Original Article

How has the COVID-19 pandemic influenced prostate cancer?—a tertiary single-centre analysis of oncological results, diagnosis and treatment times

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Background: The coronavirus disease 2019 (COVID-19) pandemic has affected care for diseases like cancer. The aim was to evaluate the impact of COVID-19 on waiting times for diagnosis and treatment of prostate cancer (PC), as well as the possible effect on the treatment results in PC patients undergoing radical prostatectomy.

Methods: We compared the results of 497 patients who underwent biopsy prior to the COVID-19 pandemic (1 January–31 December 2019) with those of 290 patients biopsied during the COVID-19 pandemic (1 January–31 December 2020). Demographic data, tumour characteristics, type of treatment and diagnosis times were comparable. Prostate specific antigen (PSA) levels were recorded at consultation prior to biopsy and after treatment. Mann-Whitney and chi-square tests were used to compare continuous variables and percentages, respectively.

Results: In 2020, there were fewer urology consultations (35,160 *vs.* 40,225 in 2019). The median PSA in 2020 was significantly higher (14.3 *vs.* 9.9 ng/dL in 2019). In 2019, 53.1% (N=264) of the biopsies were positive for cancer *vs.* 47.2% (N=137) in 2020 (P=0.104). In 2020, more patients presented with metastatic disease (7.3% *vs.* 1.9%, P=0.009). Also, in 2020 there was a longer waiting time for prostate biopsy (42.1 *vs.* 35.3 days in 2019, P=0.019). A total of 132 patients underwent laparoscopic radical prostatectomy (LARP). The median time until surgery was similar in both years (71.9 *vs.* 58.29 days). During 2020, a higher percentage of patients had ISUP grade 4 in the surgical specimen (34.3% *vs.* 17.5%, P=0.07). Furthermore, a higher percentage of aggressive (pT3) tumours were diagnosed (37.2% *vs.* 27.2%, P=0.08), and the percentage of patients with involvement of surgical margins was also higher (48.6% *vs.* 29.3%, P=0.027). There were no differences between the groups in terms of biochemical recurrence or persistent PSA at one year (P=0.711).

Conclusions: Delayed biopsy during the COVID-19 period did not appear to adversely impact biopsy results. Patients biopsied in 2020 had higher PSA, possibly due to proper triaging. A higher rate of adverse pathology outcomes was observed in patients undergoing radical prostatectomy during the pandemic, probably due to understaging of the biopsy. This study serves to raise awareness of the risk of deterioration of care of PC patients due to possible underdiagnosis.

Keywords: Prostate cancer (PC); coronavirus disease 2019 (COVID-19); laparoscopic radical prostatectomy (LARP); diagnosis; oncological outcomes

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Introduction

The global pandemic of the novel beta coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is generating severe effects on individuals and health care systems (1). The heavy demand for resources, exacerbated by limited excess health system capacity, means that health care systems have quickly become overwhelmed (2).

To provide sufficient intensive care unit capacity, medical specializations have had to develop new routines and risk-strategy protocols. The impact has also been felt by the urology community, and several organisations have developed specific information hubs and resource centres on how to manage urology and the care of patients with urological neoplasms during the pandemic (3,4).

Prostate cancer (PC) is the commonest non-cutaneous male malignancy in the Western world. According to estimates, there were 1,276,000 new cases of PC and 359,000 deaths worldwide in 2018 (5). PC is a heterogeneous neoplasm that encompasses both non-clinically significant or slowly progressive disease and high-risk, clinically significant and life-threatening cancers.

In the context of the current pandemic, it is relevant that PC is more common in men at risk of adverse outcomes from coronavirus disease 2019 (COVID-19). For example, the incidence of PC increases with age and in black men (6) and >50% of affected men have one or more comorbidities (7).

Studies reported in the literature have yielded conflicting conclusions on whether delayed diagnosis and treatment of PC worsens the long-term prognosis (4), with some studies affirming that delays in diagnosis and performance of radical prostatectomy have no impact on oncological results. Even if this is the case, patients with high-risk PC could potentially be at greater risk of biochemical recurrence or distant spread due to delayed surgery (8,9).

