteristics and pathologic outcomes. High-P was associated with RT failure-free survival ($P = 0.004$), OS ($P = 0.046$), and CSS ($P = 0.027$). In a multi-variable Cox proportional hazards regression analysis, seminal vesicle invasion, lymph node invasion, the absence of prostatic intraepithelial neoplasia (PIN), and high-P were identified as significant risk factors for RT failure.

Conclusion: High-P was significantly unfavorable with RT failure-free survival, OS, and CSS in patients who underwent RT after radical prostatectomy with concurrent HT. Seminal vesicle invasion, lymph node invasion, and the absence of PIN were identified as significant prognostic factors for RT failure.

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1. Introduction

Prostate cancer is the second most common cancer in men worldwide, with the second highest incidence and fifth highest mortality rate.[1] Treatment for prostate cancer is based on life expectancy and risk stratification. The main treatment options for localized prostate cancer are radical prostatectomy (RP) and radiation therapy (RT).[2,3] Other options include brachytherapy, active surveillance, and watchful waiting.

Recurrence rates are reported to be in the range of 20–60% following localized prostate cancer treatment such as RP or RT.[4,5] Imaging studies, physical examinations, and prostate-specific antigen (PSA) measurements are used to monitor recurrence. The pattern of PSA changes is often used to evaluate biochemical recurrence (BCR).[6,7] If recurrence is suspected after RP, additional treatments, such as RT or hormone therapy (HT), may be administered.[8,9]

The potential for distant metastasis must be considered. At the time of BCR, it is challenging to differentiate between local recurrence and distant metastasis. However, the risk of distant metastasis may be increased if appropriate treatment is not initiated at the time of BCR. There has been an ongoing debate regarding the timing of RT initiation and the starting PSA level.[10–15] Lee et al and Stish et al conducted research based on a pre-RT PSA of 0.5. Pre-RT

* Corresponding author. Department of Urology, Seoul National University College of Medicine, Seoul, Korea.
E-mail address: skhong@snubh.org (S.K. Hong).
☆ Present postal address: Building 1, 7th floor Urology office, 300-0, Bundang-gu, Seongnam-si Gyeonggi-do, Korea.

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PSA is defined as the PSA level at the time of deciding to proceed with RT. Bartkowiak et al conducted their study based on a threshold of 0.2.[10,11] Aikawa et al also identified 0.44 as a threshold through the receiver operating characteristic (ROC) curve.[16] Research also continues on adjuvant or salvage therapy criteria and radiation dosage.[17-20]

Despite the use of a variety of treatment modalities, a rebound in PSA levels is often considered to be an indication of treatment failure. We sought to determine the association between the pre-RT PSA 0.5 and RT failure-free survival. RT failure-free survival was defined as the period from the time of administering adjuvant or salvage RT after RP to the occurrence of RT failure. Our study also investigated the prognostic factors for the failure of RT given concurrently with HT after RP.

2. Materials and methods

2.1. Study population

This retrospective study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (approval number: B-2312-873-104). We reviewed the data of patients who underwent RP and postoperative RT in our tertiary hospital between July 2004 and November 2021. Patients without concurrent HT were excluded. The patients were divided into 2 arms: High pre-RT PSA (high-P) and low pre-RT PSA (low-P). Patients were classified into the high-P arm when the pre-RT PSA was $\geq$0.5 and into the low-P arm when it was below 0.5. The following criteria were used to define RT failure: (a) a serum PSA level higher than 0.2 ng/mL after the post-RT nadir; and (b) a continuous increase in PSA levels despite RT. The review of RT data did not differentiate between adjuvant and salvage treatments. A continuous increase in PSA was defined as a rise of more than twice without any decline during follow−up.

2.2. Variables

The baseline characteristics included age, body mass index (BMI), National Comprehensive Cancer Network (NCCN) risk stratification group, family history, hypertension (HTN) history, diabetes mellitus (DM) history, smoking history, PSA, PSA density, clinical T (cT) stage, and prostate biopsy Gleason score. For pathologic outcomes, we compared the pathologic Gleason score, pathologic T (pT) stage, lymph node invasion, and various microscopic findings. For a subanalysis on factors influencing RT failure, peri-radiation RT outcomes were examined in patients who experienced RT failure and those who did not. This analysis included pre-RT PSA levels, the proportion of patients with high P, RT dosage, RP-RT interval, RT setting (adjuvant or salvage), the type of concurrent hormone therapy, and outcomes of radiologic modality follow-up.

