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Early Results of Salvage Radiotherapy for Prostate Carcinoma—Cerrahpaşa Experience

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Abstract

Objective: Salvage radiotherapy ± androgen deprivation therapy is the most preferred treatment for relapsed prostate cancer. The oncological outcomes of these patients vary according to pathologic and disease characteristics. We aimed to evaluate the factors affecting the oncological outcomes of patients who received salvage radiotherapy.

Methods: Eighty-four patients who received salvage radiotherapy ± androgen deprivation therapy between 2003 and 2020 were reviewed. Salvage radiotherapy was administered to the prostate bed with a median dose of 66 (60-76) Gy. Pelvic lymphatic irradiation was added to 15 (18%) patients with a dose of 45-54 Gy. Half of the patients received androgen deprivation therapy. No acute grade 3-4 genitourinary and gastrointestinal side effects were observed. Late grade 3 gastrointestinal toxicity was observed in 1 patient. Kaplan–Meier test was used for survival analysis.

Results: The median age was 64 (48-77) years, and the median follow-up was 42 (6-168) months. After salvage radiotherapy, 32 (38%) patients had a biochemical recurrence. The 2-year and 5-year biochemical recurrence-free survival were 82% and 55.6%, respectively. Patients who had seminal vesicle involvement ($P < .001$), positive pelvic lymph node ($P = .002$), and relapse less than 1 year ($P = .002$) had lower biochemical recurrence-free survival rates than others. In the multivariate analysis, recurrence within a year after surgery ($P = .047$; CI, 2.3 (1.0-5.1)) and seminal vesicle involvement ($P = .001$; CI, 4.9 (2.0-12.5)) were found to be negative factors for biochemical recurrence-free survival.

Conclusion: Salvage radiotherapy achieved disease control at 5 years in half of the patients with recurrent prostate cancer. Patients with seminal vesicle involvement and early prostate-specific antigen increase after prostatectomy are at high risk of disease relapse after salvage radiotherapy.

Keywords: Prostate cancer, salvage radiotherapy, radical prostatectomy

Introduction

Prostate cancer is the most common cancer diagnosed in men worldwide.[1] The main treatment approaches for localized prostate cancer are radical prostatectomy, external beam radiotherapy (RT), brachytherapy, hormone therapy, and combinations thereof. The decision on the type of treatment depends on the patient's age, clinical stage, prostate-specific antigen (PSA) level, and Gleason score. The D'Amico risk stratification has been used for 2 decades in order to guide treatment choice.[2] The most commonly used treatment method is radical prostatectomy, and the second is RT.[3] On the other hand, definitive RT plus androgen deprivation therapy (ADT) is the preferred treatment option in locally advanced diseases and/or in the presence of aggressive disease features (Gleason score ≥ 8, PSA ≥ 20). In the last decades, there is an increasing trend toward surgery, especially in younger patients, after the widespread usage of minimally invasive surgical procedures, which leads to less toxicity than open prostatectomy procedures.[4] However, at follow-up, approximately 15%-40% of these patients are at risk of biochemical relapse 5 years after surgery.[5] Most recurrences occur in patients with high-risk factors such as seminal vesicle involvement, R1 resection, and extraprostatic extension.[6] In these high-risk patients, surgery is often followed by adjuvant RT, according to the results of previous randomized trials that reported higher biochemical relapse-free survival rates favoring postoperative RT.[7-9] The 2 postoperative RT approaches for patients with high-risk factors after surgery are immediate adjuvant RT and salvage RT at biochemical relapse. Adjuvant RT is implemented 4-6 months after prostatectomy, after recovery of urinary continence. Salvage RT, which has increasingly been adopted in last years, is early RT at the first sign of biochemical recurrence following observation. Three recent large multicenter randomized trials reported that adjuvant RT has no advantage over early salvage RT.[10] The main purpose of delaying RT is to select patients who will not relapse and do not need adjuvant therapy. However, delaying RT may also reduce the chance of cure. Therefore, it is crucial to administer salvage RT at low PSA levels. Although salvage RT is a potentially curative treatment modality for patients who developed biochemical failure, oncological outcomes of these patients vary according to the pretreatment risk classification or pathological characteristics on radical prostatectomy specimens. Our aim here is to evaluate the factors affecting the biochemical disease control rates of patients receiving salvage RT.

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Material and Method

Study Population

We identified 101 patients treated with salvage RT after radical prostatectomy ± pelvic lymph node dissection between 2003 and 2020. Seventeen patients who had no available follow-up data were excluded. The remaining 84 patients were included in our cohort and analyzed retrospectively. Salvage RT was performed when PSA

was elevated after prostatectomy, particularly when ≥0.1 ng/mL or in the presence of detectable PSA after surgery. Patient characteristics are presented in Table 1. The study protocol was approved by the ethics committee of İstanbul University-Cerrahpaşa (Date: March 4, 2022 No: E-83045809-604.01.01-329315).

