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Treatment outcomes of patients with prostate cancer who underwent postoperative radiotherapy

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ABSTRACT

Aims: Prostate cancer is one of the most common cancers in men. Surgery, radiotherapy or active surveillance are the treatment options.Treatment is decided according to risk group of the patient.Postoperative radiotherapy is delivered in selected patients to increase the local control rates.The aim of this study is to report the treatment results of patients who received postoperative radiotherapy for localized prostate cancer.

Methods: This retrosepctive study included 78 prostate cancer patients who received postoperative radiotherapy between 2011 and 2023.All patients except who had pathologically positive lymph nodes were included into the study. Overall survival, progression free survival, and associated pathological parameters were evaluated by using IBM SPSS programme version 20.

Results: The mean follow-up time was 66.7 (IQR 25-75:41,6-89,6) months. Five and 10-year overall survival rates were 93%, and 67.3% respectively; (median (95% CI); NR (not reach): while 5 and 10-year progression-free survival rates were 90.3%, and 50.4, respectively; (median (95% CI); 135.3±(105.9-165.7). Postoperative prostate specific antigen (PSA) and pre-RT PSA values, and the effects of these parameters on progression-free survival was analyzed, median progression-free survival was higher in patients with postoperative PSA values ≤ 0.185 (135.6±24.4 vs 113.3±6.4, p:0.001). Five and 10 year overall survival and progression-free survival rates of patients with a high gleason score who underwent postoperative radiotherapy was observed lower than the others (86.9% and 46.3%, p=0.006;86.9% and 33.8%, p=0.009 respectively).

Conclusion: Postoperative radiotherapy is generated best results in progression free survival and overall survival in patients with low pre-rt psa and high gleason score prostate cancer cases

Keywords: Prostate cancer, radiotherapy, postoperative radiotherapy

INTRODUCTION

Prostate cancer is the second most common cancer in men after lung cancer.[1] The treatment approach in prostate cancer is performed as monotherapy or in combination therapy according to risk groups, and surgery, radiotherapy (RT), and active surveillance are among the treatment options in patients with localized prostate cancer.[2] Approximately 35% of patients with localized prostate cancer suffer from biochemical recurrence (BCR) after surgical treatment.[3] Therefore, additional treatments to improve biochemical and local regional control are needed.It is known that especially the group with surgical margin positivity benefits from adjuvant RT, but it has been observed that not every case with margin positivity recurs. Viers et al.[4] found decreased progression-free survival and cancer-specific survival rates in patients with tumors with a Gleason grade of ≥4 at the surgical margin.Another study evaluating the effect of Gleason grade and tumor length at the surgical margin on BCR has shown that the presence of a tumor longer than 3 mm at the surgical margin is more important than the Gleason scores in terms of BCR.[5] The clinical course of BCR is highly variable and does not always cause cancer-specific death

In a systematic review; it was observed that 30% of the patients who developed biochemical recurrence showed clinical recurrence and only 16.4% of them died from the disease, and low and high risk groups for biochemical recurrence were determined after publication of this systematic review. The group with PSA (prostate specific antigen) doubling time >1 year and ISUP (International Society of Urological Pathology) grade

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<4 was consideredat low risk, and the group with PSA doubling time <1 year and ISUP grade 4-5 as high risk for biochemical recurrence.[6] In addition, 3 randomized studies have shown that the addition of adjuvant RT to the treatment in stage T3a or T3b cases with post-surgical margin positivity, contributes favorably to biochemical recurrence-free survival.[7-9] Although there are randomized controlled studies showing the contribution of adjuvant RT, not every patient evaluated have the same disease state and application of salvage radiotherapy is allowed for these patients. However, it is not clear which patients should receive salvage treatments. In recent years, 3 important randomized controlled studies have been published on the application of postoperative adjuvant or salvage RT. When these studies and the prospectively planned ARTISTIC study were evaluated together; BCR-free survival was reportedly better in the early salvage RT group than in the adjuvant RT group, but without any statistically significant difference and approximately 50% of the patients who were scheduled for salvage RT continued to be followed up without treatment.[10-13] Studies have shown that follow-up with frequent PSA monitoring and early salvage RT in well-selected patients can provide survival results comparable with adjuvant RT by protecting patients from possible RT-related toxicity.[14,15]

Several studies evaluating predictive factors for postoperative RT have reported that salvage RT showed better biochemical recurrence-free survival at lower PSA values.[8,16] In another study, other factors predicting biochemical recurrence-free survival included pathological tumor stage, Gleason score and surgical margin positivity.[17]

The aim of this study is to evaluate patients who underwent surgery for prostate cancer and received postoperative radiotherapy in our clinic in terms of treatment outcomes and factors affecting these outcomes.

