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Has the COVID-19 outbreak changed the way we are treating prostate cancer? An EAU – YAU Prostate Cancer Working Group multi-institutional study

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Introduction The COVID-19 outbreak has become the dominant issue throughout the world whilst the governments, nations and health services are trying to deal with its impact. The aim of our study is to assess the impact of COVID-19 on patients treated with radical prostatectomy (RP) for prostate cancer (PCa) at European referral centers in terms of surgical volume (SV), waiting list meant as time from biopsy to surgery (WL) and risk of adverse pathologic findings at RP due to the selection of men with more adverse disease characteristics at final pathology.

Material and methods Consecutive patients with a diagnosis of histologically proven PCa treated with RP between March 2020 (WHO declaration of pandemic) and December 2020 were identified. Patients with metastatic disease not eligible to local treatment and recurrent prostate cancer after RP or RT were excluded. Patients treated at the same institutions between March 2019 and December 2019 were considered as the control group. Multivariable logistic regression analysis tested the impact of the COVID-19 outbreak on the risk of adverse pathologic findings at RP after adjusting for confounders. The percentage change of SV and WL was assessed comparing the months of pandemic with the equivalent timespan of the previous year.

Results A total of 2,574 patients treated with RP (927 cases and 1647 controls) were identified in 8 European tertiary referral centers. At multivariable analysis patients who were treated during the pandemic had higher risk of extra prostatic disease (OR:1.35, p = 0.038) and lymph node invasion (LNI) (OR:1.72, p = 0.048). An average 23% reduction of the SV with the equivalent timespan of the previous year allowed an illusory reduction of the WL after the peak gained during the first wave of COVID-19.

Conclusions Our results showed that the COVID-19 outbreak resulted in a delay in the administration of curative-intent therapies in patients with localized PCa. This, in turn, resulted in a stage migration phenomenon with a potential impact on oncologic control.

Key Words: prostate cancer ‹› radical prostatectomy ‹› COVID-19 ‹› surgical volume ‹› waiting list ‹› stage migration

The COVID-19 outbreak caused a sudden global health emergency. Especially within the first wave, in the attempt to minimize the virus transmission, many outpatient and procedural attendances were postponed or canceled with the aim to safeguard patients and healthcare workers. EAU guidelines faced the new need of allowing the best medical treatment whilst minimizing the risk of transmission within this health crisis [1]. However, prostate cancer (PCa) is characterized by a relatively slow progression and excellent 10-year cancer–specific mortality rates [2] with the majority of the patients presenting with localized disease at diagnosis [3]. Consequently, the adoption of expectant management policies was further encouraged during the first phase of the pandemic period with the goal of postponing active treatment options within 3–6 months, when feasible. In particular, the use of radical prostatectomy (RP) was rationalized using the EAU risk classification tool, age and risk factors for COVID-19 adverse outcomes [4]. In addition, some uncertainties arose regarding the widespread adoption of minimally invasive surgery in the surgical management of PCa patients, where it has been hypothesized that the pneumoperitoneum typical of laparoscopic or robot-assisted surgery might generate aerosol which could favour the diffusion of the novel coronavirus [5, 6]. Nonetheless, whether all these factors concretely contributed to alter the management of PCa patients and delay the use of RP still remains undocumented. Of note, the delay in the administration of curative-intent therapies might theoretically result in a stage migration phenomenon with a higher increase in the number of patients with adverse pathologic findings at RP. Hence, we aimed to report the impact of COVID-19 on PCa surgical volumes and waiting list of multiple European Tertiary Referral centers and to investigate whether COVID-19 outbreak increased the risk of aggressive PCa at final RP histology.

Patients undergoing RP between March 11th 2020 (WHO declaration of pandemic) and 31st December 2020 at 8 European urological centers were retrospectively identified from institutional prospective registries. Metastatic and recurrent PCa cases after non-surgical treatment were excluded. The centers provided both data regarding RPs during pandemic (cases) and records from patients who were treated between March 11th 2019 and 31st December 2019 which were considered as controls. Data collection included the total numbers of surgeries (i.e., surgical volume [SV]), waiting list (defined as time from biopsy to surgery (WL)), demographic, pre- and postoperative variables.

