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Comparative examination of patients with suspect and diagnosis of prostate cancer before and during the COVID-19 pandemic

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ABSTRACT

Aims: We aimed to determine the clinical stage (CS) alteration in recently diagnosed prostate cancer (PCa) patients with a delay in outpatient diagnostic evalutions and procedures due to COVID-19.

Methods: We reviewed patients that underwent 12 quadrant biopsies in our clinic between January 2018 and April 2022, 86 pre-pandemic (group-1) and 86 pandemic admission. The outcomes of patients with PCa, during pandemic (group-2) were evaluated cross-sectionally. Serum PSA levels, prostate volume, biopsy parameters, Gleason score and groups, CS, presence of high and low volume metastatic disease, clinical risk assessments were compared in both groups.

Results: In group-1, 440 patients were included and PCa was reported in the pathology results of 86 patients (19.54% of biopsies performed). Group-2 encompassed 287 patients in which we identified 86 patients with PCa. We identified PCa in 29.96% of biopsies performed in the group-2. Probablity of encountering a malignant prostate biopsy was found to be significantly higher in the group-1 (p=0.001). The median CS was T2b in group-1, and T2c in group-2 which was found statistically significant (p=0.019). The number of cancer-positive cores was 4 in group-1 and 5 in group-2 (p=0.007). The average values of tumor percentages in cancerous cores were determined as 47% in group-1 and 57% in group-2 (p=0.024). The probability of a patient with a malignant biopsy being in the local stage is higher in group-1 (p=0.043).

Conclusion: Serum PSA levels, CS, number of cancer-positive cores and average tumor percentages in cancerous cores during the pandemic are significantly higher compared to the group-1. Postponing prostate biopsy in suspected PCa; may negatively affect disease-related survival or overall survival.

Keywords: COVID-19, pandemic, prostate cancer

INTRODUCTION

Timespan during the diagnosis and treatment of PCa, does not affect outcome in patients with low-risk disease. However, treatment delay may have a detrimental effect in high-risk patients.[1] The observed decline in these common screening and diagnostic procedures reflects the impact of the COVID-19 pandemic on early detection and points to possible downstream effects on the timing and staging of future cancer diagnoses.[2] The reduction of the number of patients undergoing prostate biopsies and outpatient screening, which were inevetiably postponed during the COVID-19 period, may have caused patients to be subject to higher risk classes and Gleason scores in the future.

A comprehensive review of the literature, relays studies on PSA screening and cases of delayed prostate biopsy with multiparemetric MRI and high PI-RADS score during the COVID-19 pandemic. Accordingly, it has been shown that when men with PI-RADS 5 lesions and no previous biopsy screened earlier, a delay of up to 8 months between imaging and biopsy does not affect subsequent findings.[3]

The aim of this study is to investigate the effect of delay due to COVID-19 pandemic on prostate biopsy outcomes and clinical stages (CS) of the patients who were unable to have an appointment to an outpatient clinic and have routine prostate examination along with screening tests timely.

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METHODS

Ethics

The study was conducted with the permission of the Non-interventional Researches Ethics Committee of Kırıkkale University (Date: 10.02.2022, Decision No: 2022.02.03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The clinical records of 172 male patients between the ages of 49 and 87, who were diagnosed with prostate cancer (PCa) between January 2018 and April 2022, were retrospectively collected from electronic archive of Kırıkkale University Hospital for the study. The decision to perform a prostate biopsy was made based on serum PSA elevation, suspicion of malignancy on digital rectal examination (DRE), and/or suspicious image parameters on magnetic resonance imaging.

Patient Selection Criteria

- Having received PCa diagnosis in between Jan 2018 and Apr 2022.
- Being able to give informed consent for the study and having an adequate mental state to give written consent
- Not having secondary malignancy or any disesase affecting 10 year survival outcome of the patient. (e.g. Terminal stage malignancy, refractory HIV infection, terminal bone marrow diseases…)
- Adherence to follow-up appointments
- Having a minimum of blood work-up of PSA, BUN, cretainine and radiological study of bone scintigrphy, contrast enhanced thoracal and abdominal CT.

Patients; Age, serum total PSA value, DRE findings, prostate volume, clinical PCa stages, metastasis volumes, Gleason score, Gleason grade group, number of positive cores, and average tumor percentage in positive cores were examined and recorded.

Serum PSA values of the patients; It was run on a Roche-Cobas E801 device with the Roche-PSA 801 kit. DRE was performed by two different urologists. All patients underwent prostate biopsy under TRUS guidance and intrarectal local anesthesia containing lidocaine-prilocaine combination. TRUS; It was performed using the Voluson P8 ultrasonography device and standard rectal probe. Before the procedure, patients were given standard ciprofloxacin prophylaxis and an enema was administered.