2.3. Statistical analysis

Propensity score matching was performed using R with a 1:1 matching ratio, using the “nearest” method and a caliper of 0.1. The matched variables included age, BMI, DM history, HTN history, pT stage, pathologic Gleason score, seminal vesicle invasion, and margin positive. Chi-squared tests and independent t-tests were performed to compare the two groups. Kaplan−Meier (KM) curve analysis was employed for RT failure-free survival, overall survival (OS), and cancer-specific survival (CSS). All KM curves were compared between the high-P arm and the low-P arm using the log-rank test. Cox regression analyses were used for the RT failure hazard ratio (HR). For the multivariable Cox regression analysis, only variables with a P-value less than 0.2 in the univariable Cox regression analysis were included. All statistical analyses were performed using Statistical Package for the Social Sciences version 25 (IBM Corp., Armonk, NY, USA) and R statistical software. A two-tailed $P < 0.05$ indicated statistical significance.

3. Results

In this study, 805 patients were reviewed. A total of 634 patients who received postoperative radiotherapy after RP were evaluated after data evaluation and exclusion. The baseline characteristics of the two groups before propensity score matching are shown in the Supplementary Table. After propensity score matching, 193 patients were assigned to the high-P arm, and 193 patients were assigned to the low-P arm. Table 1 shows the baseline characteristics. There were no significant differences between the two arms after propensity score matching. Table 2 shows the pathologic

Table 1
Baseline characteristics

Variable	Pre-RT PSA <0.5	PreRT PSA ≥0.5	*P*
Age, y, mean [IQR]	66.2 [6.9]	66.2 [6.7]	0.947
BMI, kg/m^2 [IQR]	24.9 [2.9]	24.6 [2.9]	0.316
DM, *n* (%)	20 (20.0)	74 (18.5)	0.731
HTN, *n* (%)	40 (40.0)	185 (46.3)	0.261
Family history, *n* (%)	5 (5.0)	20 (5.0)	>0.999
Smoking history, *n* (%)	46 (46.0)	211 (52.9)	0.218
PSA, ng/mL, mean [IQR]	27.797 [30.420]	26.969 [33.431]	0.822
PSAd, ng/mL/cc, mean [IQR]	0.76 [0.79]	0.76 [0.80]	0.975
cT stage, *n* (%)			0.381
1	21 (21.0)	89 (22.3)	
2	23 (23.0)	116 (29.0)	
3	56 (56.0)	195 (48.8)	
NCCN stratification, *n* (%)			0.141
Low	0 (0.0)	0 (0.0)	
Intermediate	11 (11.0)	68 (17.0)	
High	89 (89.0)	332 (83.0)	
Biopsy Gleason score, *n* (%)			0.057
6	3 (3.0)	22 (5.5)	
7	28 (28.0)	154 (38.5)	
8−10	69 (69.0)	224 (56.0)	

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; PSAd, prostate-specific antigen density; RT, radiation therapy.

Table 2
Pathologic outcomes

Variable	Pre-RT PSA ≥0.5	Pre-RT PSA <0.5	*P*
Pathologic Gleason score, *n* (%)			0.628
7	95 (49.2)	92 (47.7)	
8	32 (16.6)	27 (14.0)	
9	66 (34.2)	74 (38.3)	
pT Stage, *n* (%)			0.861[a]
2	48 (24.9)	43 (22.3)	
3	143 (74.1)	148 (76.7)	
4	2 (1.0)	2 (1.0)	
LNI, *n* (%)	20 (10.4)	13 (6.7)	0.203
Extracapsular evasion, *n* (%)	142 (73.6)	137 (71.0)	0.570
Seminal vesical invasion, *n* (%)	80 (41.5)	87 (45.1)	0.472
Bladder neck invasion, *n* (%)	32 (16.6)	23 (11.9)	0.190
Angiolymphatic invasion, *n* (%)	111 (57.5)	96 (49.7)	0.126
Venous invasion, *n* (%)	5 (2.6)	4 (2.1)	>0.999[a]
Perineural invasion, *n* (%)	179 (92.7)	180 (93.3)	0.842
Multicentricity, *n* (%)	135 (69.9)	142 (73.6)	0.429
PIN, *n* (%)	169 (87.6)	175 (90.7)	0.327
Margin positive, *n* (%)	112 (58.0)	110 (57.0)	0.837

LNI, lymph node invasion; PSA, prostate-specific antigen; pT, pathologic T; PIN, prostatic intraepithelial neoplasia; RT, radiation therapy.
[a] Fisher exact test.

results. Pathologic outcomes also showed comparable results between the two arms.

