The possibility of hormone-mediated PSA derangement in prostate cancer treatment

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ABSTRACT

Background: This study was designed to suggest the possibility of hormone-related derangement in salvage radiotherapy (SRT) after radical prostatectomy in terms of prostate-specific antigen (PSA) control. *Materials and Methods*: Among 160 consecutive prostate cancer patients who received radical prostatectomy, 34 with SRT between 2004 and 2012 were retrospectively reviewed. The numbers of patients with pathologic T3-T4 stage, Gleason score 8-10, and positive resection margin were 11 (32.4%), 10 (29.4%), and 17 (50.0%), respectively. Median SRT dose was 64.8 Gy (range, 52.9-70.0 Gy) with 1.8-2.3 Gy fractionations. Biochemical failure-free survival after SRT was counted and the median follow-up period was 32.5 months (range, 10-118 months). *Results:* After SRT, the median time for PSA to decrease to less than 0.2 ng/mL was four months (range, 0-25 months). The three-year survival rate was 60.3%. On univariate analysis, preferential hormone therapy (PHT) (p=0.022), higher PSA at SRT (p=0.005), and higher PSA after surgery (p=0.003) were related to a shorter biochemical survival period. On multivariate analysis, lower PSA at SRT (p=0.016), higher radiation dose (p=0.007), and non-PHT (p=0.046) suggested a consistent PSA control. *Conclusion:* According to these results, low PSA values by hormonal intervention need to be reconsidered with a different way to look at the relationship between the PSA and hormone therapy. SRT should be considered for postoperative salvage treatment regardless of the hormone-related PSA values.

Keywords: Hormone therapy, Prostate cancer, Salvage radiotherapy.

INTRODUCTION

Radiotherapy as a postoperative salvage treatment is essential for loco-regional control of prostate cancer [1-6]. Hormone therapy is preferred as an adjuvant or salvage treatment for biochemical failure (BCF) after radical prostatectomy because of its synergistic effect to salvage radiotherapy (SRT) and excellent prostate-specific antigen (PSA) control capacity [7-11]. However, BCF management is still controversial. Although many SRT studies were reported, the benefits of hormone therapy and proper SRT timing have not yet been established in post-prostatectomy condition [12, 13].

Occasionally, even with poor prognostic surgical pathology, SRT tends to be suspended when the PSA remains low. At present, the relationship between biochemical control and hormone therapy needs to be reconsidered. This study was conducted to reassess the influence of hormone therapy in SRT-required patients after radical prostatectomy in terms of BCF-free survival.

MATERIALS AND METHODS

We retrospectively reviewed the medical data of 160 consecutive prostate cancer patients who underwent radical prostatectomy. Among them, there were 34 SRT cases between 2004 and

2012. Despite the small number of patients caused by poor SRT reliance background in some Asian countries in the past, this study was attempted to find the true meaning of hormone-related biochemical control with the approval of the institutional review board of our institution (Approval number: 14-5-029). The study was performed in agreement with applicable laws and regulations, and ethical principles.

Initial diagnosis and treatment

All pathologic diagnoses were adenocarcinoma for 34 SRT patients. Median age at diagnosis was 65.5 years (range, 48-73 years).

PSA value was greater than 10 ng/mL in 19 patients (55.9%). The numbers of patients with locally-advanced T stage (T3a to T4) and a high Gleason score (8-10) were 11 (32.4%) and 10 (29.4%), respectively. Pelvic lymph node metastasis was not detected. Half of the patients (17 patients, 50.0%) showed a positive resection margin. Patient characteristics at initial treatment are shown in table 1. All patients had a performance status of ECOG 0 or 1. One patient had received right hemicolectomy nine years prior due to colon cancer and had been recurrence-free since that time. No one had previous pelvic irradiation or chemotherapy.

Table 1. Patient demographic and clinical features related to the pretreatment status, surgery, and pathology.

