Original Article

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Obstructive Uropathy in Advanced Prostate Cancer

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Abstract

Objective: The incidence of advanced prostate cancer increases in proportion to new treatment options and prolonged life expectancy. Especially in advanced disease, prostate cancer is a progressive disease that can cause obstructive uropathy. This study investigated the relationship between the characteristics of advanced prostate cancer and obstructive uropathy.

Materials and Methods: This study retrospectively evaluated the data of prostate adenocarcinoma patients admitted to the Urology Clinic of Manisa Celal Bayar University Hospital between 2017 and 2021. Of them, 48 were advanced prostate cancer patients, and they were all included. All patients in the study received hormonal therapy along with chemotherapy for prostate cancer treatment. The relationship between hydronephrosis and patient age, creatinine and prostate-specific antigen (PSA) values, urinary tract infections, prostate volume, pathological features of cancer, and castration resistance was evaluated.

Results: Parameters that we found to be associated with obstructive uropathy (OU) are as follows: high creatinine level at the time of diagnosis of cancer ($p<0.001$), increase in creatinine at follow-up ($p=0.001$), urinary infection at the time of diagnosis of cancer ($p=0.002$) and at follow-up ($p=0.003$), development of castration resistance during treatment ($p=0.038$) and high PSA values at the time of diagnosis of prostate cancer ($p=0.011$).

Conclusion: Renal functions should be observed very carefully in advanced prostate cancer patients who develop or are at risk of developing OU. High PSA values and/or castration resistance should be approached carefully in terms of the patients prognosis. It should not be forgotten that their significant relationship with OU has been demonstrated.

Keywords: Azotemia, hydronephrosis, prostate cancer

Introduction

The incidence of advanced prostate cancer increases in proportion to new treatment options and prolonged life expectancy (1). Obstructive uropathy (OU) is a condition in which urine flow is restricted in the urinary system by internal or external obstruction. Subsequent aseptic dilatation of the renal pelvis and calyces by filling with urine is called hydronephrosis (2). Especially in advanced stages, prostate cancer is a progressive disease that can cause OU (3). OU requires strict follow-up and intervention, and it has an important place in quality of life (4). Progressive dilation of the upper urinary tract can lead to acute renal failure and, if not treated, nephron loss (5). Castration-resistant and/or metastatic prostate cancer is a patient group whose life expectancy is increasing. Thus, it is clear that OU, one of the most important complications of this patient group, should be studied again. This study investigated the relationship between the characteristics of advanced prostate cancer and OU.

Materials and Methods

This study retrospectively evaluated the data of prostate adenocarcinoma patients admitted to the Urology Clinic of Manisa Celal Bayar University Hospital between 2017 and 2021. Of these, 48 were advanced prostate cancer patients at the time of diagnosis with at least one bony metastasis. They were all included in the study. There was no patient with distant lymph node metastasis at the time of diagnosis. All patients in the study received hormonal therapy with chemotherapy together. Subcutaneous luteinizing hormone-releasing hormone agonist (goserelin acetate) was administered to the patients every 12 weeks. They also received intravenous docetaxel chemotherapy (75 mg/m^2) every 21 days for 6 cycles.

In our study, the relationship between hydronephrosis and the patient's age, creatinine levels, prostate-specific antigen (PSA) values, urinary tract infections, prostate volume, pathological features of cancer, and castration resistance was evaluated. The urinary tract infection (UTI) was diagnosed with a positive urine culture. All biopsies were performed under transrectal

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ultrasound guidance. The expression 'time of diagnosis' in the article refers to the moment when the patient is diagnosed with prostate cancer, not hydronephrosis. This study was accepted by the Ethics Committee of Manisa Celal Bayar University Faculty of Medicine with decision number 20.478.486 (date: 02.12.2020).

Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, New York, United States) programs were used in the analysis of variables for statistical calculations. In the comparison of two independent groups according to quantitative data, the independent samples t-test was used together with the bootstrap results, while the Mann-Whitney U test was used together with the Monte Carlo results. Pearson chi-square and Fisher's exact Monte Carlo simulation techniques were used to compare categorical variables with each other. Less than 0.05 for p value was accepted as significant.

Results

Forty-eight patients were included in the study (n=48). Minimum age was 48, maximum was 86, and mean age was 69.2 years. The shortest follow-up period was 22 months, while the longest was 48 months. The median follow-up was 35 months. The minimum prostate volume was 30 cc, and the maximum was 140 cc. The median volume was 54.6 cc. Forty-four patients (91.7%) had a bilateral prostate lobe involvement. Perineural invasion was found in 33 patients (68.8%) on biopsy. The number of patients with extraprostatic involvement in biopsy was 20 (41.7%). The patients were divided into 2 groups: those with (n=19) and without (n=29) hydronephrosis. The detection of hydronephrosis at the time of diagnosis or during follow-up was also studied as two separate subgroups. In 11 (22.9%) of 48 patients, hydronephrosis was present at the time of diagnosis of cancer. Hydronephrosis developed in 8 (21.6%) of 37 patients who were not found to have hydronephrosis at the time of diagnosis. The mean development time of hydronephrosis at follow-up was 22 months.