Factors associated with radiotherapy are shown in Table 3. The RT failure group had a higher proportion of high−P patients ($P = 0.017$). RP-RT intervals were longer in the no-RT failure group than in the RT failure group ($P < 0.001$). Salvage settings were more common in the RT failure group than in the no-RT failure group ($P = 0.004$). The RT failure group had more distant metastases than the no-RT failure group at radiologic follow-up ($P < 0.001$).

The KM curves are presented in Fig. 1. High-P was associated with RT failure-free survival ($P = 0.004$), OS ($P = 0.046$), and CSS ($P = 0.027$). The predictors of RT failure after RP were evaluated and shown in Fig. 2. After univariable Cox proportional hazards regression analysis, HTN, pathologic Gleason score, high-P, RP-RT interval, and microscopic findings of multicentricity, lymph node invasion, seminal vesicle invasion, venous invasion, prostatic intraepithelial neoplasia (PIN), and angio-lymphatic invasion were employed for multi-variable Cox proportional hazards regression analysis. In a multi-variable Cox proportional hazards regression analysis, seminal vesicle invasion (HR 1.78, 95% confidence interval (CI) 1.09−2.93), lymph node invasion (HR 3.04, 95% CI 1.62−5.72), the absence of PIN (HR 3.78, 95% CI 2.24−6.38), and pre-RT PSA ≥0.5 (HR 2.09, 95% CI 1.28−3.40) were identified as significant risk factors for RT failure.

4. Discussion

After propensity score matching, the high-P arm and low-P arm were comparable in terms of baseline characteristics and pathologic outcomes. However, the low-P arm showed favorable RT-failure-free survival, OS, and CSS. High-P, seminal vesicle invasion, lymph node invasion, and the absence of PIN were confirmed as prognostic factors for RT failure.

A study by Lee et al of patients undergoing salvage radiotherapy (SRT) after radical prostatectomy (RP) found that pre-RT PSA ≤0.5 improved metastasis-free survival.[10] Research by Stish et al also showed a significant reduction in BCR, distant metastasis, cancer-specific mortality, and all-cause mortality with pre-SRT PSA ≤0.5.[11] A study by Song et al on SRT settings showed an association between pre-RT PSA ≥1.0 and RT failure after RP.[12] However, patients who had been treated with HT were excluded from the study.[12] Bartkowiak et al's research suggested that performing SRT

Table 3
Peri-radiation therapy outcomes

Variable	RT fail ($N = 70$)	No − RT fail ($N = 316$)	*P*
Pre − RT PSA, ng/mL, median [IQR]	0.725 [0.321−3.649]	0.462 [0.301−0.937]	0.124[a]
Pre − RT PSA ≥0.5 ng/mL, *n* (%)	44 (62.9)	149 (47.2)	0.017
RT dosage, gray, median [IQR]	66.6 [66.0−68.0]	66.0 [66.0−68.0]	0.528[a]
RP-RT interval, mo, median [IQR]	6.0 [4.0−15.8]	12.0 [6.0−27.0]	<0.001[a]
RT setting, *n* (%)			0.004
Adjuvant	33 (47.1)	207 (65.5)	
Salvage	37 (52.9)	109 (34.5)	
HT type, *n* (%)			0.054
LHRH agonist/antagonist	3 (4.3)	23 (7.3)	
Bicalutamide	40 (57.1)	131 (41.5)	
LHRH agonist/antagonist + bicalutamide	27 (38.6)	162 (51.3)	
Radiologic abnormality, *n* (%)			<0.001[b]
No suspicious lesion	32 (45.7)	312 (98.7)	
Local recurrence	1 (1.4)	0 (0.0)	
Distant metastasis	37 (52.9)	4 (1.3)	

HT, hormone therapy; IQR, interquartile range; LHRH, lutenizing hormone releasing hormone; PSA, prostate specific antigen; RP, radical prostatectomy; RT, radiation therapy.
[a] Independent t-test.
[b] Fisher exact test.

