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State-of-the-Art Reviews

Effect of COVID-19 pandemic on diagnosis and treatment pattern of prostate cancer: a comprehensive literature review, phase 1

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Abstract

Since its outbreak in late 2019, the COVID-19 pandemic has brought many changes to medical practice, including the care and management methods regarding prostate cancer. Patients with prostate cancer are exposed to high risk of infection, hospitalization, and death due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while other elements including male gender, old age, and pre-existing comorbidities increased the possibility of infection. Although patients with prostate cancer need intensive support and care, high concerns of infection resulted in delay or avoidance of medical care, especially during the initial phase of the pandemic, which led to needs of revisions in diagnostic procedures and treatment plans. Our review illustrates the changes that have occurred in prostate cancer diagnosis, treatment, and prognosis since the emergence of the COVID-19 pandemic. We further conducted a review on topics recently being highlighted which include the protective role of androgen deprivation therapy on SARS-CoV-2 infection, vaccination and immune response in patients with prostate cancer, and the outcomes of altered treatment plans. As with the many efforts in treating cancer since the outbreak of COVID-19, identifying the changes in research and clinical practice of patients with prostate cancer worldwide is essential in providing appropriate patient care in rapidly changing circumstances.

Keywords: COVID-19; SARS-CoV-2; prostate cancer; urology.

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1. Introduction

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) near the end of 2019 caused a global pandemic that led to unprecedented measures of lockdowns and restrictions in order to slow the rapid development of the virus.[1] The COVID-19 pandemic has also brought many changes to medical practice, including urology practice, and more specifically, the care and management regarding prostate cancer.

Patients with cancer, compared with the general public, are at a greater risk of infection due to the immunosuppressed status of some patients, which potentially exposes them to more severe

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infections as well as serious complications.[2] Other negative prognostic factors which include male gender, old age, and pre-existing comorbidities, pose additional risks to those patients with prostate cancer.[2] Patient concerns about COVID-19 have resulted in delay or avoidance of medical care, even cases needing urgent or emergency care.[2] Telemedicine and mobile health are seen as successful tools that help diagnosing and monitoring patients while reducing transmission of COVID-19, and vaccination status became a factor that influenced patient management and treatment.[3]

The aim of this paper is to analyze the evolving trend in the urological clinical practice, particularly in the diagnosis, treatment, and prognosis of prostate cancer after the occurrence of the COVID-19 pandemic. We further reviewed novel topics related to the association between COVID-19 and prostate cancer which are recently receiving, as well as the management and nature of the disease itself (Table 1 and 2).

Table 1. Main findings of studies on COVID-19 and prostate cancer

Main findings
1. Androgen deprivation therapy (ADT) and COVID-19
- There is no significant relationship between the protective role of ADT on COVID-19 infection and mortality.[6-13]
2. Diagnosis, treatment, and mortality of patients with prostate cancer during the COVID-19 pandemic
- Local anesthetic transperineal prostate biopsy (LATP) was the preferred method of prostate biopsy by clinicians during the pandemic.[16]
- Decrease in diagnostics and treatment was pronounced during the first lockdown with a rebound late-pandemic.[19-26]
- Patients were more likely to have a malignant pathology at diagnosis[22] or in a more advanced stage after prostatectomy.[27]
- Clinical visits, prostate biopsy, and men enrolled in active surveillance were significantly lower while the number of advanced and metastatic prostate cancer cases increased during a year of the pandemic.[27]
- Although there was a consistent reduction in radical prostatectomy (RP), radiotherapy (RT) had a lesser reduction or was increased in some studies.[20, 21, 23, 27]
- Overall hospitalization and mortality rates were higher in patients with prostate cancer and COVID-19 compared with patients with solid cancers and COVID-19.[28]
3. The effect of delayed treatment
- Patients with localized prostate cancer who were treated during the pandemic had a higher risk of extra-prostatic disease and lymph node invasion due to a delay in the administration of curative-intent therapies.[31]
- There is no significant difference in early adverse oncologic outcomes between intermediate, high-risk patients who received immediate RP and any level of delay up to 12 months.[32]
- Overall and cancer-specific survival was significantly worsened among intermediate-risk patients receiving monitoring compared to immediate RP (but not in low-, high-risk patients).[33]
4. Quality of life of patients with prostate cancer during the COVID-19 pandemic
- Patients with prostate cancer and delayed operations had higher state anxiety than trait

anxiety, especially higher in young patients[34]
- Cognitive deterioration was more frequent in patients treated with ADT, even more after the COVID-19 pandemic.[35]

