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ORIGINAL ARTICLE

Medicine Science 2022;11(4):1720-4

Medicine Science International Medical Journal

The safety of deferring operation for prostate carcinoma during the COVID-19 period

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Received 11 May 2022; Accepted 15 November 2022
Available online 01.12.2022 with doi: 10.5455/medscience.2022.05.111

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Abstract

The COVID-19 pandemic has led to the restructuring of healthcare delivery. There have been delays in fighting against leading problems such as cancer in this process. Prostate cancer (PCa) is the most common cancer among urological malignancies. We aim to evaluate the differences between patient populations diagnosed with PCa before and during the pandemic and underwent radical prostatectomy (RP) as a treatment. The study was designed retrospectively in a single center. The pathologic, clinic and demographic of patients who underwent RP between 11.03.2020, which is the first date of the pandemic in Turkey, and 31.12.2020 and between 11.03.2019 and 31.12.2019 were compared. 327 patients were appropriate for inclusion criteria. 125 of them were operated during the pandemic and 202 of them before the pandemic. The median between prostate biopsy and RP was 82 days before the pandemic and 97 days during the pandemic (p=0.04). Although there was a significantly longer time between biopsy and RP during the pandemic, gleason score upgrading, upstaging, biochemical recurrence and lymph node involvement were not found significantly different. Additionally, in groups made by the D'amico risk classification, no significant difference was found between the two periods in Gleason Score Upgrading and Upstaging. The deferrability of malignancy treatment is an important problem for the health system due to the high number of oncology patients. The current pandemic has increased the importance of patient selection to minimize the harmful effects of deferred operations. This study showed that the delay of surgery does not affect the oncologic results for PCa.

Keywords: Prostate carcinoma, surgical delay, COVID-19 pandemic

Introduction

The SARS-Cov-2 virus, which is estimated to have emerged in Wuhan, China, on December 12, 2019, spread rapidly and led to a pandemic called COVID-19 [1]. With the first case seen on March 11, 2020, the epidemic and its effects spread rapidly in Turkey, affecting the health system deeply as it did worldwide [2,3]. Governments have revised their health policies and devoted a significant amount of health personnel and equipment to the fight against the COVID-19 pandemic for the health of society. The number of outpatient clinics and appointments was reduced, the operating rooms were partially closed, and the number of intensive care and inpatient services was revised to fight against the pandemic. Besides these, patients and their relatives canceled their appointments due to fear of possible COVID-19 infection or turned to alternative treatments. Also, In this process, the pace of the epidemic was tried to be slowed down from time to time with quarantine practices. However, all these measures and practices put the health system into difficulties in the fight against malignancies, which are an important cause of mortality and morbidity in the society, and the diagnosis and treatment were delayed or had to be postponed [2,4,5].

Prostate Cancer (PCa) is one of the most common non-cutaneous malignancies in men in western society, and the number of newly diagnosed PCa patients is 1 414 259 people and the number of deaths due to PCa is 375 304 people worldwide in 2020, according to estimates. It is the second most common cancer and the leading cause of death in male patients after lung cancer [6]. These statistical values are similar for Turkey and PCa constitutes 14.6% of newly diagnosed male patients. PCa is the 6th most common type of cancer that causes mortality, regardless of gender [7]. PCa, which is the most common urological malignancy, is usually seen in men over 50 years of age [8]. Considering the comorbidities generally seen in this age group, the caught SARS-CoV-2 virus causes more severe results [9]. Due to the fear of catching the disease, patients avoid screening, imaging and biopsy procedures for PCa,

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and there are delays in diagnosis and treatment [10]. Although there are previous studies on the effect of delaying or deferring definitive treatments on the outcome of the disease in patients with PCa, there are different results in the literature [2,5]. One of the definitive treatment methods for PCa is RP operation. With this single-center retrospective study, we would like to contribute to the literature by comparing the patient group who were operated in the COVID-19 pandemic with the patients who were operated in the pre-pandemic period, by investigating whether there is a significant difference between oncological outcomes due to delay in treatment and recurrences during follow-up.

Materials and Methods

Patient characteristics and data collection

Our data were collected retrospectively. A total of 202 patients who were diagnosed and underwent RP from March 11, 2019, before the COVID-19 pandemic to December 31, 2019, were included in our study. Comparative analysis of the first group was made with 125 patients who were diagnosed and underwent RP from March 11, 2020, the first date of COVID-19 cases in Turkey, to December 31, 2020. Patients who received radiotherapy (RT) or hormonotherapy (HT) after the diagnosis of PCa and patients with a period of more than one year between their diagnosis and RP surgery were not included in the study.