Radiation Therapy

Radiotherapy planning simulation was performed in a comfortable supine position with a full bladder (half liter of water 1 hour before simulation) and empty rectum to reduce internal organ motions. Patients were given a list of recommendations to reduce rectal volume, including a low-fiber diet and minimizing gas-producing foods, before RT planning computerized tomography and during treatment. Clinical target RT volumes were contoured in ISIS 3D (Technology Diffusion, France) or—after 2010—Eclipse version 8.6 and Velocity Contouring stations (Varian Medical Systems, Palo Alto, Calif, USA). Clinical target RT volumes were contoured according to Radiation Therapy Oncology Group (RTOG) Consensus Guidelines.[11] Target RT volume covered the prostate and seminal vesicle bed with or without the pelvic lymphatic region. Patients were treated with Saturne-42 (GE-CGR, Buc, France) or—after 2010—Varian RapidArc DHXI (Varian Medical Systems) linear accelerator treatment machines. Three-dimensional conformal RT technique with 15 MV photon energy or, more recently, intensity-modulated RT technique with 6 MV photon energy have been used in 12 (14%) and 72 (86%) patients, respectively. The median time between surgery and salvage RT was 10 (3-146) months. The median RT dose was 66 (60-76) Gy in 2 Gy per fraction. Pelvic lymphatic irradiation was administered to 15 (18%) patients, and lymphatic field RT doses were varied between 45 and 54 Gy. Forty-two patients received ADT as well. Details of the treatment are given in Table 1.

Follow-Up

All patients were examined weekly during RT. After the end of RT, patients were followed up every 3 months for the first 2 years, every 6 months for up to 5 years, and annually thereafter. Prostate-specific antigen was monitored at each follow-up, and additional examinations such as pelvic magnetic resonance imaging and/or—after 2014—Gallium-68 prostate-specific membrane antigen positron emission tomography were done according to the PSA result.

Statistical Analysis

Descriptive statistics included the frequency and proportion for categorical variables and the minimum, maximum, and median for continuous variables. Biochemical recurrence-free survival (bRFS) was calculated as the time from the end of RT to biochemical or clinical relapse. We used the Kaplan–Meier method to calculate 2- and 5-year bRFS rates. Univariate analysis of time to biochemical recurrence was performed using Kaplan–Meier plots and log-rank tests. Multivariate analysis of time to biochemical recurrence was conducted using a Cox proportional hazards model with 95% CIs. The acute and late genitourinary and gastrointestinal side effects were evaluated by the Common Terminology Criteria for Adverse Events v4.0. Statistical Package for the Social Sciences version 21 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. A *P* value of <.05 was considered for significance.

Results

The median follow-up was 42 (6-168) months, and the median age was 64 (48-77) years. Biochemical relapse was observed in 32 (38%) patients after salvage RT. Distant metastases were detected in 26 of these patients, within a median of 3 (0-81) months after biochemical recurrence. Of them, 12 (46%) had bone metastases, 9 (35%) had pelvic lymphatic metastases, 4 (15%) had non-regional lymphatic metastases, and 1 (4%) had visceral metastases. Five patients died a

Table 1. Patient and Salvage Treatment Characteristics

	n (%)
Age, median (range)	64 (48-77)
Surgery	
Open	62 (74)
Minimal invasive	22 (26)
Lymph node dissection	
Present	52 (62)
Absent	32 (38)
Nodal involvement	
Present	16 (19)
Absent	68 (81)
Gleason score	
5-6	9 (11)
7	58 (69)
8-9	17 (20)
T stage	
2	22 (26)
3a	22 (26)
3b	40 (48)
Surgical margin	
Negative	20 (24)
Focal positive	31 (37)
Multifocal positive	33 (39)
PSA level at diagnosis (ng/mL)	
<10	12 (14)
10-20	55 (66)
>20	17 (20)
PSA level (ng/mL) before RT, median (range)	0.42 (0.05-8.38)
RT dose, median (range)	66 Gy (60-76 Gy)
Pelvic lymphatic irradiation	
Absent	69 (82)
Present	15 (18)
Androgen deprivation therapy	
Absent	42 (50)
≤6 months	15 (18)
>6 months	27 (32)

PSA, prostate-specific antigen; RT, radiation therapy.

