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ORIGINAL ARTICLE

Comparison of Oncological Results of Patients who Developed Systemic Metastasis After Radical Prostatectomy and Patients Receiving Androgen Deprivation Treatment due to Primary Systemic Metastatic Disease

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Abstract

Introduction: In this study, we aimed to compare the overall survival and the time until castration resistance developed between the patients who developed systemic metastasis after radical prostatectomy and who started androgen deprivation therapy (ADT) and those who started ADT due to primary systemic metastasis.

Methods: In our clinic, between 2009 and 2017, we compared 61 patients who have metastatic prostate cancer at the time of diagnosis and ADT was initiated primarily and 28 patients who developed systemic metastasis after radical prostatectomy and after ADT was initiated, in terms of the overall survival, development status of castration resistance, the duration of development to castration resistance, and prostate specific antigen (PSA) changes in follow-up retrospectively. LHRH agonist + antiandrogen (for only 1 month) therapy was started immediately after diagnosis in ADT group (Group 1). In the radical prostatectomy group (Group 2), LHRH agonist + antiandrogen therapy (1 month) was initiated due to PSA elevation or developing systemic metastasis.

Results: In the study, at Group 1, the age of patients (69.18±7.7 vs. 64.21±5.03, p=0.001), PSA values before biopsy (7508.24±26406.98 vs. 21.24±19.62, p=0.001), and total gleason score mean (p=0.001) were significantly higher than Group 2. Between two groups There was no significant different in terms of the rate of development to castration resistance (49.2% vs. 39.3%, p=0.38), time to castration resistance (46.8 months vs. 48.9 months, p=0.068), and overall survival (130.48 months vs. 97.43 months, p=0.207).

Discussion and Conclusion: In our study, if radical prostatectomy was performed before systemic metastasis developed, there was no difference in terms of castration resistance development, time to castration resistance, and overall survival with primarily metastatic disease.

Keywords: Local treatment; metastatic prostate cancer; radical prostatectomy.

Prostate cancer is the first most common type of cancer in the European Union countries and the United States, and the second most common cancer in the world and in Turkey. Prostate cancer, which ranks second in all age groups in Turkey, is the most common cancer with a prevalence of 19.8% in the population over the age of 70

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[1,2]. The estimated number of new diagnoses was 180,190 and there were 26,120 prostate cancer deaths in 2016 in the USA [3]. For prostate cancer, the American Cancer Society predicted that 160,000 men would be newly diagnosed and 26,700 men would die from the disease in 2017 [4].

Prostate cancer is classified as low, intermediate, high-risk disease, locally advanced and metastatic disease according to prostate specific antigen (PSA) levels, digital rectal examination (DRE) and pathological data [5]. The treatment pathway of prostate cancer can be determined with this classification. At the time of diagnosis, approximately 84% of patients are clinically in the local stage and 4% are in the metastatic stage [6].

Today, radical prostatectomy has begun to be considered in the treatment of clinical locally advanced prostate cancer in young patients (with a life expectancy of more than ten years), without additional comorbidities and low tumor burden. Locally advanced disease includes patients with extracapsular invasion, seminal vesicle and adjacent organ invasion, but without distant metastases, proven by physical examination or radiological imaging [7].

Since the risk of progression is high in locally advanced prostate cancer, if the disease is not treated adequately, it may result in death due to progression. Although the primary goal in this disease is to provide local control, it is useful to control possible microscopic metastases. For this reason, surgery, radiotherapy, hormone therapy and even chemotherapy treatments should be considered among the options in locally advanced disease.

In our study, we aimed to compare the overall survival and disease-free times of 61 patients who underwent androgen deprivation therapy (ADT) for systemic metastasis and 28 patients who underwent radical prostatectomy and subsequently developed systemic metastases and started ADT, between 2009 and 2017.

Materials and Methods

After obtaining the approval of the Health Sciences University Ümraniye Training and Research Hospital Ethics Committee (28.09.2017 Ethics Committee Decision No: 146) for the study, we retrospectively compared the pre-treatment PSA values, clinical stages, age at diagnosis, Gleason scores, metastasis status, PSA levels after hormone therapy, whether castration resistance developed, if so, the time to castration resistance, the overall survival rates and the time from diagnosis to death of 61 prostate cancer patients (Group 1) with systemic metastases who underwent ADT and 28 patients who underwent radical prostatectomy and developed systemic metastasis during their follow-up between 2009 and 2017. Patients with other primary cancer diagnoses were not included in the study, and the fact that they did not receive any other treatment for existing prostate cancer is inclusion criteria.