Bilateral hydronephrosis was in 10 (90.9%) of 11 patients with hydronephrosis at diagnosis. Only 1 patient (9.1%) had isolated left hydronephrosis. In 8 patients who developed hydronephrosis during follow-up, the numbers of those with bilateral, left, and right kidney involvement were 4 (50%), 3 (37.5%), and 1 (12.5%), respectively. Among the patients who had hydronephrosis at the time of diagnosis (n=11), there were 2 patients (18.2%) with grade 1, 6 people with grade 2 (54.5%), 2 people with grade 3 (18.2%), and 1 with grade 4 (9.1%) hydronephrosis. In patients who developed hydronephrosis during the follow-up, there was no patient with grade 1 detected. There were 3 people (37.5%) with grade 2, 4 people (50%) with grade 3, and 1 person (12.5%) with grade 4. Four of 11 patients (36.4%) with hydronephrosis at the time of diagnosis were treated with percutaneous nephrostomy. The treatment of 5 patients (45.5%) was provided by placing a retrograde ureteral stent. Two patients (%18.2) were under active surveillance. Of 8 patients who developed hydronephrosis during follow-up, 6 (80%) were treated with percutaneous nephrostomy and 1 (12.5%) with transurethral resection (TUR). One of them (12.5%) was followed up with no invasive procedure (Table 1).

The mean age was 68.4 years in the group with hydronephrosis, whereas it was 69.7 years in the group without hydronephrosis. Median prostate volume was 50 cc in the hydronephrosis group and 45 cc in the non-hydronephrosis group. At the time of diagnosis, UTI was detected in 13 of 48 patients (27.1%). In follow-up, this rate was 15 (31.3%). There was a significant correlation between the presence of hydronephrosis in the whole patient group and the detection of UTI at the diagnosis (p=0.002). Of the 19 patients who were found to have hydronephrosis, 10 (52.6%) had UTI at the time of diagnosis. There was also a significant relationship between the presence of hydronephrosis in the whole patient group and the detection of UTI in the follow-up (p=0.003). Of the 19 patients who were found to have hydronephrosis, 11 (57.9%) had UTI at follow-up (Table 2).

There is a significant correlation between hydronephrosis and creatinine level at the time of diagnosis (p<0.001). The median creatinine value at the time of diagnosis in 19 patients with hydronephrosis was 1.33 mg/dL. The median creatinine value at the time of diagnosis in 29 patients without hydronephrosis was 0.82 mg/dL. In addition, a significant correlation was found between the increase in creatinine in the follow-up and the diagnosis of hydronephrosis (p=0.001). An increase in creatinine was detected in the follow-up of 8 (42.1%) of 19 patients with hydronephrosis (Table 2).

There was a significant correlation between PSA value at the time of diagnosis and hydronephrosis at diagnosis (p=0.011). The median PSA value at the time of diagnosis was 155 ng/mL in 11 patients with hydronephrosis at the time of diagnosis. The median PSA value of 37 patients without hydronephrosis at diagnosis was 59.6 ng/mL. Therefore, the detection of hydronephrosis at the time of diagnosis and PSA values are significant when

Table 1. Features of hydronephrosis and treatment

		Diagnosis		Follow-up	
		n	%	n	%
Hydronephrosis (HN)					
	Negative	37	77.10%	40	83.30%
	Positive	11	22.90%	8	16.70%
HN side					
	Right	0	0.00%	1	12.50%
	Left	1	9.10%	3	37.50%
	Bilateral	10	90.90%	4	50.00%
HN grade					
	I	2	18.20%	0	0.00%
	II	6	54.50%	3	37.50%
	III	2	18.20%	4	50.00%
	IV	1	9.10%	1	12.50%
HN Treatment					
	Nephrostomy	4	36.40%	6	75.00%
	Retrograde stent	5	45.50%	0	0.00%
	TUR	0	0.00%	1	12.50%
	Active surveillance	2	18.20%	1	12.50%

TUR: Transurethral resection

evaluated as a subgroup. However, no significant correlation was found with PSA values for hydronephrosis patients in the whole group.

