



## ORIGINAL ARTICLE

# Comparison of Surgery with Radiotherapy and Androgen Deprivation Treatment Combination in the Management of High-risk Prostate Cancer

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## Abstract

**Introduction:** We aimed to compare the outcomes of high risk prostate cancer treatments with radical prostatectomy (RP) or radiotherapy (RT) and androgen deprivation therapy (ADT).

**Methods:** 83 patients who were treated with RT and ADT or radical prostatectomy for high risk prostate cancer between April 2010 and May 2018 and whose data were retrospectively analyzed were included in our study. While 40 patients received RT and ADT combination therapy, 43 patients received RP. The groups were compared in terms of pre-treatment general features, post-treatment biochemical recurrence, metastasis, disease-free survival and overall survival.

**Results:** The mean age of the patients was 64.05 (50-74) years in the surgical group and 69.35 (49-79) years in the RT group. The mean prostate-specific antigen baseline value was 22.79 (3-93) ng/ml in the surgical group and 40.60 (3-201) ng/ml in the RT group. Biochemical recurrence was observed in 15 (34.8%) patients in the surgical group and 2 (5%) patients in the RT group. Disease-free survival time was 31.12 (12-68) months in the surgical group and 41.4 (16-88) months in the RT group.

**Discussion and Conclusion:** Our study results revealed that RT and ADT application has more advantageous oncological results in the treatment of high-risk prostate cancer, as in many studies.

**Keywords:** Androgen deprivation therapy (ADT); prostate cancer; radical prostatectomy; radiotherapy.

While prostate cancer is the most common cancer in men worldwide, in Turkey it only takes second place after lung cancer<sup>[1]</sup>. It is the most commonly diagnosed solid organ tumor among men in America. It is reported that in 2018, 164.690 new cases developed in America and 29.430 people died due to prostate cancer<sup>[2]</sup>. In the pres-

ence of prostate cancer in first degree relatives, the risk is doubled. If it is seen in two or more first-degree relatives, this risk increases 5-11 times<sup>[3,4]</sup>.

With the widespread use of the prostate-specific antigen (PSA) test, rates of diagnosing prostate cancer have increased significantly. Patients diagnosed with prostate

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cancer are divided into low, medium and high risk groups according to Gleason score (GS), PSA level and T stage. According to the D'Amico risk group classification, high-risk prostate cancer should have a PSA value > 20 ng/mL at the time of diagnosis or GS >7 or clinical T stage  $\geq 3a$ <sup>[5,6]</sup>. Approximately 40% of cases at the time of diagnosis are high-risk prostate cancer. These cases may show progression and go up to death<sup>[7]</sup>.

When making a treatment decision in a patient diagnosed with prostate cancer, many factors such as the patient's stage, risk group, patient's age, expected life span, and performance status should be considered. If the tumor is limited in the prostate tissue, radical prostatectomy is generally recommended, while curative radiotherapy (RT) is recommended in the presence of extracapsular disease, seminal vesicle invasion, lymph node positivity during diagnosis, and patients classified in the high-risk group<sup>[8]</sup>. In addition to patients undergoing curative RT as a primary treatment, androgen deprivation therapy (ADT) is applied for 2-3 years<sup>[9,10]</sup>. In metastatic prostate cancer, chemotherapy and ADT treatment come to the agenda<sup>[11]</sup>.

While men with high-risk disease commonly are treated by RT and ADT, there are also instances when RP is beneficial<sup>[10,12]</sup>.

In our study, we aimed to compare the results of RP with curative RT and ADT in the treatment of high-risk prostate cancer.

## Materials and Methods

In our research, we studied with 83 patients who were treated with RT and ADT or radical prostatectomy for at least 12 months due to high-risk prostate cancer between April 2010 and May 2018, and retrospectively analyzed data were included. The protocol was approved by the Bursa Yüksek İhtisas Education and Research Hospital Ethics Committee (2011-KAEK-25 2019/02-03). While 40 patients received RT and ADT combination therapy, 43 patients received RP. Patients who did not have metastasis at the time of diagnosis, followed up for at least 3 months after treatment participated in the study.

Intensity-modulated RT (IMRT) technique was used in all patients receiving RT with the Tomotherapy Hi-Art device. Prostate, seminal vesicle and pelvic lymph nodes were included in the RT area. The patients were treated with bladder-filled and rectum empty. Prostate was applied with 74 Gy in 33 fractions, 60 Gy for seminal vesicles and 52 Gy for pelvic lymph nodes. Curative doses are provided in target tissues by adjusting dose densities with the IMRT tech-

nique, while maximum protection is provided in neighboring organs (bladder, rectum and femoral heads). ADT is starting 2 months before the treatment for all patients receiving RT and was applied for 2-3 years. In the post-treatment follow-up, the increase of the PSA rare level above 2ng/ml was considered as recurrence.