Feature	Total	PHT	Non-PHT	p-value*
No. of patients	34	11	23	
Age at diagnosis (years)				0.833†
Mean	63.1 ± 6.7	62.7 ± 7.3	63.3 ± 6.6	
Median	65.5	66	64	
Range	48-73	50-71	48-73	
PSA at diagnosis				0.758‡
<4	1 (2.9%)	0 (0.0%)	1 (4.3%)	
≥4, <10	14 (41.2%)	4 (36.4%)	10 (43.5%)	
≥10, <20	8 (23.5%)	2 (18.2%)	6 (26.1%)	
≥20	11 (32.4%)	5 (45.5%)	6 (26.1%)	
Surgery type				0.805§
Open	17 (50.0%)	5 (45.5%)	12 (52.2%)	
Robot-assisted	17 (50.0%)	6 (54.5%)	11 (47.8%)	
Gleason score at surgery				0.324‡
2-6	8 (23.5%)	1 (9.1%)	7 (30.4%)	
7	16 (47.1%)	7 (63.6%)	9 (39.1%)	
8-10	10 (29.4%)	3 (27.3%)	7 (30.4%)	
Resection margin				0.714§
Positive	17 (50.0%)	5 (45.5%)	12 (52.2%)	
Negative	17 (50.0%)	6 (54.5%)	11 (47.8%)	
Perineural invasion				0.295‡
Yes	20 (58.8%)	8 (72.7%)	12 (52.2%)	
No	14 (41.2%)	3 (27.3%)	11 (47.8%)	
Beyond capsule				>0.999‡
Yes	5 (14.7%)	1 (9.1%)	4 (17.4%)	
No	29 (85.3%)	10 (90.9%)	19 (82.6%)	
Seminal vesicle invasion				0.060‡
Yes	6 (17.6%)	4 (36.4%)	2 (8.7%)	
No	28 (82.4%)	7 (63.6%)	21 (91.3%)	
Pathologic T stage				0.333‡
T2a-T2b	8 (23.5%)	2 (18.2%)	6 (26.1%)	
T2c	15 (44.1%)	4 (36.4%)	11 (47.8%)	
T3a	5 (14.7%)	1 (9.1%)	4 (17.4%)	
T3b-T4	6 (17.6%)	4 (36.4%)	2 (8.7%)	

PHT: preferential hormone therapy; PSA: prostate-specific antigen.
*Statistical analysis between PHT and non-PHT.
†Student t test.
‡Fisher exact test.
§Chi-square test.

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Initial PSA follow-up after radical prostatectomy

After surgery, patients had their PSA levels checked monthly until nadir was reached and trimonthly once the level stabilized. Loco-regional and distant workup was performed using abdominopelvic CT, prostate MRI, or bone scan. We defined surgical eradication (SE) as a PSA decrease to less than 0.2 ng/mL within two months after surgery without additional therapeutic intervention. First BCF (BCF1) was determined as a PSA increase greater than 0.2 ng/mL after SE. No acquirement of SE was categorized as BCF1.

SRT

The timing and schedule of salvage treatment were decided by physicians' discretion. Every SRT was administered after BCF1. All patients were scanned with abdominopelvic CT in the supine position using a 3-5-mm slice thickness. Radiation was delivered with external beam X-ray from LINAC. Median total dose was 64.8 Gy (range, 52.9-70.0 Gy) with 1.8-2.5 Gy fractionation per day. The pelvic lymph node area was irradiated in 30 patients (88.2%). Elective pelvic node irradiation was determined mainly according to Roach node score [14]. For contouring the surgical bed of the prostate gland or seminal vesicle, the location of surgical clips was used as a reference point. SRT-related patient characteristics are shown in table 2.

Table 1. Patient demographic and clinical features related to the pretreatment status, surgery, and pathology.

Feature	Total	PHT	Non-PHT	p-value*
No. of patients	34	11	23	0.605†
Age at SRT (years)	6.7 ± 64.2	7.2 ± 63.4	6.5 ± 64.7	
Median	66	67	65	
Range	75-49	72-51	75-49	
PSA at SRT				0.715‡
<0.6 ng/mL	15 (%44.1)	4(%36.4)	11(%47.8)	
≥ 0.6 ng/mL	19 (%55.9)	7(%63.6)	12(%52.2)	
Total dose				>0.999‡
<65 Gy	27(%79.4)	9(%81.8)	18(%78.3)	
≥65 Gy	7(%20.6)	2(%18.2)	5(%21.7)	
Whole-pelvis irradiation				0.280‡
Yes	30(%88.2)	11(%100.0)	19(%82.6)	
No	4(%11.8)	0(%0.0)	4(%17.4)	
Initial salvage treatment				
Radiation	23(%67.6)	0(%0.0)	23(%100.0)	N/A
Radiation and hormone	3(%8.8)	3(%27.3)	0(%0.0)	
Hormone	8(%23.5)	8(%72.7)	0(%0.0)	
BCF1-SRT interval				
<6 months	19(%55.9)	6(%54.5)	13(%56.5)	>0.999‡
≥6 months	15(%44.1)	5(%45.5)	10(%43.5)	