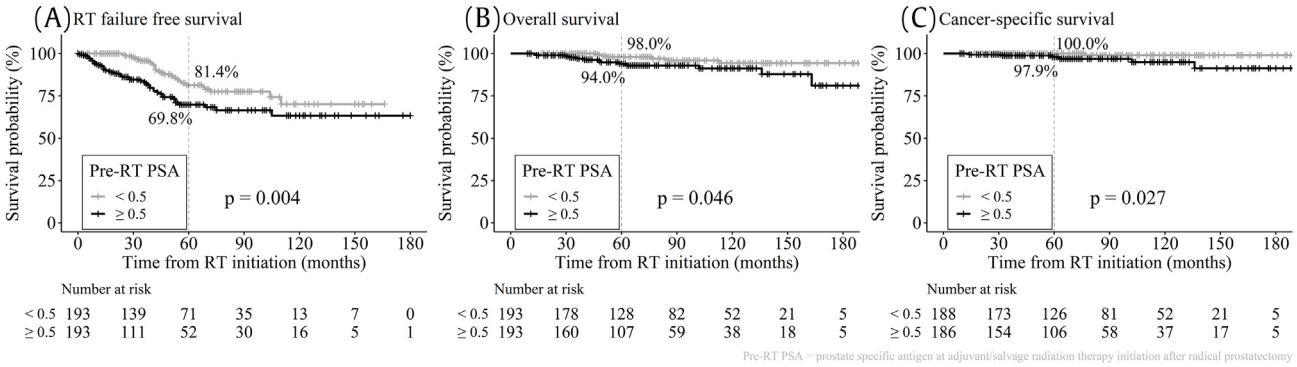

Fig. 1. Survival outcome comparison between pre-RT PSA ≥0.5 arm and pre-RT PSA <0.5 arm (A) radiation therapy failure-free survival (B) overall survival (C) cancer-specific survival.

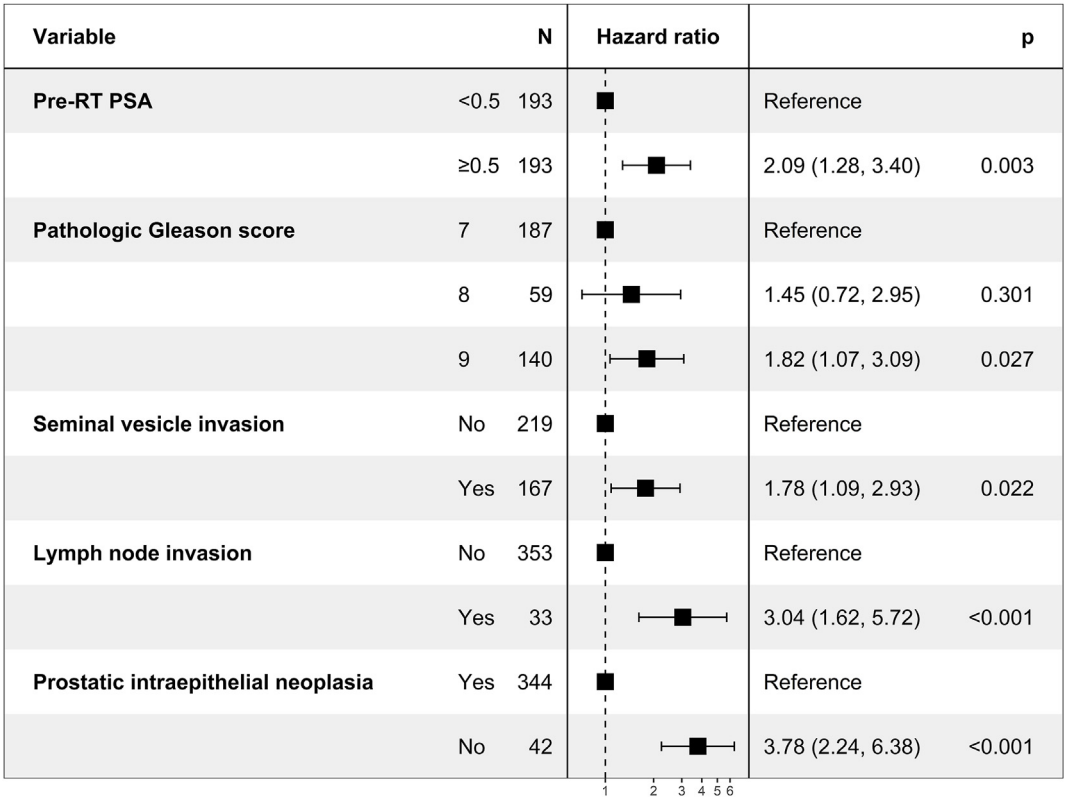

Fig. 2. Radiation therapy failure is multivariable Cox proportional analysis outcome.