Patients in Group 1 were started with 50 mg bicalutamide once a day simultaneously with LHRH agonist treatment for exacerbation prophylaxis, and treatment was continued with only LHRH agonist at the end of the first month.

Extended lymph node dissection was performed on patients in Group 2, who were evaluated preoperatively as moderate-high risk patients, and Gleason score, surgical margin, presence of extraprostatic spread, cancer volume, seminal vesicle invasion, presence and extent of lymph node metastasis, and prostate volume were evaluated. Androgen deprivation therapy was started in patients who developed systemic metastases during their follow-up.

During the follow-up, the patients underwent routine physical examination and laboratory tests including PSA and total testosterone, and no imaging was performed unless clinical symptoms or increased PSA were observed. Castration resistance was assessed as a progressive increase in PSA or the development of new bone/visceral metastases when testosterone was at castrate level (<20 ng/dL).

While evaluating the findings obtained in the study, IBM SPSS Statistics 22 (IBM SPSS) program was used for statistical analysis. The conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilk test. In addition to descriptive statistical methods (mean, standard deviation, frequency), when comparing quantitative data, Student's t-test was used for comparisons of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Wilcoxon signed-rank test was used for in-group comparisons of non-normally distributed parameters. Chi-square test, Fisher's Exact test and Yates's correction for continuity were used to compare qualitative data. Kaplan-Meier analysis was used for survival analysis, survival rates were evaluated with log-rank test. Significance was evaluated at the $p<0.05$ level.

Results

The study was conducted with a total of 89 patients, aged between 50 and 86, between 2009 and 2017. The mean age of the patients was 67.62±7.32. Of the patients, 61 (68.54%) were in the ADT (Group 1) and 28 (31.46%) prostatectomy + ADT (Group 2) groups. The age and survival information of the patients are given in Table 1. In addition, other infor-

Table 1. Evaluation of general characteristics between groups

Group		Min-Max	Mean±SD
Group 1	Age (n=61)	50-86	69.18±7.7
	Duration in those who developed castration resistance (months) (n=30)	3-36	16.13±12.44
	Time to death (months) (n=61)	2-198	57.08±33.51
Group 2	Age (n=28)	50-76	64.21±5.03
	Duration in those who developed castration resistance (n=11)	1-16	9.09±3.72
	Time to death (months) (n=28)	10-101	47.71±27.64

mation about clinical stage and survival are given in Table 2 (Table 1, 2).

he mean age of Group 1 (69.18±7.7) was statistically significantly higher than Group 2 (64.21±5.03) (p=0.001; p<0.05).

The development of castration resistance was not statistically significant between the two groups (p=0.38). There was no statistically significant difference between the groups in terms of distribution rates of clinical stages (p>0.05). There was no significant difference in the overall survival of the patients between the groups (p=0.131).

Group 1's Gleason score before treatment was significantly higher than that of the prostatectomy arm (p=0.001) (Table 3).

During the follow-up of the patients, biochemical recurrence developed in 11 patients in Group 2. Biochemical recurrence was observed in 1, 3, 3, 3 and 1 patients at 3 months, 6 months, 9 months, 12 months and thereafter, respectively. In group 1, biochemical recurrence was observed in a total of 30 patients; in 7, 2, 3, 6, and 12 patients at 3 months, 6 months, 9 months, 12 months and thereafter, respectively.

Table 2. Evaluation of general characteristics between groups

	Group 1 n (%)	Group 2 n (%)	p
Clinical stage n (%)			
T1c	23 (37.7)	18 (64.3)	[1]0.064
T2	28 (45.9)	7 (25)	
T3	10 (16.4)	3 (10.7)	
Castration resistance development status n(%)			
Not developed	31 (50.8)	17 (60.7)	[1]0.38
Developed	30 (49.2)	11 (39.3)	
Survival n (%)			
Death	13 (21.3)	2 (7.1)	[2]0.131
Alive	48 (78.7)	26 (92.9)	

[1]Chi-Square Test; [2]Fisher's Exact Test; *p<0.05.

During pre-biopsy and subsequent follow-ups, the PSA results of Group 1 were found to be statistically significantly higher than the PSA results of Group 2 (p=0.001) (Fig. 1).