The number of people who developed castration resistance during their follow-up was 23 (47.9%). There was a significant correlation between castration resistance and hydronephrosis (p=0.038). Castration resistance was detected in 13 (68.4%) patients with hydronephrosis during follow-up. The median time to develop castration resistance was 22.4 months. The median duration of castration resistance development in the group of patients with hydronephrosis was 21 months and 25 months in patients without hydronephrosis (Table 2). In the subgroup of patients with hydronephrosis at diagnosis, the median time to reach castration resistance was 16 months.

No statistically significant correlation was found between hydronephrosis and patients' age, perineural invasion in biopsy, prostatic apex or extraprostatic involvement in biopsy, time to develop castration resistance, and prostate volume.

Discussion

Oefelein (6) was designed with 260 patients with advanced prostate cancer. The number of patients with OU was 51 (19.6%). This study included patients with one of the following two conditions for the diagnosis of advanced prostate cancer: a newly diagnosed patient with metastasis or a patient with biochemical recurrence after primary local curative therapy. It is seen that the percentage of patients with OU in the study of Oefelein (6) was 19.6%, which is lower than the rate of 39.5%

Table 2. Hydronephrosis and statistical analysis

		Hydronephrosis		p-value
		Negative	Positive	
		(n=29)	(n=19)	
		Mean (SD)	Mean (SD)	
Age (year)		69.7 (8.34)	68.4 (6.13)	0.592[t]
		Median (min/max)	Median (min/max)	
Castration resistance time (month)		25 (7/44)	21 (5/38)	0.317[u]
PSA at diagnosis (ng/mL)		89.9 (10.2/1540)	89 (10.6/1200)	0.928[u]
Creatinine at diagnosis (mg/dL)		0.82 (0.5/1.71)	1.33 (0.6/13.2)	<0.001[u]
Prostate volume at diagnosis (mL)		45 (30/120)	50 (30/140)	0.606[u]
		N (%)	N (%)	
UTI at diagnosis				
	Negative	26 (89.7)[B]	9 (47.4)	0.002[p]
	Positive	3 (10.3)	10 (52.6)[A]	9.6 (2.2-43)[or]
Prostate apex involvement				
	Negative	4 (13.8)	3 (15.8)	0.999[f]
	Positive	25 (86.2)	16 (84.2)	
Perineural invasion				
	Negative	10 (34.5)	5 (26.3)	0.751[f]
	Positive	19 (65.5)	14 (73.7)	
Extraprostatic extension				
	Negative	17 (58.6)	11 (57.9)	0.999[p]
	Positive	12 (41.4)	8 (42.1)	
Creatinine increase at follow-up				
	Negative	28 (96.6)[B]	11 (57.9)	0.001[f]
	Positive	1 (3.4)	8 (42.1)[A]	20.4 (2.3-182.4)[or]
UTI at follow-up				
	Negative	25 (86.2)[B]	8 (42.1)	0.003[p]
	Positive	4 (13.8)	11 (57.9)[A]	8.6 (2.1-34.6)[or]
Castration Resistance				
	Negative	19 (65.5)[B]	6 (31.6)	0.038[p]
	Positive	10 (34.5)	13 (68.4)[A]	4.1 (1.2-14.1)[or]

SD: Standard deviation, UTI: Urinary tract infection, t: Independent Samples t-test (Bootstrap), [u]: Mann-Whitney U test (Monte Carlo), [p]: Pearson chi-square test (Monte Carlo), [f]: Fisher's Exact test (Monte Carlo), [or]: Odds ratio (95% confidence interval), [A]: Significant compared to the non-hydronephrosis group, [B]: Significant compared to the hydronephrosis group

in our study. In our study, there were only patients with bony metastases at the time of diagnosis. We think that the rates are different in this way because we have a more advanced stage patient group that does not include the recurrence group after local treatment.

In the same study (6), 45% transurethral resection of prostate (TUR-P), 15.6% ureteral double J stent, 15.6% percutaneous nephrostomy, 9.8% TUR-P, and ureteral stent were applied together. In our study, 52.6% nephrostomy, 26.3% ureteral stent, and 5.2% TUR-P were applied, while 15.7% of the patients were followed without invasive treatment. This difference is thought to be due to more than one reason. One of them is that the patient needs regional or general anesthesia to perform TUR-P, while this anesthesia is not necessary for percutaneous nephrostomy. Therefore, as mentioned before, we think that the fact that our study was conducted with a more fragile patient group with a more advanced cancer compared to this study was effective in this decision. In addition, TUR passage application in prostate cancer has a higher rate of failure and the need for repeat TUR compared with TUR-P for benign prostate enlargement (7).