METHODS

The study was carried out with the permission of the University of Health and Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies Ethics Committee (Date: 22.09.2022, Decision No: 2022-09/169). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The clinical data of patients who underwent postoperative adjuvant or salvage RT in our clinic between January 2011 and January 2023 were evaluated retrospectively. All patients who received postoperative radiotherapy for prostate cancer excluding the patients with pathological pelvic lymph node involvement in operative pathology specimen were included in the study. The planning CT scan was performed with 3-mm slices in the supine position with empty rectum and full bladder.Prostate fossa and entire seminal vesicles bed were included in the CTV. The planning treatment volume (PTV) was generated by adding 6-8 mm isotropic expansion to the CTV, excepting 4-6 mm posteriorly. According to the International Commission of Radiation Units and Measurements recommendations, the dose was prescribed at the isocentre with a + 7%and - 5% heterogenity.18For treatment planning, the dose-volume constraints for the bladder were V65 Gy<50%;for the small bowel V45≤195 cc; for the rectum: V50 Gy≤50%, V60 Gy≤35%, and V70 Gy≤ 20%. Dose constraints for the organs at risk (OAR) were selected based upon Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data.[19] Cone beam-CT (CBCT) scan were taken prior to each delivery. Shifts were performed by aligning finally to soft tissue on CBCT. All patients have been treated with IMRT technique with daily imaging guidance. RT was delivered in 2 Gy daily fractions with 6 MV photon beams five days a week with total dose of ranging 64-72 Gy.PSA values at the time of diagnosis, first PSA values in the postoperative period, PSA values before RT after recurrence, Gleason scores indicated in pathology reports, presence of (if any) perineural (PNI), lymphovascular (LVI), and/or seminal vesicle (SV) invasion, extracapsular extension (ECE), surgical margin (SM), whether or not the patient received androgen deprivation therapy, salvage or adjuvant RT, RT volume and dose information were recorded. The treatment outcomes were assessed in terms of progression-free (PFS), and overall survival (OS) rates. Patients with a PSA value of 0.2 ng/ml and above during follow-up were considered to have relapse and PFS was evaluated as the time from the time of initial diagnosis to the time when the PSA was above 0.2 ng/ml. The effects of variables on PFS and OS were also evaluated. The final status of the patients were checked from the national death notification system.

Statistical Analysis

IBM SPSS version 20 was used in all statistical analyzes. Chi-square test was used to evaluate the frequencies of categorical variables and to compare them with each other. Independent samples t- test was used for normally distributed parameters.Mann-Whitney U test was used to compare the means between groups for non-normally distributed continuous numerical data. ROC (receiver Operating Characteristic) analysis was performed to determine the intercept value for statistically significantly different parameters between

groups and the intercept value was determined according to Youdens J index. Survival rates between groups was estimated and compared using Kaplan-Meier method. The statistical significance level was accepted as p<0.05.

RESULTS

The study population consisted of 78 patients with operated prostate cancer who received postoperative RT in our radiation oncology department between January 2011 and January 2023. Patients received adjuvant RT (n:39) or salvage RT (n:39). The mean follow-up time was 66.7 (IQR 25-75:41,6-89,6) months. The mean age was 64.9±6.7 (range 44-80 years) years. The mean PSA value at diagnosis of the patients was 14.7±9.2 ng/ml, and the median was 11 ng/ml (range 3 -42 ng/ml).The mean RT dose of the patients was 67.3±2.2 Gray (Gy), and the median was 66 Gy (range 64-72 Gy). Patients' characteristics are summarized in Table 1.