According to the Kaplan-Meier survival analysis results between the groups, the estimated mean time to castration resistance was found to be similar; it was approximately 46.8 months in Group 1, while it was calculated as 48.9 months in Group 2 (p=0.068) (Fig. 2).

Multiple bone metastases developed in 1 patient in the 6th year after the prostatectomy in Group 2, and then he died within 2 years. In 1 patient, multiple bone metastases developed in the postoperative 12th month and chemotherapy was applied.

In Group 1, additional bone metastases developed in 7 patients and liver metastases developed in 1 patient during the follow-up period. In Group 1, 16 (26.2%) patients had to undergo additional surgical interventions for the prostate, bladder or urethra (transurethral resection of the prostate (TURP), percutaneous cystostomy, endoscopic intervention due to the development of bleeding requiring erythrocyte transfusion, etc.).

When the survival rates of the patients in both groups were evaluated with the log rank test, no statistically significant difference was found between the groups (p=0.207; p>0.05) (Fig. 3).

Table 3. ISUP classification among groups

Isup Grade Group	Group 1 Number of patients (%)	Group 2 Number of patients (%)	p
Group-5	29 (47.5)	0 (0)	0.001*
Group-4	12 (19.6)	3 (10.7)	0.001*
Group-3	7 (11.4)	8 (28.5)	0.001*
Group-2	7 (11.4)	9 (32.1)	0.001*
Group-1	6 (9.8)	8 (28.5)	0.001*

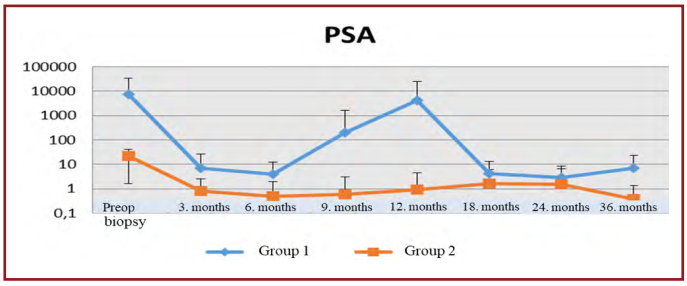

Figure 1. PSA follow-up schedule after starting ADT treatments.

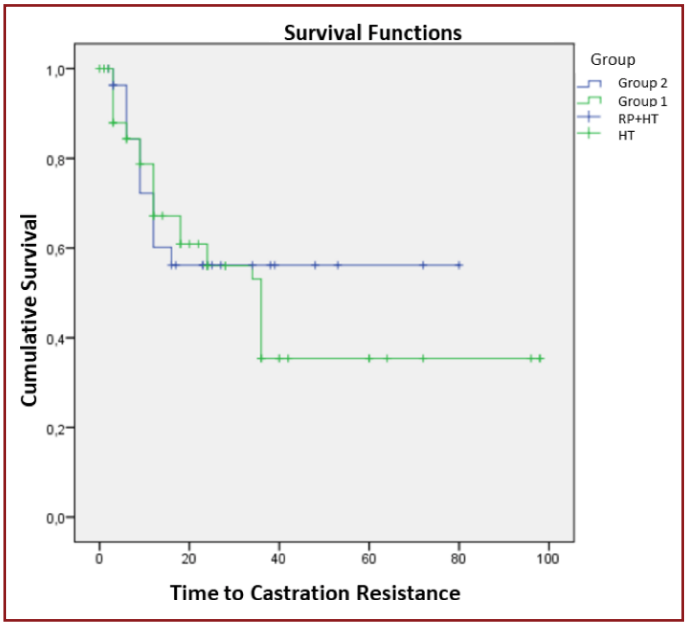

Figure 2. Time to castration resistance between two groups.