5. Vaccination and prostate cancer
- CD4+ T cells of SARS-CoV-2-unexposed patients with hormone-resistant metastatic prostate cancer had decreased CD4+ T cell immune responses to antigens from SARS-CoV-2 spike glycoprotein but not from the spiked glycoprotein of the human coronavirus 229E (HCoV-229E). [36]
- Similar median titers of neutralizing antibodies against SARS-CoV-2 were observed in twenty-five prostate cancer under treatment with androgen receptor-targeted agents such as abiraterone or enzalutamide with healthy controls.[37]

Abbreviations; ADT, androgen deprivation therapy; LATP, local anesthetic transperineal prostate biopsy; RP, radical prostatectomy; RT, radiotherapy

Table 2. Characteristics of included studies

Author, year	Study period	Study design	Exposure	Outcome	Database/ cohort
Duarte, 2021[13]	Outbreak of COVID-19 to April, 2021	Retrospective cohort	ADT versus non-ADT	Cumulative incidence of Death	Brazilian Unified Health System
Fujiwara, 2021[38]	Apr to Jun, 2020	Retrospective cohort (pilot study)	Prostate cancer which switched from GnRH antagonist to long-acting LH-RH agonist	Serum testosterone, PSA	Cancer Institute Hospital, Japanese Foundation for Cancer Research
Gedeborg, 2021[39]	Mar to Dec, 2020	Case-control	ADT	COVID-19 mortality	Prostate Cancer data Base Sweden (PCBaSe) RAPID 2019
Gedeborg, 2021[7]	2015 to 2020	Retrospective cohort	ADT	COVID-19 mortality	Prostate Cancer data Base Sweden
Klein, 2021[8]	Mar to Jun, 2020	Prospective cohort	ADT	COVID-19 positivity and disease severity	Cleveland, Ohio
Jiménez-Alcaide, 2021[9]	Mar to May, 2020	Retrospective cohort	ADT	COVID-19 severity	Hospital Universitario Fundación Alcorcón
Koskinen, 2020[10]	Mar to May, 2020	Retrospective cohort	ADT	COVID-19 positivity	Hospital District of Helsinki and Uusimaa, Finland
Schmidt, 2021[11]	Mar, 2020 to Feb, 2021	Retrospective cohort	ADT	COVID-19 mortality	COVID-19 and Cancer Consortium registry

Table 2. Continued

Author, year	Study period	Study design	Exposure	Outcome	Database/ cohort
Kwon, 2021[12]	Feb to Dec, 2020	Retrospective cohort	ADT	COVID-19 incidence	University of California Health System registry
Montopoli, 2020[5]	Start of COVID-19 to Apr, 2020	Retrospective cohort	ADT	COVID-19 incidence	68 hospitals in Veneto, Italy
Karimi, 2021[40]	Search: Dec, 2020	Meta-analysis	ADT	COVID-19 infection risk, hospitalization rate, ICU admission, and mortality risk	Four eligible studies
Motlagh, 2022[15]	Search: July, 2021	Meta-analysis	ADT	COVID-19 infection risk, severity	6 Retrospective studies
Stroman, 2021[16]	Apr to May, 2020	Cross-sectional		Prostate biopsy method	Centres in United Kingdom
Caffo, 2020[41]	Feb to Jun, 2020	Retrospective cohort	Metastatic castrate-resistant prostate cancer	COVID-19 incidence	20 Italian oncological centres
Chakravarty, 2021[28]	Mar to Dec, 2020	Retrospective cohort	Prostate cancer	COVID-19 hospitalization and mortality	Mount Sinai Hospital system
Deukeren, 2022[22]	Mar to May, 2020	Cross-sectional		Prostate cancer diagnosis	Netherlands Cancer Registry (NCR)
Fallara, 2021[23]	Mar to Jun, 2020	Cross-sectional		Prostate cancer diagnosis and staging, treatment	National Prostate Cancer Register (NPCR) of Sweden
Ferrari, 2021[19]	2016 to 2020	Cross-sectional		Prostate cancer routine screening	University Hospitals of Verona
Klaassen, 2022[29]	Jan, 2018 to Mar, 2021	Retrospective cohort	Race	Prostate biopsies and diagnoses	Veterans Affairs Health Care System
Bernstein, 2021[30]	Mar to May, 2020	Retrospective Cohort	Race	Prostatectomy rate	Pennsylvania Urologic Regional Collaborative (PURC)
Nossiter, 2022[21]	Mar to Dec, 2020	Cross-sectional		Prostate cancer diagnosis and treatment	English National Health Service
Pepe, 2021[27]	2020 to 2021	Cross-sectional		Prostate cancer diagnosis and treatment	Catania, Italy