In another article by Oefelein et al. (8) with a similar patient group, 254 patients on androgen deprivation therapy were evaluated in terms of survival. Although there are no survival data in our study, the factors that have an effect on survival were investigated in this study and are similar to our data. In this study (8), it was shown that the presence of OU, high nadir PSA values, diagnosis at a later age, lower testosterone levels before treatment, history of tobacco use, and high alkaline phosphatase levels have negative effects on survival. It was shown that both high age at diagnosis and OU had a negative effect on survival. According to these results, it can be said that the patient group, whose age at diagnosis is older and who develops OU in the follow-up, is more disadvantageous in terms of survival. Again, in this study (8), a high nadir PSA was found to have a negative effect on survival. According to our study, OU at diagnosis has a relationship with high PSA levels at the time of diagnosis and castration resistance in treatment. When the results of the two studies are evaluated together, it can be said that the survival of the patient with high nadir PSA will be worse, and if there is high PSA level at diagnosis and/or castration resistance in this patient group, the risk of developing OU, which also has a negative effect on survival, will increase.

Paul et al. (9) was conducted with 820 patients with prostate cancer at different stages. When those with bladder outlet obstruction were excluded, it was observed that 36 (4.3%) patients had bilateral ureteral obstruction and elevated urea levels. There are some reasons why this 4.3% rate is very low compared to our study (19/48 patients, 39.5%). As mentioned earlier, patients with bladder outlet obstruction were excluded in this study; therefore, this patient group was included in our study. In addition, this study was conducted with 820 patients with prostate cancer of all stages. It is seen that the majority of this sample consisted of local disease. Because our group of patients were more advanced-stage patients, there is a difference between the rates. Also, this rate by Paul et al. (9) is for patients with both "bilateral obstruction" and "high urea". In our study, all unilateral or bilateral dilatations were included in the statistics, with or without azotemia.

In the study published by Paul et al. (9), 10 (28%) of 36 patients with bilateral ureteral obstruction and elevated urea were initially referred to hospitals with symptoms of azotemia and were diagnosed with prostate cancer after further investigations (9). In our study, unilateral or bilateral hydronephrosis was present in 11 (22.9%) patients at the time of diagnosis, and creatinine elevation was found in 9 (18.75%) of them. Of the 36 patients in the study by Paul et al. (9) who had bilateral ureteral obstruction and elevated urea, 16 patients received invasive treatment. Of these, 9 were treated with nephrostomy, 5 with stents, and 2 with ureteroneocystostomy. The reason why there is no TUR passage or catheter option among these treatments is that patients with bladder outlet obstruction were excluded from the study, as mentioned before. In our study, 10 nephrostomy, 5 ureteral stents, and 1 TUR-P were performed for treatment, while 3 of the patients were followed without invasive treatment.

Emrich et al. (10) investigated the prognostic factors of 1,020 patients with advanced prostate cancer. According to the results of this study, some parameters that negatively affect the survival time, which were also evaluated in our study, are as follows: inadequate response to hormonal therapy, presence of obstructive symptoms, advanced tumor stage, and advanced patient age at diagnosis. As mentioned before, our study cannon be compared in this way because it does not have survival data. Nevertheless, a comment can be made on similar factors in the studies. Emrich et al. (10) determined that the patients inadequate response to hormonal therapy was a poor prognostic factor. In our study, castration resistance ($p=0.038$) and high PSA level at the time of diagnosis ($p=0.011$) were found to be significantly associated with OU. Emrich et al. (10) also found the presence of obstructive symptoms in the patient as a poor prognostic factor. Emrich et al. (10) determined that a high tumor stage is a poor prognostic factor, and in our study, castration resistance during treatment ($p=0.038$) and high PSA value at the time of diagnosis ($p=0.011$) were significantly associated with OU, and these findings are compatible with each other.

Study Limitation

There are certain natural limitations due to the retrospective nature of the study. Complications related to prostate cancer were either diagnosed when symptomatic or discovered during routine follow-up at wide intervals as a result of the retrospective design. In a prospective study, these complications could have been detected earlier by more frequent monitoring. Additionally, patients could not be evaluated for genetic predisposition, which is believed to lead to faster cancer spread and development of complications, as it is not yet used in routine clinical practice.

Conclusion

Our study examined the parameters affecting the development of OU in patients with advanced prostate cancer. It can be said that advanced prostate cancer is a disease that requires both a multidisciplinary approach and multimodal treatment. Renal

functions should be observed very carefully in patients at risk of developing OU. It is obvious that physicians should be very careful against urinary infections. The development of high PSA values and/or castration resistance should be approached carefully in terms of the patient's prognosis, and it should not be forgotten that their significant relationship with OU has been demonstrated.

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Ethics

Ethics Committee Approval: This study was accepted by the Ethics Committee of Manisa Celal Bayar University Faculty of Medicine with decision number 20.478.486 (date: 02.12.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.E., T.M., Concept: O.E., T.M., Design: O.E., T.M., Data Collection or Processing: O.E., Analysis or Interpretation: O.E., Literature Search: O.E., Writing: O.E.

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