The main objective of this study was to evaluate the impact of COVID-19 on waiting times for the diagnosis (prostate biopsy) and treatment [laparoscopic radical prostatectomy (LARP), external beam radiotherapy (EBRT), active surveillance and hormonal treatment] of PC in a hospital with a high volume of patients during the COVID-19 phase and to compare the results with those during a period of identical length prior to the pandemic. As secondary objectives we analysed the positive biopsies for PC in each group and evaluated the pathological findings in patients undergoing radical prostatectomy. We also assessed the results after the application of radiotherapy. Finally, the presence of biochemical recurrence and persistent prostate specific antigen (PSA) at one year of follow-up was analysed. We present the following article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-360/rc).

Methods

This study was conducted in accordance with the Declaration of Helsinki (revised in 2013). The study was approved by the institutional ethics board of Ramón y Cajal Hospital of Madrid (No. 18-286), which also waived the written informed consent for this retrospective study. After approval of the study by the institutional review board, we performed a retrospective analysis which included all patients who had undergone a prostate biopsy for suspected PC at our institution over the course of one year before (1 January–31 December 2019) and one year during (1 January 2020–31 December 2020) the COVID-19 pandemic. The aforementioned periods were stipulated because they facilitated data collection and analysis.

Mean waiting times between diagnosis and treatment were compared. The anatomo-pathological data of the prostate biopsy and the surgical specimen were evaluated, including the ISUP grade (International Society of Urological Pathology), tumour stage and lymph node invasion. PSA levels were recorded at consultation prior to biopsy and after treatment.

The baseline variables collected in order to calculate waiting times were: the date of the initial consultation when the prostate biopsy was requested, the date of prostate biopsy and the date of the post-biopsy consultation at which the biopsy results were communicated and a treatment decision was made. In addition, data relating to the pathological anatomy of the surgical specimen after prostatectomy were collected. In cases in which radical surgery was performed, the date of the prostatectomy was recorded. If the patient was referred to radiation oncology, the dates of the post-biopsy consultation and the start of radiotherapy were recorded. If active surveillance was indicated, the dates of magnetic resonance imaging and confirmatory biopsy were recorded. With these collected dates, the waiting times to be compared were calculated: time to biopsy, time between biopsy and results and time between results and applied treatment (surgery, EBRT etc.).

Oncological outcomes were recorded in terms of PSA after treatment. Biochemical recurrence was defined as a confirmed serum PSA level of >0.2 ng/dL after surgery or a

Table 1 Demographic data

Demographic variables	Year 2019, N=497	COVID-19, year 2020, N=290	P
PSA (ng/dL) at biopsy, (median, IQR)	9.9 (3.7–28.9)	14.3 (4.9–52.0)	0.011
Biopsy waiting time (days), (median, IQR)	35.3 (15.1–55.2)	42.1 (12.2–72.3)	0.019
Time from biopsy to pathological report (days), (median, IQR)	6.1 (2.3–10.5)	6.3 (2.2–10.4)	0.448
Time between biopsy and results (days), (median, IQR)	38.1 (13.1–63.2)	35.6 (10.8–59.5)	0.096
Results prostate biopsy, n (%)			0.104
Prostate cancer	264 (53.1%)	137 (47.2%)	
ASAP/HG-PIN	23 (4.6%)	9 (3.1%)	
Negative biopsies	210 (42.3%)	144 (49.7%)	

COVID-19, coronavirus disease 2019; PSA, prostate specific antigen; IQR, interquartile range; ASAP, atypical small acinar proliferation; HG-PIN, high-grade prostate intraepithelial neoplasia.

PSA level 2 ng/dL higher than the nadir value after EBRT. Persistent PSA was defined as PSA >0.1 ng/dL.

Statistical analysis

Mann-Whitney and chi-square tests were used to compare continuous variables and percentages, respectively. Descriptive statistics of categorical variables focussed on frequencies and proportions. Medians and interquartile ranges (IQR) were reported for continuously coded variables. Statistical analysis was performed with IBM SPSS Statistics v. 25 software (Chicago, IL, USA). All tests were two sided with the level of significance set at P<0.05.

Results

We compared the results of 497 patients suspected of having PC who underwent a biopsy prior to the COVID-19 pandemic with those of 290 patients biopsied during the COVID-19 phase.