Measurement and definition of parameters

Age, PSA value, prostate-specific antigen density (PSAD), time from biopsy to RP, biopsy scores according to the Gleason Scoring System, ISUP grade, prostate volumes, pathological and clinical Stages, upgrading and upstaging status, lymph node involvement, presence of biochemical recurrence of the patients included in the study were recorded. The prostate volume was found by multiplying the prostate's length, width, and height in millimeters by 0.52 during the biopsy taken from the patients with the transrectal ultrasound probe. Biopsy was performed with transrectal ultrasonography (Mindray- DC-7T Diagnostic Ultrasound System). The seventh edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) Staging Manual was used for patients' clinical and pathologic classification. The upgrade was defined as the ISUP grade of the surgical material being higher than the biopsy ISUP result. Upstaging was defined as at least pT3 or pN1 in patient's surgical material. A PSA value of ≥0.2 ng/mL in two independent postoperative measurements was defined as biochemical recurrence. After the patients were divided into two general categories as before and after the COVID-19 pandemic and statistical analyzes were made, they were grouped according to D'Amico's risk classification system and their data were analyzed again.

Statistical analyses

Statistical Package for Social Sciences (SPSS), version 22.0 (SPSS Inc. Chicago, USA), was used for the statistical analysis. For the descriptive statistics, categorical variables were presented as numbers, percentages, and continuous variables as median (min-max). The suitability of continuous variables to normal distribution was evaluated using visual (histogram and probability charts) and analytical methods (Kolmogorov- Smirnov). The non-normally distributed parameters were compared using the Mann-Whitney U-test. Categorical variables between independent groups were compared using the Chi-square test. $P<0.05$ was considered statistically significant.

Ethic statement

This study was approved by the Institutional Review Board (IRB) of Ankara City Hospital (approval number: E-2-21-168). Written informed consent was obtained from each subject.

Results

A total of 327 patients who met the study criteria were included in the study. Group 1 refers to patients diagnosed and treated prior to the COVID-19 pandemic, while group 2 is used to describe patients who were diagnosed and treated during the pandemic. While the median waiting time from biopsy to RP was 82 days for patients in group 1, it was found to be 97 days for patients in group 2. (P=0.04). The mean age of the patients was 65 years in group 1 and 63 years in group 2 (P=0.47). The mean PSAD of group 1 was not significantly different from group 2 (0.17 vs. 0.16, respectively; P =0.84). The mean follow-up after RP was 25.2 months for group 1. Group 2 patients were followed for an average of 14.6 months. While upgrading was observed in 73 of 202 (36.1%) patients in group 1, the upgrade was detected in 44 of 125 (35.2%) patients in group 2. (P=0.9). Similarly, while upstaging was observed in 38.1% of group 1 patients, this rate in group 2 patients was found to be 37.6%. (P=0.92). When the pathologies of the patients were examined, no significant difference was found between the two groups in terms of lymph node involvement, 16.2% and 12.3%, respectively (P=0.49). There was no statistically significant difference in the biochemical recurrence rates detected during the postoperative follow-up between the two groups (P=0.24) (Table 1). These patients, who were in two different groups, were grouped according to the D'Amico risk classification system. According to this risk grouping, no significant difference was found in upstage and upgrading in the comparative analysis of group 1 and 2 patients in low, medium, and high-risk groups (Table 2,3,4).

Discussion

During the COVID-19 pandemic circumstances, the deferability of the malignancy treatment is a widespread debate among clinicians [4,5]. There is an increased risk of death in electively operated patients due to COVID-19 [4,5,11]. The hospital's increased circulation rates make the patients more vulnerable to the virus [2,4,12].

So, the admission rates to the hospital due to malign or benign problems have decreased. The patients started to live without malignancy control during this period [12]. Especially in the high-risk periods of the pandemic, people have had anxiety about virus transmission, which was the main reason for this decrease [2,4,12]. Also, the quality of healthcare services and facilities has decreased, so the patient acceptance to the outpatient clinics got lower [2,4, 5,12,13]. Although the renal and bladder cancer admission rates were increased during the low-risk periods of the pandemic, PCa admission rates decreased for all periods of it [12]. In our study, the PCa diagnosis rates were also reduced significantly according to the previous year's same time. Therefore, the possibility that the patients who are diagnosed and treated in the new period, when the pandemic conditions have disappeared, are more advanced and have a higher ISUP degree, should not be ignored. So our results can be applied to only mandatory situations like pandemics.