Table 2. Continued

Author, year	Study period	Study design	Exposure	Outcome	Database/ cohort
Sciarra, 2020[20]	Mar 2020	Descriptive study		Diagnostic, therapeutic elective procedures requested and performed for cancer management	Rome, Italy
Surasi, 2021[18]	2021	Descriptive study		Prostate MRI studies, biopsies	Radiologists from five continents
Ip, 2021[25]	Jun 2018 to Jun 2021	Temporal trend analysis		Cancer diagnostics, treatments, and physician attendances	Services Australia Medicare Benefits Schedule Item Reports
Kaufman, 2021[24]	Jan 2018 to Dec 2020	Temporal trend analysis		PSA, prostate biopsy, and diagnoses	Quest Diagnostics database
Barrett, 2021[42]	Jan 2019 - Oct 2020	Analysis of descriptive statistics and interrupted time series		Prescription of gonadorelins	English Prescribing Dataset
Ginsburg, 2020[32]	2010 to 2016	Retrospective cohort	Delayed radical prostatectomy	Oncological outcome	National Cancer Database
Lee, 2022[43]	1988 to 2018	Retrospective cohort	Delayed radical prostatectomy	Time of castration-resistant prostate cancer, metastasis, and all-cause mortality	SEARCH cohort, U.S.
Diamand, 2021[44]	Mar 2012 to Sep 2019	Retrospective cohort	Delayed radical prostatectomy	Oncological outcome	European centers (Belgium, France, Switzerland, and Italy)
Zattoni, 2021[31]	Mar to Dec, 2020	Retrospective Cohort	Delay in radical Prostatectomy	Risk of adverse pathologic findings at RP	8 European tertiary referral centers
Chan, 2021[33]	Search: May, 2020	Meta-analysis	Delayed treatment	Disease prognosis	4 randomized trials and 33 observational studies

Table 2. Continued

Author, year	Study period	Study design	Exposure	Outcome	Database/ cohort
Loeb, et al. 2021[45]	Dec 2019 to April 2020	Computational linguistic ethnography analysis	Prostate cancer	Linguistic tone and topic of discussion online	Inspire Us TOO Prostate Cancer online support and discussion, Reddit
Irusen, 2021[46]	Jul to Sep, 2020	Prospective longitudinal study	COVID-19	Corona virus anxiety scale, state-trait anxiety inventory, the connor-davidson resilience scale, and multidimensional scale of perceived social support	Cape Town, South Africa
Araújo, 2022[35]	Before vs after COVID-19 pandemic	Prospective Cohort	ADT	Montreal cognitive assessment	NEON-PC, Portuguese Institute of Oncology of Porto
Kizilkan, 2021[34]	Mar to Jun, 2020			State-trait anxiety inventory I and II and beck depression inventory	Ankara City Hospital, Turkey
Lopez, 2020[47]	Search: Nov, 2019	Meta-analysis		Fatigue, quality of life, lean body mass, and fat mass	3 randomized trials
Liontos, 2021[37]	2021	Prospective cohort	Prostate cancer under treatment with ARTA who were vaccinated for COVID-19	Neutralizing antibody against COVID-19	Athens, Greece
Notohamiprodjo, 2022[48]	Jun to July, 2021	Retrospective cohort	COVID-19 vaccination	Prevalence, temporal response, and characteristics of vaccine-associated lymphadenopathy	Munich, Germany

Abbreviations; ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone; LH-RH, luteinizing hormone releasing hormone; PSA, prostate-specific antigen.