Patients; Considering that COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, it was divided into two: before and after this date. Group-1; Patients who underwent prostate biopsy between 01.2018 and 01.2020 were recorded as the pre-pandemic group. Group-2; During the pandemic period, patients who underwent prostate biopsy between 03.2021-04.2022 were determined as a group. During the approximately 14-month period, no prostate biopsy was performed in our clinic due to the postponement of elective procedures and disruption of outpatient services.

Statistical Analysis

The obtained data were statistically analyzed with the Statistical Package for Social Sciences (SPSS) 20.0 program. Normality evaluation of the parameters was done with the Shapiro-Wilk test. Non-parametric evaluations between independent groups were made with the Mann Whitney-U test, results are presented as median and interquartile range. Normally distributed parameters were evaluated with t test. Numerical variables are summarized by mean, standard deviation, min, max. p values less than 0.05 were considered statistically significant. Categorical variables were evaluated with the Chi-square test.

RESULTS

Prostate biopsy was performed on 440 patients in the pre-pandemic group, and the pathology result of 86 patients was reported as prostate adenocarcinoma. 19.54% of the biopsies performed before the pandemic were diagnosed with prostate adenocarcinoma. During the pandemic period, 287 patients underwent prostate biopsy to reach a diagnosis of prostate adenocarcinoma, 86 of whom were in the group. 29.96% of the biopsies were reported as prostate adenocarcinoma. The rate of encountering malignant prostate biopsy results was found to be statistically significantly higher in the pandemic group ($p<0.01$). Clinicopatolocigal features of patiens were given in Table 1 hollistically.

Table 1. Descriptive characteristics of patients

Parameters	n (%)
Patient group	
Before pandemic	86 (50.0)
During the pandemic	86 (50.0)
Findings of digital rectal examination	
Normal	64 (37.2)
Abnormal	108 (62.8)
T stage	
T1c	339 (19.2)
T2a	24 (14.0)
T2b	35 (20.3)
T2c	33 (19.2)
T3a	21 (12.2)
T3b	24 (14.0)
T4a	2 (1.2)
Gleason score	
6	57 (33.1)
7	40 (23.3)
8	44 (25.6)
9	29 (16.9)
10	2 (1.2)
Gleason grade group	
1	57 (33.1)
2	21 (12.2)
3	18 (10.5)
4	46 (26.7)
5	30 (17.4)
	Mean±SD
Age	66.85±7.28
Serum total PSA	20.53±22.59
Prostate volume	47.90±10.95
Number of cancer positive cores	4.68±3.11
Tumor pertencage of cancer positive cores	51.60±28.49

SD: Standard deviation

Table 2 thoughroughly covers the numerical patient characteristics; whereas Table 3 covers categorical variables in both groups. The median values of serum PSA levels of "before-pandemic" and "during-pandemic" groups were determined as 11.00-12.55, respectively. Serum PSA levels

were statistically significantly higher during the pandemic period (p=0.046). The mean prostate volume between the groups were determined as 48.14+11.03 (min:26, max:96) and 48.00+9.88 (min:28, max:69) (p=0.930).

Table 2. Distribution of data before and during the pandemic according to some characteristics

Parameters	Before pandemic Mean±SD (min-max)	During the pandemic Mean±SD (min-max)	Test
Age	67.35±7.57 (49-87)	66.35±6.98 (49-87)	t=0.900 p=0.369
Prostate volume	48.14±11.03 (26-96)	48.00±9.88 (28-69)	t=0.087 p=0.930
	Median	**Median**	
Serum total PSA (IQR)	11.00 (13.4-20.6)	12.55 (18.27-29.8)	MWU=3045.500 p=0.046
Number of cancer positive cores, (IQR)	3.00 (3.49-4.74)	4.50 (4.55-5.93)	MWU=2830.500 p=0.007
Tumor pertencage of cancer positive cores (IQR)	50.00 (40.34-50.91)	60.00 (50.80-62.34)	MWU=2963.500 p=0.024