SRT: salvage radiotherapy; N/A: not applicable; BCF1: first biochemical failure; other abbreviations as in table 1.
* Statistical analysis between PHT and non-PHT.
† Student t test.
‡ Fisher exact test

PSA follow-up after SRT

PSA checkup schedule after salvage treatment was the same as after initial treatment. For the radiation effect analysis, we devised a concept of radiotherapeutic eradication (RTE) defined as a PSA decrease to less than 0.2 ng/mL after SRT without supplementary treatment. Second BCF (BCF2), whose definition was a PSA increase to greater than 0.4 ng/mL or hormonal intervention due to a steep increase in PSA, was used as an index of biochemical control after SRT. The cases of no RTE gain were categorized as BCF2.

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Statistical analysis

Radiotherapeutic survival (RTS), which means biochemical control after SRT, was the major endpoint of this study. The correlation between clinical factors and RTS was evaluated by Kaplan-Meier method. Log-rank test was used for comparing RTS according to each clinical factor. For continuous variables, Cox proportional hazard regression model was applied for univariate analysis. Statistical significance was defined as p value <0.05 level. Multivariate analysis was conducted for the factors with a significant univariate association (p <0.10). The SPSS (20.0) program (SPSS Inc., Chicago, IL, USA) was used for analysis.

RESULTS

BCF1 and SRT

At two months after surgery, the median PSA value of all patients was 0.17 ng/mL (range, 0.0-24.27 ng/mL). SE was obtained in 19 patients (55.9%), whose median immediate postoperative PSA level was 0.1 ng/mL (range, 0.0-0.60 ng/mL). The median interval from surgery to BCF1 was 4 months (range, 0-31 months) for all patients and 10 months (range, 3-31 months) for patients of SE. No one complained of any suspicious clinical symptoms at BCF1 occurrence. No gross loco-regional or distant recurrence was detected on the CT, MRI, or bone scan. SRT was initiated median 5 months (range, 1-30 months) after BCF1 occurrence, which corresponded to median 9.5 months (range, 2-42 months) after surgery. All patients had a performance status of ECOG 0 or 1 during SRT. Hormone therapy was administered to 11 patients (32.4%) before SRT. When patients were categorized according to hormone priority, no discrepancy was seen between preferential hormone therapy (PHT) and non-PHT groups for most clinical features, such as pretreatment status, surgery, and pathology (table 1). Radiation factors such as age, PSA, total dose, irradiated volume, and BCF1 to SRT interval did not show definite differences between the two groups (table 2). Median PSA value at the start of SRT was 0.79 ng/mL (range, 0.0-24.27 ng/mL).

Salvage treatment response and RTS

Median follow-up period from the final SRT date was 32.5 months (range, 10-118 months). All patients experienced RTE after SRT. Median time to RTE was 4 months (range, 0-25 months). In thirteen patients (38.2%), RTE was achieved within one month after SRT. At the time of last follow-up, 15 patients were experiencing BCF2, including eight patients (53.3%) in the PHT group and seven patients (46.7%) in the non-PHT group. No one complained of any suspicious clinical symptoms at BCF2 occurrence, and no gross loco-regional or distant lesion was detected on imaging studies available. Most patients with BCF2 received second-line hormone therapy. The overall median RTS was 32.5 months, and the three-year RTS rate was 60.3% (figure 1). It was 36.4% for the PHT group and 76.0% for the non-PHT group. On log-rank test, the non-PHT group exhibited higher RTS than the PTH group (p=0.014) (figure 2). Other factors such as surgery to BCF1 interval (p=0.024) and SE (p=0.036) seemed to be associated with higher RTS rates. Initial high Gleason score (p=0.483), positive resection margin (p=0.493), and seminal vesicle invasion (p=0.535) did not have a significant influence upon poor RTS rate.