in patients with pre-RT PSA <0.2 was associated with achieving undetectable PSA levels after RT.[13] Patients were excluded from the study if they had undergone androgen deprivation therapy between RP and SRT.[13] In a systematic review by Ghadjar et al an improvement in OS was observed with a pre-RT PSA <0.7.[21] Pfister et al's review showed improved BCR-free survival with pre-SRT PSA <0.5.[14] However, they noted that the favorable outcomes may also have been influenced by the use of high-dose RT and androgen deprivation therapy.[14] A systemic review by Kishan et al recommends starting SRT when the pre-SRT PSA is low, although they could not derive an absolute threshold.[15] Aikawa et al conducted a multicenter retrospective study of the administration of SRT after RP, regardless of HT status.[16] In particular, they used a receiver operating characteristic curve to establish a PSA threshold of 0.44 for their study and concluded that SRT should be administered before the PSA level reaches 0.44.[16] Our study threshold could be formed below 0.5 when drawing an ROC curve. However, in view of the retrospective setting and the fact that many studies report a threshold of 0.5, we also chose 0.5 as our threshold. In our research, high-P significantly increased the RT-failure-free survival, the OS, and the CSS, and also significantly increased the HR for RT failure.

There have also been several studies with a focus on microscopic pathology findings. A study by Liauw et al reported that seminal vesicle invasion and lymphovascular invasion were associated with RT failure.[22] It is important to note that the definition of RT failure in this study included cases with added HT.[22] In a multicenter study by Stephenson et al, seminal vesicle invasion was identified as one of the predictors of disease progression after SRT.[23] In this study, androgen deprivation therapy (ADT) was one of the criteria for the definition of SRT failure.[23] In contrast, a systemic review and meta-analysis by Jia et al suggested that seminal vesicle invasion did not have a significant effect.[24] However, it is important to note that this

study was conducted in a SRT setting without the combination of ADT.[24] In our study, seminal vesicle invasion and lymph node invasion were significant prognostic factors for RT failure. There were few mechanisms or studies that clearly explained prostatic intraepithelial neoplasia (PIN). PIN is considered a precursor to prostate cancer.[25,26] Although mechanisms may link a high precursor ratio to a better radiotherapy response, further research is needed.

In the RT failure group, the RP-RT interval was short, and many of the cases were in the salvage setting. While pre-RT PSA was not significantly different, there was a trend toward higher levels in the RT failure group, which may be related to a higher incidence of distant metastases. SRT is more likely indicative of the high possibility that distant metastasis has already occurred rather than influencing the failure itself. This would lead to a rapid rise in PSA levels, resulting in a shorter RP-RT interval, and thus RT would have been performed more frequently in a salvage setting. Adjuvant therapy and salvage therapy have been topics of interest for several research institutions, and several randomized controlled trials (RCTs) have been conducted. A meta-analysis by Vale found no evidence that adjuvant RT improved event-free survival in comparison with early SRT.[17] The TROG 08.03/ANZUP RAVES RCT compared adjuvant RT versus early salvage therapy in patients with pre-RT PSA $\geq$0.2.[18] The 5-year freedom from biochemical progression was not significantly different between the groups.[18] The GETUG-AFU 17 RCT compared adjuvant radiotherapy with early salvage radiotherapy combined with short-term HT.[19] The 5-year event-free survival did not differ significantly between the two groups.[19] In the RADICALS-RT RCT, there was no significant difference in 5-year biochemical progression-free survival between the adjuvant group and the salvage group.[20] Those RCTs consistently reported that adjuvant therapy was associated with more side effects than salvage therapy.[20] In our study, although there were differences in RT setting and RP-RT interval between the RT failure group and the no-RT failure group, the fact that the multi-variable Cox proportional analysis did not significantly increase the RT failure HR suggests that the results of these RCTs and our study are consistent.

4.1. Limitations and strength

Several limitations existed in this study. First, during the propensity score matching process, the low-risk group, according to NCCN risk stratification, was excluded. As a result, the effect of pT stage and Gleason score may not be clear in our study. All patients with pT stage 1 and a pathologic Gleason score of 6 were deleted. Second, because this study focused on patients who received concurrent HT, the observed results may not be solely attributable to RT. Third, the study may have been susceptible to selection bias because it was conducted as a retrospective study of patients who underwent surgery at a tertiary center. However, despite these potential limitations, the study has the strength of using a large data set and employing propensity score matching to minimize bias.

5. Conclusion

In conclusion, our study showed that high-P was significantly unfavorable with RT failure-free survival, OS, and CSS in patients who underwent RT after radical prostatectomy with concurrent HT. Seminal vesicle invasion, lymph node invasion, and the absence of PIN were identified as significant prognostic factors for RT failure.

Conflicts of interest

There is no conflict of interest.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2024.03.001.

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