Table 1. Demographic and Pathologic Results Before and During COVID-19 Pandemic

	Before COVID-19(202)	During COVID-19(125)	p
Age (year)(min-max)	65(46-79)	63(48-75)	0.47
PSA (ng/ml) (min-max)	8.1(3.4-72.39)	6.3(3-55)	0.01
PSADT (min-max)	0.17(0.02-1.91)	0.16(0.04-1.38)	0.84
Waiting Time (day)	82(15-365)	97(26-269)	0.04
Bx GS (%)			**0.56**
6	105(52)	66(52.8)	
7	61(30.2)	41(32.8)	
8	26(12.9)	14(11.2)	
9	7(3.5)	1(0.8)	
10	3(1.5)	3(2.4)	
Pathology GS (%)			**0.21**
6	60(29.7)	46(37.1)	
7	104(51.5)	62(50)	
8	23(11.4)	6(4.8)	
9	14(6.9)	10(8.1)	
10	1(0.5)	0(0)	
Bx ISUP (%)			**0.83**
1	105(52)	66(52.8)	
2	43(21.3)	26(20.8)	
3	18(8.9)	15(12)	
4	26(12.9)	14(11.2)	
5	10(5)	4(3.2)	
Pathology ISUP (%)			**0.21**
1	60(29.7)	46(37.1)	
2	74(36.6)	40(32.3)	
3	30(14.9)	22(17.7)	
4	23(11.4)	6(4.8)	
5	15(7.4)	10(8.1)	
cT (%)			**<0.001**
t1c	84(41.6)	23(18.4)	
t2a-b	77(38.1)	64(51.2)	
t2c	41(20.3)	38(30.4)	
pT (%)			**0.65**
t2a-b	28(13.9)	22(17.6)	
t2c	94(46.5)	56(44.8)	
t3	80(39.6)	47(37.6)	
Upgrading (%)			**0.9**
No	129(63.9)	80(64.5)	
Yes	73(36.1)	44(35.5)	
Upstaging (%)			**0.92**
No	125(61.9)	78(62.4)	
Yes	77(38.1)	47(37.6)	
Relapse (%)			**0.24**
No	164(86.3)	99(90.8)	
Yes	26(13.7)	10(9.2)	
LN (%)			**0.49**
No	98(83.8)	50(87.7)	
Yes	19(16.2)	7(12.3)	
D'amico (%)			**0.98**
Low	77(38.3)	49(39.2)	
Medium	50(24.9)	30(24)	
High	74(36.8)	46(36.8)	

Bx: Biopsy, GS: Gleason Score, ISUP: International Society of Urologic Pathology, LN: Lymph Node, PSA: Prostate Specific Antigen, PSADT: Prostate Specific Antigen Doubling Time

Table 2. The Oncologic Results of Low Risk Patients Before and During Pandemic

	Low-Risk		
	Before COVID-19(77)	**During COVID-19(49)**	**p**
Upgrading (%)			**0.22**
No	37(48.1)	29(59.2)	
Yes	40(51.9)	20(40.8)	
Upstaging (%)			**0.87**
No	62(80.5)	40(81.6)	
Yes	15(19.5)	9(18.4)	
Waiting Time (day)(min-max)	86(41-317)	111.5(42-246)	0.31
Age (year)(min-max)	65(46-76)	62.5(48-75)	0.96
PSA (ng/ml) (min-max)	6.5(3.4-13.92)	5.91(3-9.98)	0.01
PSADT (min-max)	0.11(0.03-0.41)	0.14(0.04-0.3)	0.83

PSA: Prostate Specific Antigen, PSADT: Prostate Specific Antigen Doubling Time

Table 3. The Oncologic Results of Medium Risk Patients Before and During Pandemic

	Medium Risk		
	Before COVID-19 (50)	**During COVID-19 (30)**	**p**
Upgrading (%)			0.89
No	39(78)	23(76.7)	
Yes	11(22)	7(23.3)	
Upstaging (%)			**0.61**
No	34(68)	22(73.3)	
Yes	16(32)	8(26.7)	
Waiting Time (day)(min-max)	82(15-256)	104(66-190)	0.06
Age (year)(min-max)	66(54-78)	62.5(52-75)	0.72
PSA (ng/ml) (min-max)	8.84(4.07-18)	6.41(3.96-16.5)	0.09
PSADT (min-max)	0.18(0.04-0.46)	0.14(0.06-0.47)	0.84