For all patients, risk factors associated with RTS were assessed using Cox proportional hazards regression model. Continuous variables were directly analyzed without categorization. On univariate analysis, PHT (p=0.022), SE failure (p=0.047), higher PSA at SRT (p=0.005), shorter surgery-BCF1 interval (p=0.033), and higher PSA at two months after surgery (p=0.003) resulted in low RTS (table 3). High PSA at diagnosis (p=0.070) and a lower radiation dose (p=0.062) showed a borderline association with poor RTS. BCF1-SRT interval (p=0.377) and the other candidate factors were not related to RTS. In multivariate analysis using a backward stepwise method for the variables with p < 0.10, lower PSA at SRT (p=0.016), higher radiation dose (p=0.007), and non-PHT (p=0.046) were drawn as possible prognostic factors via a four-step adjustment for other potential variables (table

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3). At the time of BCF2 occurrence, some patients had started to receive second-line hormone therapy, and others were followed-up closely with regular PSA checkups. No additional surgery or radiotherapy was administered.
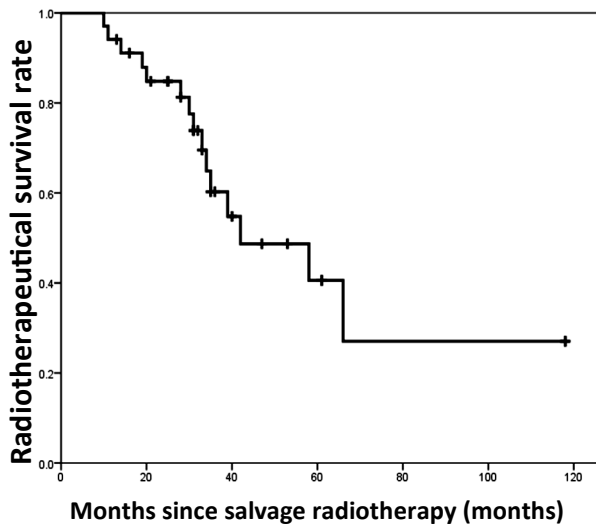

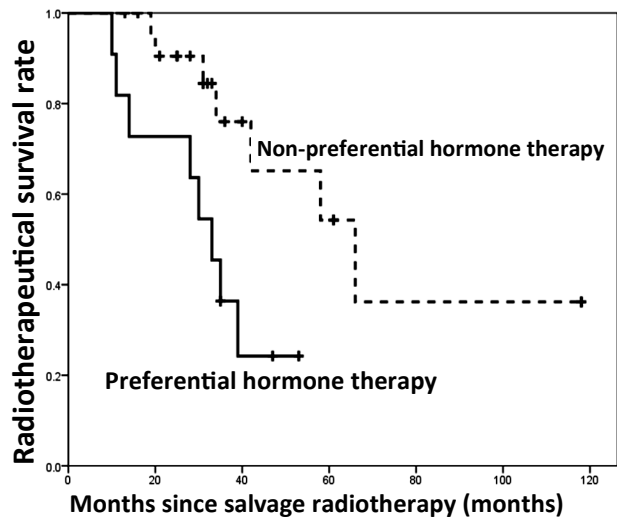**Figure 1.** Radiotherapeutics survival for all patients.

Figure 2. Radiotherapeutics survival in the PHT (preferential

Table 1. Patient demographic and clinical features related to the pretreatment status, surgery, and pathology.

Variable	Univariate analysis			Multivariate analysis (Four-step adjustment)		
	HR	*p*-value	%95CI	HR	*p*-value	%95CI
PSA at diagnosis (continuous)	1.018	0.070	1.037-0.999			
PSA at two months after surgery (continuous)	1.161	0.003	1.281-1.053			
PSA at SRT (continuous)	1.155	0.005	1.277-1.044	1.142	0.016	1.272-1.025
SE failure (yes vs. no)	3.316	0.047	10.835-1.015			
Total dose (continuous)	0.999	0.062	1.000-0.997	0.998	0.007	0.999-0.996
PHT (yes vs. no)	3.695	0.022	11.341-1.204	3.838	0.046	14.384-1.024
Surgery-BCF1 interval (continuous)	0.888	0.033	0.990-0.796			

DISCUSSION

The objective of this study was to reassess the role of hormone therapy in postoperative SRT with a different point of view. To some extent, this small retrospective review contributed to our understanding of salvage treatment for BCF1. Our approach to the PSA profile showed novel findings from the previous results which emphasize the PHT in prostate cancer salvage treatment. BCF-free survival rate, which is known to be 46–51% at three years after SRT [15], is a significant therapeutical issue in most reports. However, clinical factor analyses have not been homogeneous. That is, hormonal

agents, treatment period, radiation dose, and cancer stage are different from study to study. In our study, despite small number of cases, patient distribution was quite homogeneous. None of the patients had the condition of PSA<10 ng/mL, <T2a, and Gleason score <7 concomitantly, and SRT was performed for a relatively balanced patient group.