SD: Standard deviation, Min: Minimum, Max: Maximum, IQR: Interquartile range

Table 3. Chi-square test results for nonparametric variables

Clinicopathological parameters		Before pandemic n (%)	During the pandemic n (%)	p value
T stage	T1c	24 (27.9)	9 (10.5)	p=0.015
	T2a	13 (15.1)	11 (12.8)	
	T2b	15 (17.4)	20 (23.3)	
	T2c	15 (17.4)	18 (20.9)	
	T3a	5 (5.8)	16 (18.6)	
	T3b	12 (14)	12 (14)	
	T4a	2 (2.3)	0	
Gleason score	6	35 (40.7)	22 (25.6)	p=0.029
	7	13 (15.1)	27 (31.4)	
	8	24 (27.9)	20 (23.3)	
	9	14 (16.3)	15 (17.4)	
	10	0	2 (2.3)	
Gleason grade group	1	35 (40.7)	22 (25.6)	p=0.036
	2	8 (9.3)	13 (15.1)	
	3	4 (4.7)	14 (16.3)	
	4	25 (29.1)	21 (24.4)	
	5	14 (16.3)	16 (18.6)	

Data are expressed as frequencies with percentages in parentheses (n (%))

Intergroup diffences of DRE of the patients yielded to be statistically insignificant(p>0.05). While the T2b stage had the highest frequency in group-1, T2c stage occured to have the highest frequency in group-2 (p=0.015).

Gleason score and Gleason grade group were both significantly higher in group-2 (p<0.05).

The median of tumor percentages in cancer-positive cores were determined as 50 in group-1 and 60 in group-2. The difference between the tumor percentages in cancer-positive cores between the two groups was found to be statistically significant (p=0.024).

While 47.67% (41 patients) of prostate adenocarcinoma patients in the group before the pandemic were in the clinical local stage, 32.55% (28 patients) of the prostate adenocarcinomas in the group during the pandemic were detected in the clinical local stage. The probability of the patient undergoing malignant biopsy being in the clinical local stage was found to be statistically significantly higher in the pre-pandemic group (p=0.043).

Before the pandemic, 17.44% (15 patients) of the group were detected in the clinically locally advanced stage and 34.88% (30 patients) in the metastatic stage. These rates were 19.76% (17 patients) and 47.67% (41 patients), respectively, in the group during the pandemic. The probability of a patient with malignant biopsy being in the clinically locally advanced or metastatic stage is similar in both groups (p>0.05).

When metastatic patients in both groups were divided into low and high volume using Latitude criteria; In the pre-pandemic group, 56.66% (17 patients) of metastatic patients were low volume and 43.33% (13 patients) were high volume. In the group during the pandemic, 46.34% (19 patients) of metastatic patients had low volume metastatic disease and 53.65% (22 patients) had high volume metastatic disease. No statistically significant difference was detected in terms of metastatic disease volume (p>0.05). However, in the pre-pandemic group; The probability of patients in the metastatic stage to have low volume is approximately 1.5 times higher than the group during the pandemic (odds ratio=1.514).

Prostate biopsy was recommended and planned for 25 patients because prostate adenocarcinoma was suspected before the pandemic, but prostate biopsy was performed on these patients with a delay during the pandemic period. 9 of 25 prostate biopsies were reported as prostate adenocarcinoma. In other words, the malignancy detection rate in postponed prostate biopsies was 36%, and it was found to be statistically significantly higher than the group that underwent prostate biopsy before the pandemic (p=0.047). The probability of encountering malignancy was statistically similar between patients whose prostate biopsy was planned and delayed and other patients who underwent prostate biopsy during the pandemic (p>0.05).

Although biopsy was planned, it was performed late during the pandemic period and 9 patients were diagnosed with prostate adenocarcinoma; 3 (33.33%) were detected in the clinical local stage, 2 (22.22%) in the locally advanced stage and 4 (44.44%) in the metastatic stage. All 4 patients in the metastatic stage were in the high-volume metastatic stage. Possibility of encountering local, locally advanced and metastatic stage disease; It was statistically similar for patients who had a planned but delayed biopsy before and during the pandemic (p>0.05). However, the probability of having a malignant biopsy and encountering high-volume metastatic disease was found to be statistically significantly higher in the group where the biopsy was planned before the pandemic and performed with a delay, compared to the pre-pandemic group (p=0.029), (**Figure**).