PSA: Prostate Specific Antigen, PSADT: Prostate Specific Antigen Doubling Time

Table 4. The Oncologic Results of High Risk Patients Before and During Pandemic

	High Risk		
	Before COVID-19 (74)	**During COVID-19 (46)**	**p**
Upgrading (%)			0,36
No	52 (70.3)	28 (62.2)	
Yes	22 (29.7)	17 (37.8)	
Upstaging (%)			**0.73**
No	28 (37.8)	16 (34.8)	
Yes	46 (62.2)	30 (65.2)	
Waiting Time (day)(min-max)	78 (23 - 314)	81 (26 - 218)	0.56
Age (year)(min-max)	65 (48 - 79)	63.5 (55 - 73)	0.44
PSA (ng/ml) (min-max)	13.24 (3.64 - 72.39)	11.3 (3.4 - 55)	0.65
PSADT (min-max)	0.29 (0.02 - 1.91)	0.3 (0.06 - 1.38)	0.87

PSA: Prostate Specific Antigen, PSADT: Prostate Specific Antigen Doubling Time

PCa is one of the most common malignancies, and it is essential to know which tumor treatment can be delayed [4,5,11]. In our study, we showed that PCa is a deferrable malignancy. When we assessed the risk groups, there was no difference according to the delay of the RP. We found that the COVID-19 has caused a delay of surgery significantly, but it had no impact on the biochemical relapse.

In the literature, there are controversial results about the risk group's deferability [2,5,14,15]. Some of the studies support that the low risk groups can be deferred but the intermediate and high risk groups may have increased relapse rates so that, they should not be delayed [16]. Just the opposite, some of the authors support that the delay of the low and intermediate risk patients do not have a role in increased relapse rates and high risk patients have increased relapse rates only after 6 to 12 months delay [5,14,15]. We found that the risk groups did not affect the relapse rates significantly in even more than six months of delayed patients. However, our short follow-up time may influence this result.

One of the important outcome variables of our study was whether there was a significant difference between the clinical and surgical stages of the PCa. There are studies related to upstaging in the literature and the patient group included in these studies was selected from patients with low-risk disease or those who were suitable for active follow-up and decided to have radical prostatectomy.[17-19] In these articles, the answer to the question of what affects upstaging was sought. Various and controversial results such as black race, preoperative Psa value, the positive core rate, age, PSAD value, preoperative testosterone level and presence of metabolic syndrome were found.[18,20-23] In our study, patients in all risk groups were evaluated in terms of the effect of time from biopsy to surgery on upstaging. However, no significant difference was found about upstaging in all risk groups between patients diagnosed and treated during the pre-COVID and COVID-19 pandemic period. Upgrading is also important for the follow-up of the PCa patients. It is described as the discordance between biopsy pathology and the surgery specimen pathology in the aspect of Gleason scores. According to some studies, if there is a long time between these procedures, in all risk groups the upgraded pathology ratio is higher but there are also opposite results [2,24]. In one study, upgrade results were calculated %25 in non-deferred patients and %38 in deferred patients [25]. In our study, we did not find a significant difference between these pathologies in neither low nor high risk groups. Although it is stated in the literature that a delay in definitive surgical treatment will have adverse effects on oncological outcomes, the reason why we could not reach such a result in our study was that the number of patients in our study group was small. Although there was a significant difference between the two groups in terms of surgical delay, the expected result could not be achieved because the median 15-day time difference between the groups was not long enough to cause a difference in upstage and upgrade rates. The fact that prostate cancer is a slow-growing tumor has also been effective on this result. However, the patients who couldn't be reached during the pandemic period may have upgraded and upstaged disease so these results can be applied to only mandatory situations like pandemics.

We need to find a solution not to harm PCa patients in this process. In the literature, there are recommendations about ADT or RT applications and lowering the risks of surgery during this period but these are not proven solutions [5]. If we plan to give additional therapies like ADT or RT, we have to lower patient circulation. Hypofractionation of the RT and increasing the dose intervals of the ADT are some possible solutions for this [5]. Although it was found in our study that the increased waiting times for RP, which is a definitive treatment method, did not affect the oncological results of the disease due to the COVID-19 pandemic, especially high-risk patients should be informed about alternative treatments such as ADT and RT, considering the literature.

Our study also has limitations. Primarily, our study was designed retrospectively. Secondly, the small number of patients is one of the limitations. The follow-up time was shorter, especially during the COVID-19 period.

Conclusion

The pandemic period increased the burden of the healthcare system and decreased the quality of health care services and facilities; it reduced the count and energy of health care workers. For this reason, the clinicians must know the treatment of which malignancy can be postponed. This study showed that the delay of surgery does not affect the relapse rates for PCa. So, we can prioritize patients, and the surgeries can be performed not to harm the patients and health care system.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was approved by the Institutional Review Board (IRB) of Ankara City Hospital (approval number: E-2-21-168).

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