Radiotherapy plays an important role in loco-regional control for prostate cancer. Aggressive irradiation is being tried for locally advanced cases, and even for metastases, due to decreased radiation-related toxicity results caused by sophisticated radiation techniques [16]. The SRT dose is also known as a significant

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factor for better clinical outcome [17, 18]. In our study, temporary radiation response was excellent, that is, all patients' PSA values were reduced to less than 0.2 ng/mL within median 4 months after SRT, and a higher radiation dose (p=0.007) was associated with better RTS.

Although there is no clear guideline about salvage treatment timing, surgical risk factors such as positive resection margin, seminal vesicle invasion, or SE failure are major determinants for early start of hormone therapy because of its excellent capacity for biochemical control. However, hormonal agents may result in severe complications when used for a long time. Proper interpretation of radiation effect can be limited due to hormone-related PSA disturbance. In addition, hormone therapy itself may not be reasonable for being used as loco-regional treatment. In one multivariate study by Song et al. [19], salvage hormone therapy resulted in a higher clinical failure rate for 121 patients with biochemical recurrence (p=0.028). In contrast, a correlation between PSA control and RTS in our study (p=0.016) can be explained by the significance of hormone-excluded SRT. At present, hormonal agents need to be used more cautiously, although lower PSA at SRT is regarded as a better prognostic factor [12, 20].

Hormone-dominant salvage treatment might downsize the extent or dose of irradiation. Many PHT-favored studies were basically performed with a remarkably low proportion of pelvic lymph node-positive or whole-pelvis irradiated patients [11, 21]. In one study, neither lymph node status nor whole-pelvis radiation itself was mentioned at all [22]. In the studies of lymph node-negative patients, the radiation field was confined only to the prostatic circumferential area without elective pelvic nodal irradiation [7, 23, 24]. Namely, radiation dose itself has been compared by definitely different condition between the two groups. For example, in a study by King et al. [25], the mean dose to the prostate was 64.2 Gy in the SRT alone group, which was significantly lower than the 67.0 Gy in the combined therapy group (p <0.001).

Early hormone therapy is preferred to SRT for the poor prognostic patients. However, the effect of hormonal agents needs to be reconsidered in terms of radiotherapeutics' biochemical control. Hormonal effect may not be exactly estimated without radiotherapeutics' point of view. Even in a typical report about salvage treatment versus biochemical disease-free survival, hormonal agents were usually applied to patients who received prostate-only radiation despite the condition of pelvic lymph node metastasis [4]. In another study favoring PHT, a survival benefit of early hormone ablation was observed in the patient group with an as high as 25.8% proportion of metastatic failure [26]. Those findings are in contrast to our results, in which all patients had negative lymph node status. Thus, increased biochemical disease-free survival due to treatment with hormonal agents needs to be reevaluated in terms of the relevance of pelvic lymph node metastasis and radiation field extent.

A majority of 160 patients survived without recurrence in our cases. However, whether or not the salvage treatment for BCF was PHT may affect the treatment outcome. Contrary to expectation, some surgical factors such as positive resection margin or seminal vesicle invasion were not significant. Rather, surgeon's subjective initial judgement seems to affect final treatment results. These are related to our study's defects, which may be associated with difficulty in randomized controlled trial design. Thus, at present, the general message of this study is not to deny the effect of hormone but to consider SRT actively on salvage treatment situation.

This study has another limitation stemming from its small number of patients and relatively short follow-up time, which cannot conduct apparent conclusions based on multivariate analysis. The initial surgical indication was also inappropriate because of retrospective approach focusing SRT. However, some data reminded us of cautious hormone use in terms of biochemical control and side effects. In addition, patient distribution from long ago was relatively useful for the comparison of diverse radiation dose spectra though it is another weakness of this study. Deficiencies of these results should be improved with more

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systematic approach in future studies.

In summary, low PSA values by hormonal intervention might not guarantee biochemical control in postoperative SRT. Despite a small number of cases, our study may have a meaning in that a fresh perspective was suggested for the relationship between the PSA and hormone therapy.

Conflicts of interest: *Declared none.*

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