Radical prostatectomy and extended lymph node dissection operations were performed on patients in the clinical local stage in both groups before and during the pandemic. In the pre-pandemic group, 3 (7.17%) of the 41 patients evaluated at the clinical local stage were evaluated at the pathological locally advanced stage. Of the 28 patients evaluated in clinical local stage during the pandemic, 5 (17.85%) were reported as pathological locally advanced stage and no

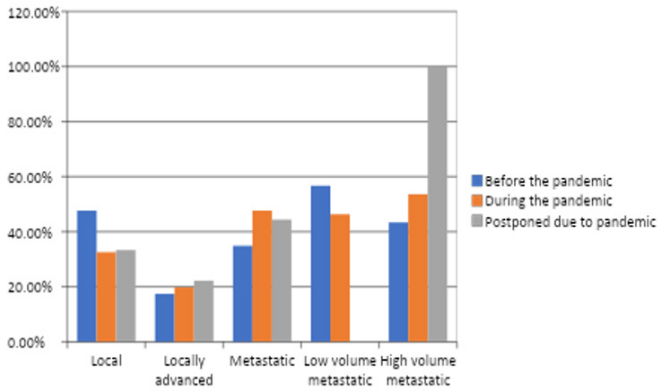

Figure. Stage differences between groups before treatment

statistically significant difference was found between the two groups (p>0.05). However, the need for additional treatment for a patient in the clinical local stage during the pandemic group is approximately 2.5 times higher due to being in a pathologically locally advanced stage (odds ratio=2.489).

According to this study, patients diagnosed with PCa during the pandemic; Serum PSA levels, clinical T stage, gleason score, gleason grade group, number of tumor-positive cores, and percentages of tumors in tumor-positive cores were found to be significantly higher than the pre-pandemic period.

DISCUSSION

The COVID-19 pandemic has presented a unique challenge for cancer patients for several reasons. Patients with cancer may be more likely to contract COVID-19 and have serious adverse outcomes, including intensive care admissions, ventilator requirements, and death.[4-7] For this reason, there is a group who cannot have a prostate biopsy and do not know the diagnosis of cancer and may be at greater risk.

Due to substantial delay caused by the lack of addmission during pandemic patients were subject to increased risk of biochemical recurrence which directly effected the patient's morbidity, mortality and quality of life.[8] Furthermore, theese delays may have caused patients to lose the chance of definitive treatment.[9] The incidence of bone metastasis may have been increased in patients with metastatic disease and delayed diagnosis.[10]

According to the results of our study, the probability of encountering a malignant biopsy result in the group during the pandemic period was found to be higher than in the group in which prostate biopsy was performed before the pandemic. This delay may also be due to an increase in the proportion of symptomatic patients with PCa. That is, compared with opportunistic screening, patients diagnosed with PCa post-pandemic are more likely to be symptomatic than the pre-pandemic group.

The time required to obtain 86 malignant biopsy results was shorter in the pandemic group. This may be attributed to the fact that patients who postponed their examinations and wanted to apply to our polyclinic without further delay as normalization returns.

In a study, 267 patients with localized PCa who were not receiving treatment were followed for approximately 8.5 years and it was found that the prognosis of patients with high initial serum PSA values and PSA rate was worse.[11]

In our study, serum PSA median values of the patients who underwent prostate biopsy during the pandemic period were found to have significantly higher levels of PSA compared to the pre-pandemic group (p<0.05). This may predict that the prognosis of PCa patients detected during the pandemic period may be worse.

In a study published in 2004; 16.321 patients diagnosed with PCa between 1989-1990 and 2001-2002 were compared. It was found that the incidence of T1 tumors increased from 16.7% to 48.5%, and the incidence of T3-4 tumors decreased from 11.8% to 3.5%, respectively.[12] This may be attributable to changes in practice patterns regarding screening and pathological grading.

In this study, the distrubution of the clinical T stages of patients are found to be statistically significantly higher in patients evaluated during the pandemic compared to the group evaluated before the pandemic (p<0.05). This situation may be related to the possible delay in the evaluation and diagnosis of patients due to the COVID-19 pandemic. This difference between patients may eliminate the chance of definitive treatment for patients or may lead to the need forcomplementary treatments in addition to definitive treatment. It may also increase the likelihood of PCa recurrence and positive surgical margins.

According to the D'Amico Risk classification, used to predict the recurrence of non-metastatic PCa; no statistically significant difference was detected between the risk groups of the patients. This may indicate that especially locally and locally advanced stage patients have similar recurrence risks between the groups before and during the pandemic and are not affected by the delay due to the negativities of the pandemic.

Statistically significant difference was detected between the two groups in terms of Gleason score and Gleason ratings of patients diagnosed with PCa before and during the pandemic(p<005). In accordance with this finding studies, high volume cross-sectional studies found that some cancers detected as low and medium risk in prostate needle biopsy actually have higher Gleason scores.[13]

In our study, the number of cancer-positive cores and the percentage of tumors in cancer-positive cores, which may have a high prediction of this risk increase, were found to be statistically significant in patients who underwent prostate biopsy during the pandemic compared to the group before the pandemic (p<0.05). Therefore, due to the pandemic-related measures, the healthcare was stalled and halted throughout the state which utterly caused the postponement of prostate biopsies. In fact, it may have caused the disease to have a higher probability of recurrence and poor prognosis.