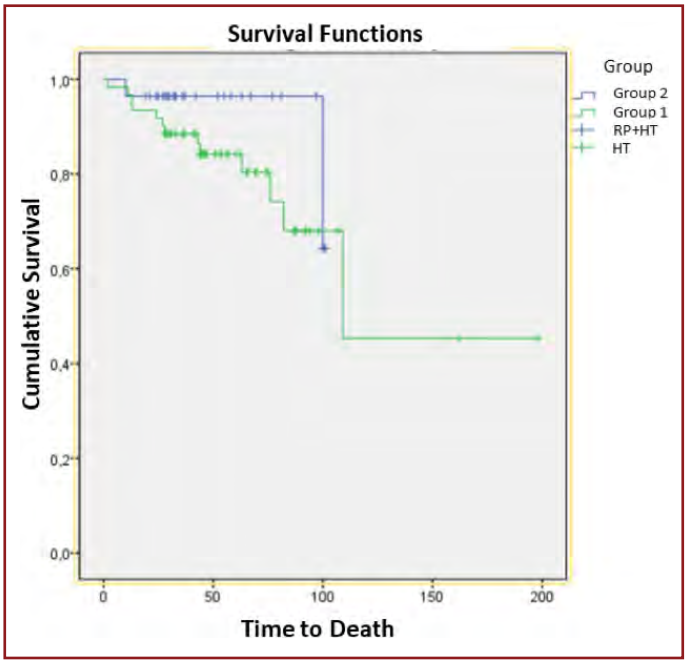

Figure 3. Graph of overall survival between the two groups.

Discussion

Prostate cancer is the most common solid tumor in men, and it is estimated that there are 3.3 million cancer cases in the United States alone and 180,900 newly diagnosed patients in 2016 [8]. Despite the advances in chemotherapy and androgen blockade in the last 20 years, the expected results in terms of overall survival and cancer-specific survival in metastatic prostate cancer patients have not been achieved [9]. However, STAMPEDE and CHAARTED trials have shown that with the addition of docetaxel treatment to the ADT treatment classically applied in metastatic prostate cancer patients, there are significant improvements in the general and disease-specific survival of the patients [10-12]. Although cancer progression is common in patients under ADT therapy, it has been suggested that local complications that develop in more than 50% of patients develop due to untreated primary tumor [13]. For these reasons, local treatment options (such as radical prostatectomy, radiotherapy) in metastatic prostate cancer are also the focus of attention.

While cytoreductive surgery is applied in many solid tumors (breast [14], ovary [15], colon [16], glioblastoma [17] and renal cell carcinoma [18,19]) because of its significant survival advantage in metastatic disease, high level of evidence on this issue in prostate cancer is still not available. Therefore, guidelines on metastatic prostate cancer do not recommend surgical or radiotherapy treatment of the primary tumor [20-22]. While the European Association of Urology (EAU) guidelines recommend primarily radiotherapy for the control of local symptoms, it does not offer surgery as a standard option [21,22]. However, recent studies suggest that radical prostatectomy as a part of multimodal treatment in metastatic prostate cancer increases the overall and disease-specific survival of patients and is applicable in selected patients.

Bhindi et al., [23] in their retrospective study scanning the surgeries performed between 1966-1995, divided the patients into 2 groups. Patients who were diagnosed with lymph node-positive prostate cancer at that time and underwent retropubic prostatectomy + bilateral orchiectomy were included in the first group (79 patients), while the patients who underwent only orchiectomy were included in the second group (79 patients). Cancer-specific survival was found to be 59% to 18% in the 20-year follow-up of the patients. While 28 of the 70 patients who died in the 1st group during their follow-up died due to prostate cancer-related causes, all the patients in the 2nd group died and the number of patients who died due to prostate cancer was 60. As a result of the study, it was stated that the overall and disease-specific survival were statistically significantly higher

in the 1st group. The major disadvantages of this study are that many patients' Gleason scores were not specified, PSA measurements were not available before 1987, and most importantly, comorbidities were not reported with sufficient accuracy in retrospective studies. There are many other studies published similar to this study, and the same bias is also present in them [24,25].

When we look at the results of the ECOG 3886 study, it was emphasized that the benefit of early ADT after radical prostatectomy increased the overall survival and disease-specific survival of the patients [26], while in the EORTC 30846 study, it was emphasized that the benefit of early ADT was not statistically significant [27]. The biggest difference of these 2 studies is that, considering that the patients in the ECOG study underwent radical prostatectomy, it can be concluded that radical prostatectomy increases the ADT response.

Analyzing the results of the SWOG 8894 study, Thompson et al. [28] examined 1286 male patients with bone metastases in 2 groups who received orchiectomy + placebo and orchiectomy + flutamide treatment, and when the results were evaluated, it was observed that the cancer-specific survival of patients with prior radical prostatectomy was significantly higher. Similar results were observed in the subgroup analysis of the IMPACT study [29]. In another retrospective study, Qin et al. [30] reported that even administration of TURP to patients with metastatic prostate cancer provided lower PSA levels and increased survival.