A total of 927 cases (i.e., patients treated during the COVID19 pandemic period) and 1647 controls (i.e., patients treated the year before) were included. The two groups were similar for most of the demographic and clinical characteristics (Table 1). However, we recorded a lower use of mpMRI, a higher PI-RADS score, cT stage and number of pelvic lymph node dissections during the pandemic phase (all p values <0.05). At multivariable logistic regression no differences were found for ISUP 4–5 at pathology, positive surgical margins and use of robotic surgery (Table 2). However, patients being treated during the pandemic had higher risk of extra prostatic disease (OR:1.35, 95% CI 1.01–1.82, p = 0.038) and of lymph node invasion (LNI) (OR:1.72, 95% CI 1.00–2.99, p = 0.048). Figure 1 depicts the monthly percentage change of SV and WL during pandemic with the equivalent timespan of the previous year. An average of 23% reduction of the SV was observed. A pro-

Table 1. *Patients characteristics*

	Controls	Cases	p
N. of surgeries	1647	927	
Age, year (median, IQR)	66.1 (61–72)	67 (61–72)	0.17
BMI kg/m^2 (median, IQR)	26.0 (24.1–28.4)	26.3 (24.3–28.9)	0.52
PSA at diagnosis mg/dl (median, IQR)	7.9 (5.5–13.6)	8.4 (5.6–13.9)	0.56
Staging with MRI	741 (45.0)	334 (36.1)	<0.01
PI–RADS ≥3	543/741 (78.8)	274/334 (85.4)	0.01
cT stage >2	259 (16.9)	179 (21.0)	0.01
ISUP grade			
I	318 (19.4)	146 (16.1)	0.13
II	549 (33.6)	337 (37.2)	
III	320 (19.6)	165 (18.2)	
IV	262 (16.0)	144 (15.9)	
V	186 (11.4)	115 (12.7)	
Time from biopsy to RP, months (IQR)	2.6 (1.8–4.1)	2.8 (1.7–4.3)	0.41
Robotic surgery	1184 (71.9)	650 (70.2)	0.35
Nerve sparing	1099 (72.8)	648 (73.9)	0.55
ISUP at final pathology			
No Tumor	2 (0.1)	1 (0.1)	0.29
1	161 (9.8)	72 (8.4)	
2	826 (50.2)	506 (54.6)	
3	280(17.0)	137(14.8)	
4	154 (9.4)	76 (8.2)	
5	224 (13.6)	129 (13.9)	
pT stage			0.86
T0	2 (0.1)	1 (0.1)	
T2	902 (54.8)	499 (53.8)	
T3	736 (44.7)	421 (45.4)	
T4	7 (0.4)	6 (0.6)	
PLND performed	1063 (76.4)	711 (80.6)	0.02
Patients with Positive nodes	113/1063 (10.6)	79/711 (11.1)	0.48

All analyses were performed on available data. IQR – interquartile range, BMI – body mass index, ISUP – International Society of Urological Pathology (ISUP) grading of prostate cancer, RP – radical prostatectomy, PLND – pelvic lymph node dissection

Table 2. *Multivariable logistic regression analyses to test the impact of the COVID-19 outbreak on the risk of ISUP 4–5, positive surgical margins, ≥pT3a, pN1, M+ and use of robotic surgery, after adjusting for confounders*