In 2020, there were fewer urology consultations (40,225 in 2019 *vs.* 35,160 in 2020), with a lower number of prostate biopsies conducted (497 *vs.* 290).

The median PSA in 2020 was significantly higher (14.3 *vs.* 9.9 ng/dL). In the pre-pandemic year, 53.1% of biopsies were positive (N=264) for PC *vs.* 47.2% (N=137) in the year 2020 (P=0.104). There were also no significant differences in the atypical small acinar proliferation (ASAP) and high-grade prostate intraepithelial neoplasia (HG-PIN) rates (*Table 1*).

Regarding delay in diagnosis, biopsy waiting time was significantly longer in 2020 (35.3 days in 2019 *vs.* 42.1 days in 2020; P=0.019). However, there was no statistically significant difference between the year groups with respect to the time interval between biopsy and results (*Table 1*).

Regarding the type of tumour identified in the biopsy, twice as many patients were diagnosed with metastases in the pandemic year compared with 2019 (10 *vs.* 5, P=0.009). However, there were no differences in ISUP grades (P=0.717) (*Table 2*). Of the patients with a positive biopsy in 2020, 8 (5.8%) were lost compared to none in the previous year (P<0.01). More than twice as many chemotherapy treatments were applied in 2020 as in 2019 (7.3% *vs.* 1.9%; P<0.01). With respect to the rest of the treatments carried out, there were no differences between the groups (*Table 2*).

A total of 132 patients underwent LARP. There were no differences between the ISUP groups with regard to the prostate biopsy or in the PSA value (*Table 3*). Time interval between biopsy and surgery was similar in both years (71.9 *vs.* 58.29 days, P=0.272).

However, a significant difference was observed with respect to ISUP grade in the prostatectomy specimen: 34.3% of patients had an ISUP grade 4 in 2020 compared with just 17.5% in 2019. Among patients with an ISUP grade 4 or 5 in the prostatectomy specimen, the upgrading rate compared with the ISUP grade in the biopsy specimen was 21.8% in 2020 compared with 14.2% in 2019 (when 4.5% of patients were upgraded to ISUP grade 4 and 9.8% to ISUP grade 5). Regarding ISUP grade 3, there was no upgrading in 2019, compared with an upgrading rate of 23.9% in 2020 (*Table 3*).

Along similar lines, in 2020 a higher percentage of pT3 tumours were diagnosed in the prostatectomy specimen, with 28.6% of patients having stage pT3a and 8.6% stage

Table 2 Prostate cancer patients, N=401

Variables	Year 2019, N=264	COVID-19, year 2020, N=137	P
PSA (ng/dL) at biopsy (median, IQR)	12.6 (4.2–25.0)	16.15 (4.8–19.9)	0.049
ISUP grade, n (%)			0.717
1	50 (18.9%)	30 (22.6%)	
2	57 (21.6%)	29 (21.2%)	
3	67 (25.4%)	28 (20.4%)	
4	59 (22.3%)	35 (24.8%)	
5	31 (11.7%)	15 (10.9%)	
Metastatic PC at diagnosis, n (%)			0.009
Yes	5 (1.9%)	10 (7.3%)	
No	259 (98.1%)	127 (92.7%)	
Type of metastases, n (%)			0.714
M1a	2 (40.0%)	5 (50.0%)	
M1b	3 (60.0%)	5 (50.0%)	
Lost to follow-up, n (%)	0	8 (5.8%)	<0.01
Treatment, n (%)			<0.01
Laparoscopic assisted radical prostatectomy	92 (34.5%)	40 (29.2%)	
External beam radiotherapy	115 (43.6%)	48 (35.0%)	
Chemotherapy	5 (1.9%)	10 (7.3%)	
Hormonotherapy	20 (7.6%)	10 (7.3%)	
Active surveillance	26 (9.8%)	17 (12.4%)	
Watchful waiting	6 (2.3%)	4 (2.9%)	

COVID-19, coronavirus disease 2019; PSA, prostate specific antigen; IQR, interquartile range; ISUP, International Society of Urological Pathology; PC, prostate cancer.

pT3b compared with 19.6% and 7.6%, respectively in 2019 (*Table 3*). There was no difference in the rate of lymphadenectomy due to lymph node involvement, but significantly more patients had involvement of surgical margins in 2020 (48.6% *vs.* 29.3%, P=0.027).