Open radical prostatectomy and bilateral lymph node dissection were performed to all patients in the surgical group. Patients who received RT or ADT before surgery were excluded from the study. Patients with a PSA level above 0.2 ng/ml in the postoperative period were considered as biochemical recurrences.

After the treatment, the cases were followed up with a total PSA every 2 months and 3 months, then every 6 months and tomography scan once a year.

## Statistical Analysis

SPSS 20.0 statistical analysis (SPSS Inc. Chicago, IL, USA) software package program was used in our study to evaluate the results. Descriptive statistics of all variables in the study were calculated. The normality of the distribution of the data was evaluated by the Shapiro-wilk test, and its homogeneity by the Levene test. Continuous variables were given as mean $\pm$ standard deviation. For comparison of numerical data between groups, Kruskal-wallis test was used for non-parametric data and student-t test was used for parametric data. In case of significance, binary comparisons were made with the Mann-Whitney U test. Categorical variables were compared with chi-square test, Pearson chi-square and Fisher's exact chi-square test. Survival analysis was performed using tiger-meier survival analysis.  $P < 0.05$  was considered to be statistically significant.

## Results

Demographic features, clinical and pathological findings of the cases were compared as surgical and RT groups. Average age was  $69.35 \pm 7.00$  (49-79) in patients undergoing RT,  $64.05 \pm 5.93$  (50-74) in patients undergoing surgery, and average baseline PSA values in the RT group was found to be  $40.60 \pm 42.87$  (3-201) ng/ml, and  $22.73 \pm 21.01$  in the surgical group (3-93) ng/mL. The mean follow-up time was 41.6 months in the surgical group and 44.37 months in the RT group. When both groups were compared in terms of clinical stage, it was seen that RT group was in an advanced stage (Table 1).

Comparing the biopsy and prostatectomy pathologies of the surgical group, upgrading was detected in 24 (55.81%) of the patients, while no downstaging was detected in any

**Table 1.** Comparison of descriptive statistics of groups

	Surgery (n=43)		Radiotherapy (n=40)		p
	Mean±SD	Minimum/Maximum	Mean±SD	Minimum/Maximum	
Age of diagnosis	64.05±5.93	50-74	69.35±7.00	49-79	0.000
PSA	22.73±21.01	3-93	40.60±42.87	3-201	0.007
Number of positive cores	6.33±1.22	4-9	6:18±1.10	4-8	0.791
Diagnostic Gleason Score	7.65±0.78	6 - 9	7:38±1.27	4-10	0.234
Clinical Stage					0.000
T1c	19		-		
T2	9		-		
t2B	4		7		
T2c	4		26		
T3	7		7		
Recurrence, n (%)	15 (34.8)		2 (5)		0.001
Bone met, n (%)	11 (25.58)		1 (2.5)		0.003
DFS	31.12±20.91	12-68	41.40±19.29	16-88	0.036
Excitius, n (%)	3.9 (6.9)		1 (2.5)	0.218	
OS	42.28±18.76	14 (70)	46.15±20.75	19-96	0.827

SD: Standard deviation; PSA: Prostate-specific antigen.

patient. Gleason pattern 5 was observed in the prostatectomy pathologies of 19 patients and BKN was observed in 10 (52.63%) of these patients. In RT group BKN was observed in 1 of 7 patients with Gleason pattern 5.

In the surgical group, the average number of positive cores in 12 core biopsies was 6.33±1.22 (4-9), while it was 4.07 in those without BKN and 7.6 in those without BKN. In RT group, the average positive core number of 12 core biopsies was 6.18±1.10 (4-8), whereas in the cases without BKN, 6.1 positive and in two cases with BKN, an average of 7.5 positive cores were detected. In the surgical group, 13 patients had SVI, 13 patients had ESR, 11 patients had CS positivity, and 6 patients had post op lymph node positivity.

All RT patients were treated with IMRT technique. Adjacent organ doses (bladder, rectum, femoral heads and small intestine) were kept within safe dose limits according to the QUANTEC criteria. PSA recurrence developed in one patient at 24 months and in another 52 months at RT and ADT, and bone metastasis developed at 60 months. These patients received CT and palliative RT for bone metastasis. In another patient, the second primary bladder was detected in the 7<sup>th</sup> year. In this patient, transurethral resection was applied to the mass in the bladder.