In another publication in the literature, 8185 M1a-c prostate cancer patients were divided into 3 groups according to SEER data, and the first group consisted of 7811 patients who did not receive local treatment. Radical prostatectomy was applied to 245 patients in the 2nd group, and brachytherapy was applied to 129 patients in the 3rd group. Cancer-specific and overall survival were found to be increased in the radical prostatectomy and brachytherapy group [31]. In Gratzke et al.'s [32] study of 1538 patients, using the Munich Cancer Registry data, the 5-year overall survival of 74 patients who underwent radical prostatectomy was determined as 55%, while the 5-year overall survival of the patients who were not applied radical prostatectomy was 21%. However, the pre-treatment clinical and pathological data of the patients were not evaluated in this publication, making it impossible to adapt them to clinical practice.

Heidenreich et al. [33] in their study in which they evaluated patients with 3 or less bone metastases and no bulky lymphadenopathy as oligometastatic, treated the patients with ADT for 6 months and applied radical prostatectomy to patients whose PSA levels fell below 1 ng/mL, and found that radical prostatectomy increased the time to develop castration resistance (40-29 months) and significantly increased cancer-specific survival (95.6-84.2 months), compared to ADT alone. However, no significant difference was found between these groups in terms of overall survival. Considering that a decrease in PSA below 1 ng/mL following the initiation of ADT is considered to be a good prognostic factor in the literature [34], it can be said that the place and contribution of radical prostatectomy in this study is questionable.

A similar study to Heidenreich's study was performed by Gandaglia et al. [35] in the literature. In this study, the concept of oligometastatic was also used, but less than 5 bone lesions and the absence of lymph node metastases were accepted as criteria. As a result of this study with 11 patients, progression-free survival was 45% and cancer-specific survival was 82% at 7-year follow-up.

In our study, only ADT was performed in 61 patients who did not receive cancer treatment before (Group 1), and ADT was applied to 28 patients after radical prostatectomy (Group 2). The median follow-up period was 40.3±29.3 months. Although there was no significant difference between the 2 groups in terms of pre-treatment clinical stages, age difference, pre-biopsy PSA levels and Gleason scores were significantly higher in Group 1. While castration resistance developed in 30 (49.1%) of 61 patients in Group 1, 11 (39.2%) of 28 patients in Group 2 developed castration resistance. There was no significant difference between the two groups in terms of development of castration resistance. Considering the mean time to castration, consistent with the literature, no significant difference was found between the two groups (46.8 vs 48.9 months). While 13 patients in Group 1 died during or after follow-up, only 2 patients died in Group 2. No significant difference was observed in terms of overall survival. Although Group 1 differed significantly from Group 2 in terms of age and comorbidity, there was no difference in overall survival, which is in line with the findings of Heidenreich et al. In our study, the initial PSA values, ISUP grade groups and mean age of the patients in Group 1 were significantly different from those in Group 2, and our study was retrospective, which may be contributed as weaknesses of our study that could affect the results. However, the fact that being a single-center study and having long-term follow-up and all data related to the disease could be examined in detail from the beginning of the study, can be considered as the strengths of the study.

Since all publications in the literature are retrospective, it should be considered that the selection of patients who underwent radical prostatectomy may not have been impartial. It does not seem possible for now to say that radical

prostatectomy plays an important role in overall survival, since it is thought that patients who underwent radical prostatectomy may have a lower volume of disease compared to the other group, may be patients with a better PSA response, and may be selected from patients with better performance status.

However, local treatments such as radical prostatectomy in metastatic disease should not be evaluated only with survival. Local effects of local treatments should also be considered. In the study conducted by Wiegand et al., [13] they stated that the rate of local symptom development was significantly higher in the group that received only ADT treatment among patients with lymph node metastasis, than in patients who received radical prostatectomy+ADT (44.6%-6.5%). Heidenreich et al. [33] reported that none of the patients who underwent radical prostatectomy developed late complications, and that complications related to local progression developed in 33% of those who received only ADT treatment. Surgical or percutaneous procedures were performed in 28.9% of these patients. In our study, while 3 (10.8%) patients in the prostatectomy+ADT group developed incontinence due to the operation, 16 (26.2%) patients in the hormone therapy group underwent additional surgery and/or percutaneous intervention. Considering that the frequency of complications after radical prostatectomy performed in high-risk patients in the literature is similar to the treatment applied in metastatic disease [36,37], radical prostatectomy can be applied as palliative, as a part of multimodal treatment in metastatic patients. However, it should be kept in mind that more radical prostatectomy will bring more complications.