Table 1: Patients' characteristics

	n (%)
Gleason score at RP	
≥ 8	21 (26.9)
≤ 7	57 (73.1)
Surgical margin	
Positive	55 (70.5)
Negative	23 (29.5)
Extracapsular extension	
Yes	33 (42.3)
No	45 (57.7)
Seminal vesicle invasion	
Yes	14 (17.9)
No	64 (82.1)
Lymphovascular invasion	
Yes	4 (5.1)
No	74 (94.9)
Perineural invasion	
Yes	36 (46.5)
No	42 (53.8)
Androgen deprivation therapy	
Yes	28 (35.9)
No	50 (64.1)

Abbrevations: RP: Radical prostatectomy

Five and 10-year overall survival rates were 93%, and 67.3% respectively; (median (95% CI); NR (not reach): while 5 and 10-year progression-free survival rates were 90.3%, and 50.4, respectively; (median (95% CI); 135.3±(105.9-165.7) (Figures 1a, and b). When the patients were evaluated according to Gleason scores and disease progression; disease progression was observed in indicated number of patients in the low risk (n:2; 9.1%), intermediate risk (n:4; 11.4%), and high risk (n: 8; 38.1%) groups. Disease progression was observed more frequently in patients with higher Gleason scores when compared with low-risk (6.15-fold:1.13-33.7), and intermediate-risk (4.77-fold:1.22-18.65) groups.

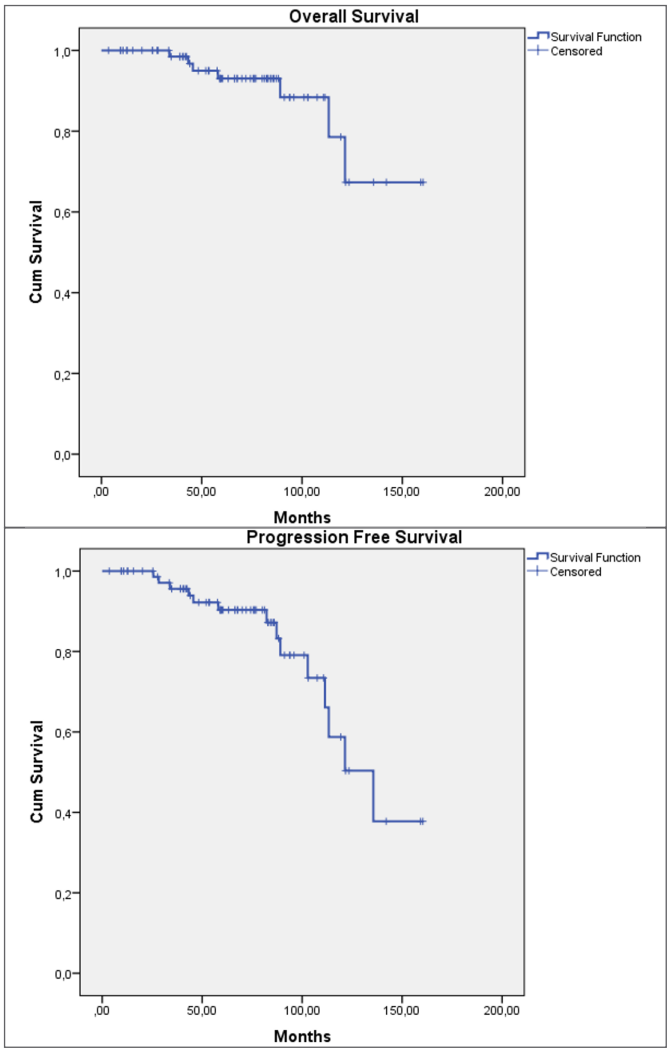

Figure 1. Overall survival **(1a)**, Progression-free survival **(1b).**

When the effects of Gleason score, PNI, LVI, SV invasion, ECE, SM, parameters on overall survival and progression-free survival were examined one by one, We observed that Gleason Score had an effect on overall and progression-free survival (Table 2).

Table 2. Relationship between gleason score and overall survival and progression-free survival

	5 years (%)	10 years (%)	Median±SD (%95 CI)	p value
Overall survival			NR	0.006
Gleason score ≤ 7	95.2	95.2	113.3± 15.4	
Gleason score ≥ 8	86.9	46.3	(83.1-143.5)	
Progression-free survival			NR	
Gleason score ≤ 7	91.5	70.6	113.3±15.7	0.009
Gleason score ≥ 8	86.9	33.8	(82.5-144.2)	

Abbrevations: SD: standard deviation; NR: not reached

When PSA values of the cases measured at the time of diagnosis, after the surgery, and before radiotherapy (pre-RT) were evaluated in terms of disease progression, We observed that the median pre-RT PSA values of the patients whose disease progressed were higher than those without disease progression. (0.28 vs 0.53, p:0.036).