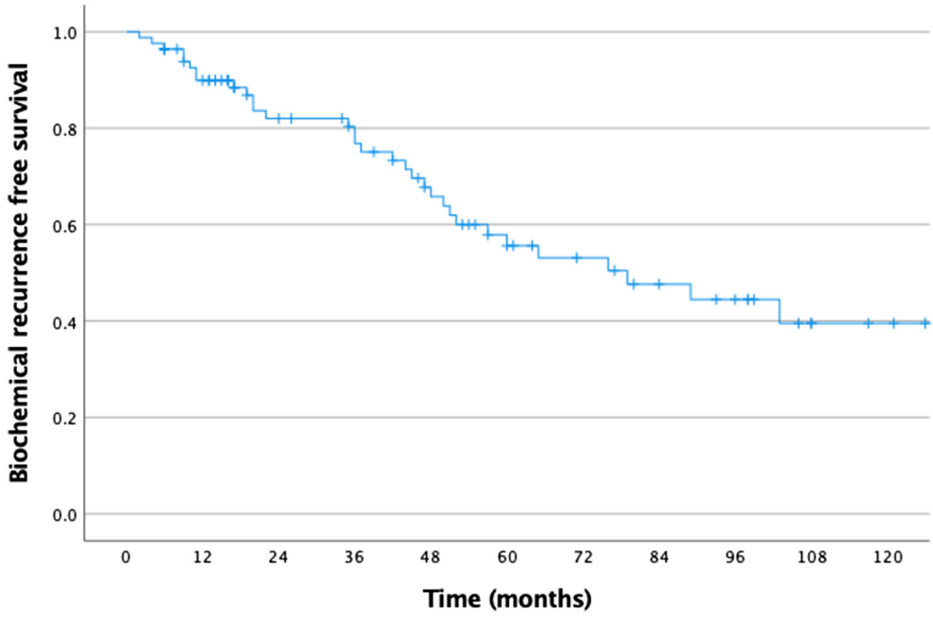

Figure 1. Biochemical recurrence-free survival after salvage radiotherapy.

Table 2. bRFS Univariate and Multivariate Cox Regression Analysis

Characteristic	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Gleason score				
7	2.41 (0.56-10.35)	.23	NS	
≥8	3.80 (0.79-18.27)	.09		
SVI	6.05 (2.45-14.97)	<.001	4.9 (2.0-12.5)	.001
SM				
Focal +	0.81 (0.31-2.12)	.67	NS	
Multifocal +	1.66 (0.72-3.83)	.23		
PNI	4.00 (0.54-29.63)	.17	NS	
Nodal metastasis	3.12 (1.46-6.68)	.002	1.29 (0.57-2.89)	.541
Recurrence time after surgery	0.31 (0.14-0.67)	.002	2.3 (1.0-5.1)	.047
ADT				
<6 months	1.04 (0.38-2.86)	.94	NS	
≥6 months	1.06 (0.49-2.26)	.89		
Pelvic RT	1.82 (0.81-4.09)	.15	NS	
PSA level before RT	0.8 (0.39-1.64)	.54	NS	

ADT, androgen deprivation therapy; bRFS, biochemical recurrence-free survival; PNI, perineural invasion; RT, radiation therapy; SM, surgical margin; SVI, seminal vesicle invasion.

median of 22 (12-44) months after metastasis. After salvage RT, the 2-year and 5-year bRFS for the patients were 82% and 55.6%, respectively (Figure 1).

In the univariate analyses, patients who relapsed less than 1 year after surgery (5-year bRFS 72.4% vs. 40.3%, $P = .002$), with nodal involvement (5-year bRFS 62.5% vs. 27.8%, $P = .002$) and with seminal vesicle involvement (5-year bRFS 84% vs. 32.3%, $P < .001$) had significantly associated higher biochemical failure after salvage RT than the others. In the multivariate analyses, relapse less than 1 year after surgery ($P = .047$; CI, 2.3 (1.0-5.1)) and seminal vesicle involvement ($P = .001$; CI, 4.9 (2.0-12.5)) were found to be negative prognostic factors for biochemical disease control. The univariate and multivariate analyses are summarized in Table 2.

Acute grade 3-4 genitourinary and gastrointestinal side effects were not observed. Late grade 3 gastrointestinal toxicity (rectitis) was observed in 1 (1%) patient (Table 3).

Table 3. Acute and Late Side Effects

	n (%)
Acute gastrointestinal	
Grade 1-2	10 (12)
Grade 3-4	0 (0)
Acute genitourinary	
Grade 1-2	27 (32)
Grade 3-4	0 (0)
Late gastrointestinal	
Grade 1-2	2 (2)
Grade 3-4	2 (1)
Late genitourinary	
Grade 1-2	12 (14)
Grade 3-4	0 (0)