Recurrence of PSA was observed in 15 (34.8%) patients after surgery. 9 (20.9%) patients of them received MAB and 6 (13.9%) patients received salvage RT. Chemotherapy was applied to one patient who relapsed after salvage RT. Bone

metastasis developed in 11 (25.5%) patients in this group.

When the disease-free survival was examined, the average of the surgery group was 31.12±20.91 (12-68) months, while it was 41.40±19.29 (16-88) months in the group receiving RT and ADT. This result was found statistically significant in favor of RT group (p=0.036).

## Discussion

Radical prostatectomy or RT is applied as the primary treatment in patients in low and medium risk groups who are thought to be local with a life expectancy of 10 years or more<sup>[13]</sup>. In high-risk prostate cancer, treatment methods are not yet clear. Despite many different definitions, the most commonly accepted definition is the classification of D'amico<sup>[14]</sup>. Today, there are studies in which surgery is recommended to patients in this group as an alternative to RT and hormone therapy combination<sup>[15,16]</sup>.

In high-risk prostate cancer, worse results are reported in terms of recurrence, disease-free survival period and survival periods compared to low and medium-risk patients. In the studies conducted, it is observed that patients with positive positivity for SVI, EKY, and CS after RP were better treated with early RT after surgery instead of RP alone<sup>[17,18]</sup>. In fact, there are studies reporting that postoperative PSA recurrence has better results in early salvage RT<sup>[19]</sup>. In our study, SVI in 13 patients, EKY in 13 patients, CS positivity in 11 patients and post op lymph node positivity in 6 pa-

tients were detected. In the surgical group, 6 patients had adjuvant RT in the early post-op period, and 6 patients was applied with salvage RT.

In conducted studies, PSA >20 ng/mL and in patients with prostate Ca, which is considered to be clinically limited to the organ, PSA failure rate at 5 years after RP monotherapy is 44-50%, the cancer specific survival rates at 10 and 15 years after RP was reported as 90% and 85%<sup>[20-22]</sup>.

In the present study, the rate of BKN was 34.09% in the surgical group and 5% in the group receiving RT and ADT. This rate was found to be 42.3% in the surgical group and 7.2% in the RT and ADT study in the study of Baker et al.<sup>[23]</sup>. In that study, patients with elevated PSA after salvage RT were accepted as BKN. In the study conducted by Watkins et al.,<sup>[24]</sup> the 5-year BKN rate was found to be 79.4% in the surgical group and 25.2% in the RT group. However, in this study, patients who received salvage RT due to the development of BKN accepted biochemical failure. In the study that was carried out by Yıkılmaz et al. in Turkey, 55% of the patients who underwent surgery due to high-risk prostate cancer had BKN, while this rate was found to be 10% in the group receiving RT<sup>[25]</sup>. In this study, the disease-free survival period was 18.1 (10-31) months in the surgical group and 45.1 (6-104) months in the RT group. In our study, disease-free survival in the surgical group was 31.1 (3-68) months while it was 41.4 (16-88) months in RT group.

One of the difficulties of comparing treatment methods in the high-risk disease group is the heterogeneity in biological behavior and clinical course being not sufficiently known. Only the treatment results of high-risk patients have different potential to respond to systemic neoadjuvant therapies according to the biological features of the tumor<sup>[26]</sup>.

There are studies showing that RT dose is effective in biochemical recurrence in patients undergoing RT. The dose given at 72 Gy and above in medium and high-risk patients has been shown to provide better biochemical recurrence-free survival than the dose administered below 72 Gy<sup>[27]</sup>. In the study conducted by Yıkılmaz et al., it was reported that 22% of patients who underwent 3D conformal RT under 72 Gy in the RT and ADT group were observed in 22% of the patients, while 4% of the patients who received 72 Gy and above IMRT were observed<sup>[25]</sup>. In our study, all patients had IMRT above 72 Gy and our rate of BKN was 5%.

## Conclusion

In parallel with previous studies, we found that patients who received RT and ADT in patients with high-risk prostate

cancer were more advantageous in terms of biochemical recurrence, development of metastases and disease-free lifetimes compared to previous studies. We have seen that surgery alone is not sufficient in this group of patients and there is a high need for postoperative adjuvant therapy. Therefore, we think that it will be appropriate to make the treatment decisions to be applied to the patients after the disease is determined by looking at the patient criteria with a multidisciplinary approach. Therefore, we think that it would be appropriate to make the treatment decisions for the patients with a multidisciplinary approach, only after the disease is fully determined in the light of patient specific test results and classification.

**Ethical Committee Approval:** The protocol was approved by the Bursa Yüksek İhtisas Education and Research Hospital Ethics Committee (2011-KAEK-25 2019/02-03).

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**Conflict of Interest:** None declared.

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