2. Androgen deprivation therapy and COVID-19

Cell surface transmembrane serine protease 2 (TMPRSS2) and the angiotensin-converting enzyme 2 (ACE2) protein are two critical molecular and clinical targets reported to facilitate the entry of SARS-CoV-2 into host cells.[4] TMPRSS2 is also an androgen-responsive gene

responsible for prostate tumorigenesis, and the hypothesis that the androgen-dependent expression of TMPRSS2 in the lung may increase men's susceptibility to severe COVID-19 symptoms led to several clinical studies to examine this relationship.[4]

A study of 9,280 patients with SARS-CoV-2 infection in Veneto was the first clinical study to propose that patients with prostate cancer receiving androgen deprivation therapy (ADT) had a significantly lower risk of SARS-CoV-2 infection compared with patients who did not receive the ADT and had an even lower risk compared to those with any other type of cancer.[5] This study caused much debate over the relationship and protective role of ADT on COVID-19 infection or mortality, but several following clinical studies demonstrated no clear evidence in support of such effect.[6-13]

A study exclusively on patients with metastatic castrate-resistant prostate cancer during the initial phase of the pandemic confirmed the rate of infection as 2.3% and mortality rate of 38.2%. Such results show a higher death rate compared to other studies with a high proportion of patients in remission or treated with curative intent.[14] Also, a meta-analysis of four studies concluded that the overall incidences of COVID-19 among patients with prostate cancer receiving ADT was 2.7% and the mortality rate was 22.7% (Table 3). Moreover, ADT did not decrease the risk of any of the major outcomes such as infection risk, hospitalization rate, intensive care unit (ICU) admission, and mortality risk.[15] The summarized risk ratio of SARS-CoV-2 infection risk in patients with prostate cancer under ADT versus no ADT or the severity of COVID-19 in patients under ADT versus no ADT was 0.80 (95% CI 0.44 to 1.47) and 1.23 (95% CI 0.90 to 1.68), respectively, in a separate meta-analysis.[15]

Table 3. Summary of four meta-analyses on COVID-19 and prostate cancer

Author, year	N. of study estimates	Main outcome	Effect metrics	Results
Karimi, 2021[40]	4	ADT (+) versus ADT (-)	Odds ratio (95% CI)	COVID-19 Infection Risk, 0.63 (0.27-1.48, p=0.29); hospitalization rate, 0.51 (0.10-2.53, p=0.41); ICU admission, 1.11 (0.43-2.90, p=0.82); and mortality risk, 1.21 (0.34-4.32, p=0.77)
Motlagh, 2022[15]	4	COVID-19 infection risk in patients with prostate cancer under ADT vs. no ADT	Relative risk (95% CI)	0.80 (0.44-1.47)
	5	Severity of COVID-19 in patients with prostate cancer under ADT versus no ADT		1.23 (0.90-1.68)

Table 3. Continued

Author, Year	N. of study estimates	Main Outcome	Effect metrics	Results
Chan, 2021[33]	4 (RCTs)	A. Expectant management versus immediate RP B. Cancer-specific survival in expectant management versus immediate RP	Hazard ratio (95% CI)	A. 1.21 (1.08-1.37, p<0.01) B. 1.63 (1.26-2.10, p<0.001)
	10 (observational studies)	Positive surgical margin in 3 months of NHT and delayed RP versus immediate RP		0.45 (0.37-0.54, p<0.01)
Lopez, 2020[47]	3	Supervised versus non-supervised exercise period (during COVID-19)	Standard mean difference (95% CI)	Fatigue, 0.2 (-0.6 to 0.2, p=0.090); quality of life, 0.0 (-1.4 to 1.5, p=0.810)
			Mean difference (kg; (95% CI)	Fat mass 0.5 (-0.4 to 1.5, p=0.141); lean mass 0.0 (-1.2 to 1.2, p=0.810)

Abbreviations; ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone; LH-RH, luteinizing hormone releasing hormone; NHT, neoadjuvant hormonal therapy; PSA, prostate-specific antigen; RCT, randomized controlled trial; RP, radical prostatectomy.