There are 6 prospective studies on the localization of local treatment in metastatic disease with new results and whose results are awaited. Three of them include radiotherapy as local treatment. These are STAMPEDE, PEACE-1 and HORRAD trials. STAMPEDE was terminated in late 2018, and it was concluded that the administration of radiotherapy in newly diagnosed metastatic prostate cancer does not increase overall survival [38]. Another prospective study is a multicenter randomized phase 2 study from North America on metastatic prostate cancer, comparing best systemic therapy (BST) versus BST + local therapy (radical prostatectomy/radiotherapy). In this study, patient recruitment was terminated and the results are awaited. The primary goal is to calculate progression-free survival. Another study is the ongoing TRoMbone trial in the UK. This study was also planned to randomize the oligometastatic patients to the radical prostatectomy + classical treatment, and only the classical treatment group. The 5-year overall survival results of this study will be announced in the near future. Another important study is the g-RAMPP trial, in which it is desired to calculate cancer-specific survival by randomizing patients to receive radical prostatectomy + ADT or only ADT. In the g-RAMPP trial, patients having at least 1 and at most 5 bone metastases and no visceral metastases are among the conditions required (Table 4).

After the results of these studies are announced, we think that we can have a more advanced idea about the place of radical prostatectomy in metastatic prostate cancer. It is believed that these studies will clarify the effect of local treatment in symptomatic local progression, its mechanism, and the relationship between radical prostatectomy

Table 4. Recent studies investigating cytoreductive radical prostatectomy in metastatic prostate cancer

TRIAL	Localization	Design	Groups	Primary Result
ISRCTN15704862 (TRoMbone)	UK	Phase 1/2	1- Best systemic therapy (BST) 2-BST + cytoreductive radical prostatectomy (CRP) and extended LND (eLND)	Quality of life and time to castration resistance
NCT01751438	United States	Phase 2	1-BST 2- BST+CRP/RT	PFS
NCT02454543 (g-RAMPP)	Germany	Phase 2	1-BST 2-BST + CRP+eLND	CSS
NCT02971358	Austria	Phase 1/2	CRP+eLND	90-day complication rates
NCT03456843 (SIMCAP)	United States	Phase 2/3	1-BST 2-BST+CRP	Castration resistance development and overall survival rate at 2 years
NCT03655886	Belgium	Phase 2	1-CRP 2-Pelvic RT	Feasibility of randomization

BST: Best systemic therapy; PFS: Progression-free survival; CSS: Cancer-specific survival; CRP: Cytoreductive radical prostatectomy; eLND: Extended lymph node dissection.

pathology and metastasis. Thus, the heterogeneous structure and biological basis of metastatic prostate cancer will be enlightened.

In order for radical prostatectomy to take place primarily in the treatment of metastatic prostate cancer in the near future, it should be clearly stated which patients it can be applied to.

Although metastatic prostate cancer constitutes approximately 5% of cancer cases at the time of diagnosis, it is a heterogeneous disease in itself. Androgen deprivation therapy has been the standard approach to treatment for over 50 years. However, the treatment protocol in this disease, which has not yet been determined by which method even ADT can be performed better, is the focus of attention of clinicians. Recent studies have gained new dimensions regarding the systemic treatment of metastatic disease and guidelines have been updated accordingly. Many retrospective studies on local control of the disease are also being published. Many studies on radical prostatectomy recommended for local control cannot show a high level of evidence due to their retrospective nature and insufficient randomization. The results of well-designed, prospective, randomized, phase 3 studies evaluating the role of radical prostatectomy in metastatic prostate cancer are awaited. Therefore, for the time being, radical prostatectomy in metastatic disease can be applied within the multimodal treatment as palliative or to prevent local progression, by informing the patients sufficiently without expecting a curative effect.

Conclusion

In our study, it was concluded that the application of ADT after radical prostatectomy to patients with metastatic prostate cancer does not have an advantage over the application of ADT alone in terms of castration resistance development, time to castration resistance and overall survival.

Ethics Committee Approval: Health Sciences University Ümraniye Training and Research Hospital Ethics Committee (28.09.2017 Ethics Committee Decision No: 146).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: B.Ş., U.B.; Design: B.Ş., E.V.K.; Data Collection or Processing: R.S., A.İ.; Analysis or Interpretation: A.B., B.Ş., U.B.; Literature Search: B.Ş., U.B., A.B.; Writing: B.Ş.

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