The effects of the patients' PSA values at the time of diagnosis, and their postoperative PSA and pre-RT PSA values on the overall survival could not be demonstrated. In the ROC analysis performed on progressive disease using the parameters of PSA values obtained at the time of diagnosis, during postoperative period, and before RT, the area under the curve of the pre-RT PSA parameter was observed to be large enough (0.680). The intercept value was determined as 0.460 according to Youdens J index (p:0.036) (Table 3).

Table 3. ROC analysis values for progressive disease

	AUC (% 95 CI)	Sensitivity-Specificity	Intersection value	Youdens J index	p value
PSA at diagnosis	0.59 (0.43-0.75)	0.86-0.36	8.340	0.22	0.274
Postoperative PSA	0.64 (0.47-0.82)	0.50-0.83	0.185	0.33	0.094
Pre-RT PSA	0.68 (0.52-0.84)	0.64-0.39	0.460	0.39	0.036

Abbrevations: PSA: prostate specific antigen; AUC: area under curve; RT: radiotherapy

When the patients were grouped according to their PSA values at the time of diagnosis, postoperative PSA and pre-RT PSA values, and the effects of these parameters on progression-free survival was analyzed, median progression-free survival was higher in patients with postoperative PSA values ≤0.185 (135.6±24.4 vs 113.3±6.4, p:0.001).

Univariate Cox regression analysis showed that disease progression was 5.8 (1.81-18.599) times more frequent in patients with postoperative PSA values >0.185 ng/ml compared to those without. Progression was observed 3.73(1.29-10.78) times more frequently in patients with higher Gleason score compared to those with low-intermediate. Also, in the univariate Cox regression analysis, 9.51 (1.72-50.64) times higher mortality rates were observed in patients with a postoperative PSA values >0.235 ng/ml compared to those with lower PSA values. Mortality rates were observed 7.22 (1.39-37.42) times more frequently in cases with higher Gleason score than those withlower-intermediate (Table 4).

Table 4. Univariable Cox regression analysis

	Hazard ratio	95% confidence interval	p-value
Progressive disease			
Postoperative PSA			
≤0.185	1	1.81-18.59	0.003
>0.185	5.80		
Gleason score			
≤ 7	1	1.29-10.78	0.015
≥ 8	3.73		
Mortality			
Postoperative PSA			
≤0.235	1	1.72-52.64	0.010
>0.235	9.51		
Gleason score			
≤ 7	1	1.39-37.42	0.018
≥ 8	7.22		

Abbrevations: PSA:prostate specific antigen

DISCUSSION

In our retrospective study, we aimed to evaluate the factors affecting progression-free survival in patients with operated prostate cancer. In a systematic review Ohri et al.[20] evaluated 25 studies, and suggested that the application of salvage RT in patients with low PSA levels undergoing postoperative RT may improve the therapeutic success rate of salvage RT. Similarly, in our study, we obtained better results in progression-free survival in patients with operated prostate cancer having low pre-RT PSA values compared to those with higher pre-RT PSA values. Although salvage RT seems to be advantageous in postoperative RT applications, adjuvant RT is still recommended especially in patients with high Gleason scores.[21] Similarly, in our study, both disease progression and mortality rates were higher in patients with high Gleason scores compared to the low-moderate risk groups. In a retrospective series by Yoshida et al.[22] evaluating postoperative salvage RT, a Gleason score ≥8 was a significant predictor for PSA recurrence after salvage RT (hazard ratio: 4.531; 95% confidence interval 1.413-14.535; p=0.011) and 5-year PSA relapse-free survival rates were 62.7% and 15.4% in patients with Gleason scores ≤7 and ≥8, respectively. In a study on the results of 236 patients where prognostic factors in postoperative prostate cancer radiotherapy were analyzed, pre-RT PSA levels and T3 disease were found to be associated with an increased risk of progression, and the researchers found 5-year disease-free survival to be 86.9%.[23] Similar results were also obtained in our study.

Study Limitations

The fact that it was a retrospective study is the most important limitation of this study.

CONCLUSION

Postoperative RT can be applied as adjuvant or salvage therapy in cases with operated prostate cancer. Patient selection should be made based on all pathologic data. Gleason score can be considered as the most important prognostic factor for both progression-free survival and overall survival. However, prospective randomized trials with a greater number of patients should be planned for better evaluation of both the timing of RT and prognostic factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the University of Health and Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies and Ethics Committee (Date: 22.09.2022, Decision No: 2022-09/169).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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