Discussion

International guidelines recommended that patients should be offered adjuvant prostate bed RT if they had high-risk features, based on the previous randomized trials for several years.[12,13] In European guidelines, positive surgical margin and extraprostatic extension are the most emphasized high-risk factors for the benefit of adjuvant RT. However, it remains unclear which patients will relapse after radical prostatectomy. Observation followed by early salvage RT has increasingly been accepted to distinguish patients who will recur or not. The results of recently published randomized trials indicate that early salvage RT is as effective as adjuvant RT.[14-16] Early salvage RT could spare approximately half of the patients from RT and the related side effects. Early salvage RT was defined as PSA levels ≥ 0.2 ng/mL in GETUG-17 and RAVES trials and PSA levels ≥ 0.1 ng/mL or 3 consecutive rises in RADICALS trial. The optimum pre-RT PSA level has not yet been clearly defined. Prostate-specific antigen is assumed to be a surrogate for disease burden, and therefore, low PSA levels may be a sign of low disease burden that is potentially curable. European guidelines emphasize the importance of initiation of RT at PSA < 0.5 ng/mL.[17] American guidelines also underlines the information of patients that the effectiveness of salvage RT is greatest when given at lower levels of PSA.[18] A systematic review, which explores the timing of salvage RT, reported a mean detrimental effect on bRFS of 2.6% for every 0.1 ng/mL increase in PSA at the time of salvage RT.[19] However, we found no statistically significant effect of PSA level on bRFS in our study. It may be due to the small sample size of the cohort, the use of androgen ablation in patients with high PSA levels, and the short follow-up period of some patients.

In addition to PSA level, pathologic characteristics and PSA doubling time appear to be other prognostic factors affecting bRFS following salvage RT and may guide the optimal timing of early salvage RT.[20] Short PSA doubling time helps to identify the patients at the highest risk for disease relapse.[21] We were unable to retrieve the information on PSA doubling time in our study; however, we found that early PSA relapse less than 1 year after surgery was associated with worse 5-year bRFS, indicating that rapidly progressive PSA kinetics affected the oncologic outcome of treatment. Additionally, seminal vesicle involvement was also associated with a higher biochemical relapse after salvage RT in our study. Caution should be taken selecting patients for salvage RT rather than adjuvant treatment if they had high-risk features such as Gleason score > 7 with seminal vesicle invasion and rapidly rising PSA levels.

Regarding the ADT, previous randomized trials have reported an overall survival benefit for concomitant ADT with definitive RT in the treatment of prostate cancer.[22] However, in the adjuvant setting, ADT is not a standard of care, and the use or duration of use of ADT with salvage RT still remains unclear. RTOG 96-01 and GETUG-16 trials have investigated the oncological consequences of salvage RT with or without concomitant ADT.[23,24] According to RTOG 96-01 trial, the addition of bicalutamide for 2 years provided an overall survival benefit to RT alone (HR, 0.77 (0.59-0.99), $P = .04$). In subgroup analyses, the benefit was much more evident in patients with PSA level ≥ 0.7 ng/mL. However, in the GETUG-16 study, most patients had PSA level less than 0.5 ng/mL, and goserelin for 6 months yielded better 5-year disease control rates compared to salvage RT alone (HR, 0.50 (0.38-0.66), $P < .0001$). Patients with a higher pre-RT PSA level are more likely to harbor regional and distant metastatic disease, for which long-term ADT may be most beneficial. The median pre-RT PSA level of our cohort was 0.42 ng/mL. We found no significant effect of ADT on bRFS regardless of the duration of ADT (short-term or long-term).

Regarding the target volume, the benefit of pelvic nodal RT in addition to prostate bed RT has been investigated. SPPORT trial randomized patients at the time of recurrence to either i) salvage RT to the prostate bed, ii) salvage RT to the prostate bed plus ADT, or iii) salvage RT to the prostate bed plus pelvic lymphatics plus ADT. Five-year progression-free survival of the groups was 71.1%, 82.7%, and 89.1% respectively. The addition of 4-6 months of androgen ablation and pelvic nodal RT to prostate bed salvage RT resulted in better disease control rates in the first report of the trial.[25] In our study, there was no statistically significant relationship found between pelvic nodal RT and bRFS. The small number of patients (15%) undergoing pelvic RT and the short follow-up period make interpretation impossible.

The retrospective nature of the study, the small sample size of the cohort with heterogeneous patient characteristics, and the short follow-up time are the main limitations of our study. Besides, the other endpoints, mean metastases-free survival and overall survival were not reached yet in our study. However, it is real-life data which can support further investigations to improve the treatment outcomes.

In conclusion, salvage RT achieved disease control at 5 years in half of the patients with relapsed prostate cancer. Patients with seminal vesicle involvement and rapidly rising PSA levels are at high risk of disease recurrence after salvage RT. These patients may be better treated with adjuvant RT with ADT. Radiation dose/volume modifications and optimal ADT duration may also be the subject of research in patients with these high-risk features.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul University-Cerrahpaşa (Date: March 4, 2022 No: E-83045809-604.01.01-329315).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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