The vast majority of patients presented a PSA level of <0.2 ng/dL, with only three (3.3%) showing detectable PSA after surgery in 2019 *vs.* 1 (2.5%) in 2020 (P=0.711). Only one patient experienced biochemical recurrence in each year.

Analysis of patients who received EBRT revealed no differences between the year groups with regard to either pretreatment PSA or ISUP grade (P=0.646 and P=0.57, respectively). While no difference was observed in the interval between biopsy and surgery, the waiting time for prostate biopsy was significantly longer in 2020 (48 *vs.* 33.6 days, P=0.044). However, time between biopsy and radiotherapy was similar in both groups (Table S1).

As shown in Table S2, patients who received EBRT had a significantly higher PSA prior to treatment, as well as prostate tumours with a worse prognosis at biopsy compared with men who underwent prostatectomy.

Discussion

It is well known that the COVID-19 pandemic has represented a real challenge for health organisations around the world. Due to the suspension of most elective surgeries, it was necessary to develop protocols to establish valid waiting times in accordance with the prognosis of urological

Table 3 Patients undergoing laparoscopic radical prostatectomy, N=132

Variables	Year 2019, N=92	COVID-19, year 2020, N=40	P
Pathological anatomy of the biopsy (ISUP), n (%)			0.734
4	12 (13.0%)	5 (12.5%)	
3	34 (35.9%)	11 (27.5%)	
2	32 (33.7%)	15 (37.5%)	
1	14 (16.3%)	9 (22.5%)	
Pathological anatomy of surgical specimen (ISUP), n (%)			0.070
5	9 (9.8%)	0	
4	16 (17.5%)	14 (34.3%)	
3	33 (35.9%)	19 (51.4%)	
2	30 (32.6%)	5 (11.4%)	
1	4 (4.3%)	2 (2.9%)	
pT stage, n (%)			0.089
T2a	21 (22.8%)	5 (11.4%)	
T2b	3 (3.3%)	6 (14.3%)	
T2c	43 (46.7%)	14 (37.1%)	
T3a	18 (19.6%)	11 (28.6%)	
T3b	7 (7.6%)	4 (8.6%)	
Positive nodes, n (%)	6 (6.5%)	2 (5.7%)	0.439
Surgical margin, n (%)			0.027
Positive	27 (29.3%)	17 (48.6%)	
Negative	65 (70.7%)	23 (51.4%)	
Preoperative PSA (median, IQR)	6.7 (2.5–10.9)	7.4 (4.8–10.1)	0.140
Biopsy waiting time(days) (median, IQR)	38.8 (8.8–68.8)	31.89 (15.1–48.5)	0.658
Time between biopsy and surgery (days) (median, IQR)	71.9 (13.2–129.9)	58.29 (17.29–99.2)	0.272
Oncological follow-up, n (%)			0.711
Persistent PSA	3 (3.3%)	1 (2.5%)	
Biochemical recurrence	1 (1.1%)	1 (2.5%)	
PSA <0.2 ng/dL	88 (95.7%)	38 (95.0%)	

COVID-19, coronavirus disease 2019; PSA, prostate specific antigen; IQR, interquartile range; ISUP, International Society of Urological Pathology.

tumours (10,11).

Multiple organisations made general recommendations for the resumption of surgical activity. The European Association of Urology (EAU) established the Rapid Response Group (GORRG; Guidelines Office Rapid Reaction Recommendations) to provide guidelines for management of the health situation during the COVID-19 pandemic. The American College of Surgeons also provided guidelines on the resumption of surgical activity (12,13). Ficarra *et al.* divided urological procedures into four groups according to the risk of postponement of surgeries (10).

In urology departments, services were significantly

reduced in preparation for a possible surge in COVID-19-related admissions and also to reduce contacts and the likelihood of disease transmission. This could be the reason why the number of urology consultations decreased and fewer biopsies were indicated in 2020.