Parameter	ISUP 4–5			pT3a			PSM			N+			Robotic surgery		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Pandemic vs no pandemic (ref)	0.9	0.69–1.34	0.83	1.3	1.01–1.82	0.03	0.9	0.68–1.26	0.63	1.7	1.00–2.99	0.04	0.9	0.57–1.66	0.99
Age (cont.)	1.0	1.00–1.05	0.03	0.9	0.98–1.02	0.9	1.0	0.98–1.02	0.82	0.9	0.91–0.99	0.01	0.9	1.05	0.53
PSA (cont.)	1.0	0.99–1.00	0.84	1.0	0.99–1.00	0.63	1.0	0.99–1.00	0.75	1.0	0.99–1.01	0.31	1.0	0.99–1.01	0.30
cT stage (≥2 vs <2)	4.6	2.24–9.51	<0.01	3.5	2.02–6.18	<0.01	1.5	0.97–2.56	0.07	3.3	1.71–6.54	<0.01	0.4	0.25–0.94	0.03
ISUP at biopsy (>2 vs ≤2)	3.1	2.69–3.77	<0.01	1.5	1.35–1.73	<0.01	1.2	1.07–1.37	<0.01	2.2	1.73–2.85	<0.01	0.6	0.55–0.82	<0.01
PI–RADS (cont)	1.1	0.98–1.44	0.08	1.6	1.33–1.92	<0.01	1.3	1.10–1.62	<0.01	1.7	1.08–2.68	0.02	0.7	0.56–1.09	0.15

ISUP – International Society of Urological Pathology grade; PSA – prostate-specific antigen; PSM – positive surgical margin; N+ – positive lymph nodes

gressive reduction of SV caused an illusory reduction of the WL after its initial 27% increase during the earliest COVID-19 wave.

Our findings offer a timely snapshot of patients treated with RP during the COVID-19 pandemic in tertiary referral European Institutions. Alarmingly, as reported by others [7], we document a stage migration phenomenon towards a more advanced stage. A decrease in cancer screening could be a possible explanation for this effect [8]. Delays and/or reduced accuracy in PCa diagnostic pathway, possibly resulting in later presentation and thus in more advanced disease may also have contributed to this shift, and triage of cases with prioritization of surgery in patients with unfavorable characteristics. The lower mpMRI use for staging during pandemic compared to the previous year, well matches with this hypothesis. Interestingly, the use of robotic surgery turned out to be similar before and after the pandemic. Indeed, the earlier discharge favored by minimally invasive surgery and minimizing the within-hospital virus infection/transmission likely overtook possible disadvantages linked to the fear of COVID-19 aerosol generating procedures [9]. At the beginning of the pandemic, PCa surgery room was hampered by hospital reorganization and shortage of healthcare workers and devices. There was an initial increase of the WL which showed subsequent decline