Of the 41 patients evaluated in the clinical local stage in the pre-pandemic group, 3 (7.17%) were detected in the locally advanced stage. Of the 28 patients evaluated in the clinical local stage during the pandemic, 5 (17.85%) were reported to have locally advanced stage. A patient in the clinical local stage in the pandemic group is actually in a pathologically locally advanced stage, so the need for additional treatment is approximately 2.5 times higher.

Patients with locally advanced PCa have significantly higher disease-specific mortality rates compared to local stage disease. In five and ten year follow-ups, respectively; Clinical

progression was reported as 22% and 75%, local progression as 22% and 84%, and distant metastasis development as 27% and 56%.[14] In our study, while 47.67% (41 patients) of prostate adenocarcinoma patients in the pre-pandemic group were in the clinical local stage, 32.55% (28 patients) of the prostate adenocarcinomas in the group during the pandemic were detected in the clinical local stage. The probability of the patient with malignant biopsy being in the clinical local stage was found to be statistically significantly higher in the pre-pandemic group. Therefore, it can be expected that the disease-specific mortality, clinical and local progression probabilities of patients diagnosed with PCa in the pre-pandemic group would be lower compared to the period during the pandemic.

The likelihood of a patient with a malignant biopsy being in the clinically locally advanced or metastatic stage is similar in both groups. However, the pandemic-group patients in the metastatic stage are approximately 1.5 times more likely to have high volume than the pre-pandemic group. The prognosis of those with high volume metastatic disease is worse than those with low volume and its treatment is more refractory and costly.[15,16] Some patients with low-volume metastatic PCa may have remained untreated due to the delay and the pandemic and may have been detected as high-volume.

Prostate biopsy was recommended and planned for 25 patients because prostate adenocarcinoma was suspected before the pandemic, but prostate biopsy was performed on these patients with a delay during the pandemic period. 9 of 25 prostate biopsies were reported as prostate adenocarcinoma. Hence, the malignancy detection rate in postponed prostate biopsies was 36% and was found to be statistically significantly higher than the group that had a prostate biopsy before the pandemic. The decision to postpone prostate biopsies during the pandemic period caused us to encounter higher malignancy rates.

There had been considerable lag in the biopsy schedule during the pandemic period and 9 patients were diagnosed with prostate adenocarcinoma; 3 (33.33%) were detected in the clinical local stage, 2 (22.22%) in the locally advanced stage and 4 (44.44%) in the metastatic stage. All 4 patients in the metastatic stage were in the high-volume metastatic stage. Possibility of encountering local, locally advanced and metastatic stage disease was statistically similar for patients who had a delayed biopsy before and during the pandemic. However, the probability of having a malignant biopsy and encountering high-volume metastatic disease was found to be statistically significantly higher in the group in which the biopsy was planned before the pandemic and performed with a delay, compared to the pre-pandemic group.

Limitations

Our study had some limitations. The biggest limitation was that patient outcomes especially those with delayed diagnosis such as long-term morbidity, mortality, and disease-related survival, were unknown. Due to relatively low budget of the healtcare facility where the study was conducted, patients were not evaluated with state-of-the-art radiological studies as Ga-68 PSMA-PET or multiparametric MRI. It was also a relatively small sample size; Therefore, the design of large-scale clinical studies may be encouraged so that the above results can be confirmed with increased statistical power.

CONCLUSION

According to the findings of this cross-sectional study, serum PSA levels, CS, Gleason score, Gleason grade group, number of cancer-positive cores and tumor percentages in cancerous cores were found to be significantly higher in prostate biopsies performed approximately 14 months late due to pandemic fear and postponements, compared to the pre-pandemic period. The probability of a patient with a malignant biopsy being in the clinical local stage was found to be higher in the pre-pandemic period compared to the pandemic period. The probability of the biopsy results being malignant and the probability of encountering high-volume metastatic PCa in patients with suspected malignancy but whose prostate biopsy was postponed due to the pandemic was found to be significantly higher than the group in which prostate biopsy was performed before the pandemic.

From a historical point of view, infectious diseases that can cause intercontinental disease may occur in the future as well. In such cases, postponing prostate biopsy in patients with suspected PCa may negatively effect physical and mental status, disease-related survival or overall survival.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Non-interventional Researches Ethics Committee of Kırıkkale University (Date: 10.02.2022, Decision No: 2022.02.03).

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.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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