Once activity could be resumed after the initial phase of COVID-19, all uro-oncological pathology was prioritised (14), with progressive resumption of PC surgeries as well as prostate biopsies. Nossiter *et al.* reported that during the COVID-19 period the number of men diagnosed with PC decreased by one-third and more advanced disease was more frequently diagnosed, with the recommendation that urgent concerted action be taken to address the COVID-19-related deficits in PC services in order to mitigate their impact on long-term outcomes (15). Similarly, Deukeren *et al.* observed a marked decline in PC diagnoses during the first COVID-19 wave, with changes in treatments that were temporary (16). In their view, although it was to be expected that the pandemic would significantly impact PC care, the magnitude of this impact is still unknown.

In this study, we describe our experience in managing PC patients during the COVID-19 pandemic. Several published studies have reported a clear delay in the diagnosis and treatment of PC during the COVID-19 pandemic (17,18). According to our data, there was a delay in the biopsy waiting times in our hospital in 2020, with no differences in the time intervals to subsequent consultation and start of treatment. Time between biopsy and treatment was similar in both years. Following the EAU recommendations, the surgical treatment of patients with high-risk PC was prioritised.

Patients who underwent a biopsy in 2020 had a higher PSA and more often had metastatic PC. Our hypothesis is that this could be because the PSA level considered to warrant biopsy was higher than usual during the pandemic in an attempt to avoid overdiagnosis of low-risk PC.

Although there were no differences in preoperative PSA and ISUP grades, we found that patients who underwent radical prostatectomy in 2020 had a worse tumour stage with more upgrading and a higher percentage of positive margins, although no difference in the rate of biochemical recurrence was observed between the groups at one year of follow-up. We think that undegrading at biopsy appears to be the most likely cause of these findings. It has been reported that the risk of transmission of COVID-19 may increase during biopsy (19). It is therefore possible that biopsy quality was affected by social distancing measures though we lack data on factors that may have influenced the quality of biopsy, such as the number of cores or the total core length affected. Our results are in line with those published by Nyk *et al.*, who concluded that the ongoing course of the COVID-19 pandemic in Poland was associated with increasing rates of adverse pathology findings in patients treated with radical prostatectomy. They suggested that epidemic-related issues may have been responsible for an increased risk of incorrect preoperative risk assessment (20).

Our results are also in agreement with other studies, such as that carried out by Johns Hopkins, which analysed 2,303 patients who underwent surgery with a delay of up to 6 months without worse oncological results (10). Along similar lines, Diamand *et al.* concluded that a delay of several months due to the COVID-19 pandemic did not appear to have adversely impacted oncological results for intermediate- and high-risk PC (21). The main differences found in the literature relate to patients with high-risk PC. A pre-COVID-19 pandemic review by van den Bergh *et al.* evaluated 17 retrospective studies and concluded that surgical delay results in worse oncological outcomes in patients with high-risk PC (22).

Similar to the findings of Moschovas *et al.* (23), our data suggest that a priori, a delay in the diagnosis and subsequent treatment does not imply a worse oncological evolution.

We are aware of certain limitations of this study: it was a retrospective, observational and single-centre study, and data on the quality of the biopsy were lacking. However, the sample of patients seems adequate to obtain conclusive results.

Compared with other urological neoplasms, the management of PC appears less capable of deferral. Even in times such as the COVID-19 pandemic, care for clinically significant and high-risk cases of PC should proceed, with correct selection of cases and procedures.

One must hope that the COVID-19 pandemic will be a short-term situation, and it is to be expected that the way in which we treat PC over the coming months will change and will influence medium-term results.

Conclusions

We observed a decline in the number of prostate biopsies performed in 2020. Delay in biopsy delay during the COVID-19 pandemic did not appear to adversely impact biopsy results. Patients biopsied in 2020 had a higher PSA, possibly due to proper triaging. However, we observed a higher rate of adverse pathology outcomes in patients

undergoing radical prostatectomy during the pandemic. A probable cause is understaging in the biopsy, but more research is needed to determine the reasons. This study serves to raise awareness of the risk of deterioration of care of PC patients during the COVID-19 pandemic due to possible underdiagnosis, though the magnitude of pandemic's impact on PC care is still unknown.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-360/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-22-360/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-360/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013). The study was approved by the institutional ethics board of Ramón y Cajal Hospital of Madrid (No. 18-286), which also waived the written informed consent for this retrospective study.

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