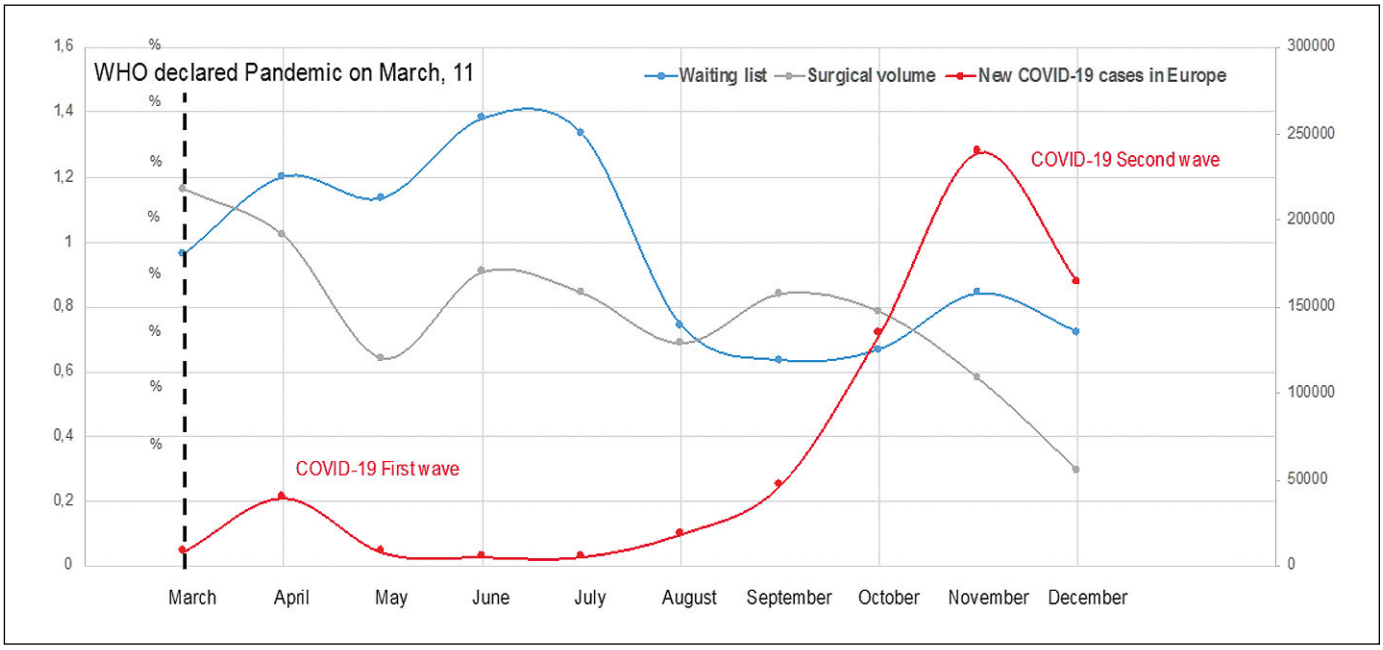

Figure 1. *Monthly percentage change of surgical volume and waiting list during the pandemic compared with the equivalent timespan of the previous year. Red line is the superimposed curve of daily increase of new COVID-19 cases in Europe.*

possibly attributable to change in the selection of candidates to RP. Impaired diagnostic paths during the pandemic, may have caused a stage migration towards higher PCa risk categories. Furthermore, it cannot be predicted if an increase of new PCa diagnosis will be observed when we will revert back from the acute phase of the COVID-19 spread, with more normal levels of urological diagnosis and care. Thus, a new phase of the pandemic may require new strategies to remodulate the SV and WL due to the stage migration and the missing diagnosis. This necessitates a reconfiguration of management pathways and proper selection of candidates for RP. In particular, telemedicine will be able to allow a timely contact with the patients and better counseling; new nomograms might also implement patients selection for the best diagnostic imaging and treatment; hospital reorganization and adapted working schedules are mandatory to guarantee the accessibility to radiological exams and surgical theater; COVID-19-free hospitals dedicated to PCa might provide the best practice care.

Our findings need to be confirmed by larger cohorts also including other PCa stages and treatment modalities. The treating physicians could make alternative therapeutic plans to surgery and consider RT or active surveillance as a deliver treatment with minimal to no disruption of the pre COVID treatment timeline. Hence, our results reflect surgical aspects of localized PCa rather than PCa features in the pandemic overall.

A false disease state shift cannot be excluded because of decreased surgical volumes and subsequent 'cherry-picking' of higher risk cases; the overall intake disease parameters may in fact be the same but because of lower volumes those patients on the border of needing therapy (eg some intermediate risk patients) may have been delayed in favor of operating on the high risk patient first. Unfortunately, no data can be obtained about those patients still on the waitlist.

Finally, a proper follow up is needed to evaluate if our findings may have implications in the natural history of the disease. There are conflicting data regarding whether postponement/delay of treatment after diagnosis leads to worse outcomes in PCa survivorship [10]. It is likely that the retrospective nature of these studies and heterogeneous patient groups play a large role in the variability of findings. Indeed, the follow up of all cancer patients postponed due to the COVID-19 pandemic will further shed light on impact of treatment delays on PCa survival and disease progression.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

COMPLIANCE WITH ETHICAL STANDARD

All included patients undergoing radical treatment provided written informed consent for surgery. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional review board number was not required due to observational and retrospective nature of the study.

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