3. Diagnostics, treatment, and mortality

A cross-sectional study on the diagnostics of prostate cancer in 148 centers in the UK shows interesting findings that the local anesthetic transperineal prostate (LATP) biopsy was the preferred method of prostate biopsy by clinicians during the pandemic; the reduction of general anesthetic transperineal prostate (GATP; 64%) and local anesthetic transrectal ultrasound-guided transrectal ultrasound (60%) was greater than the reduction of LATP (20%).[16] The transit from transrectal biopsy to transperineal biopsy started in the UK in 2019 mainly due to the decreased risk of post-procedural sepsis[17], and the pandemic has accelerated this shift. There was an overall decrease in the diagnostics during the pandemic, and according to a survey of radiologists from five continents, the number of prostate MRIs decreased significantly with a median (range) of 20 (0 to 135) per week before the COVID-19 pandemic versus 10 (0 to 30) during the lockdown period and 15 (0 to 125) after lockdown.[18]

A dramatic decline in routine prostate cancer screening was observed during the first peak of COVID-19 outbreak in the Verona province of Italy.[19] This was compensated in the post-lockdown period, with the annual number not differing significantly in 2020 compared to the previous four years.[19] In March 2020, there was a great surge in COVID-19 cases in Italy and all management experienced a significant reduction with the exception of medical therapies for advanced hormone-sensitive or castration-resistant prostate cancer.[20] During the first lockdown in England, there was a 30.8% reduction (22,419 during first lockdown versus 32,409 in 2019) in the number of men with newly diagnosed prostate cancer compared to 2019, with

men being at a more advanced stage and slightly older (stage IV, 21.2% versus 17.4%, stage IV in elderly [≥ 70 years], 57.9% versus 55.9%).[21] Also, there was a reduction in radical prostatectomies by 26.9% and external beam radiotherapy by 14.1%.[21] During the first wave of COVID-19 in the Netherlands, an initial decline of 17% of prostate cancer diagnoses was observed while the number restored to approximately 95% from May while stage at diagnosis and radical prostatectomy volumes were comparable to 2018 to 2019.[22] In Sweden, 36% fewer prostate cancer cases were registered, much more of them were pronounced in men above age 75 years (down 51%) than in men below age 70 (down 28%) while there was no decrease in the number of radical prostatectomies and an increase in radical radiotherapy.[23]

When analyzing the late-pandemic (June to December 2020) data from a database based on all US states and the District of Columbia, the average monthly number of prostate-specific antigen (PSA) showed a 36.4% decrease with a rebound to a 3.9% increase in late-pandemic and the average monthly number of prostate biopsy results saw a 37.9% decrease with a rebound to an 18.1% increase.[24] While in Australia, there was a reduction in PSA tests and general practitioner attendance in 2020 compared to 2019, but no reduction in multi-parametric MRI, prostate biopsy, nor number of radical prostatectomies or fiducial marker implantations.[25] Another long-term study in Australia estimated 14% fewer PSA tests, 12% fewer biopsies and 16% fewer prostatectomies on average, while steep decreases in PSA tests were observed during the first, second, and delta wave.[26] In an evaluation during the term of a year of the COVID-19 pandemic, the number of clinical visits, prostate biopsy, and men enrolled in active surveillance was significantly lower while the number of advanced and metastatic prostate cancer cases increased.[27] Also, there was an increase in open radical prostatectomies compared to laparoscopic approaches and an increase in external radiotherapy.[27] A study based on 286,609 patients with prostate cancer in the Mount Sinai Hospital System found that the overall hospitalization (64.91% for prostate cancer versus 47.34% for solid cancer; p-value <0.0001) and mortality rates (21.05% for prostate cancer versus 15.85% for solid cancer; p-value=0.0547) were higher in patients with prostate cancer and COVID-19 compared with those with solid cancers and COVID-19.[28]

Contrasting results were presented by two studies owing to racial disparity in prostate cancer care.[29, 30] Bernstein et al., 2021[30] suggested that black men were significantly less likely to undergo prostatectomy during the pandemic compared with white patients, despite similar conditions. While a study based on the Veterans Affairs Health Care System disputed that although prostate biopsy volume and diagnosis rates of prostate cancer decreased during the COVID-19 pandemic, there were no statistically significant changes noted by race.[29]

4. Conclusion

Our review illustrates the changes in prostate cancer diagnosis, treatment, and prognosis after the emergence of the COVID-19 pandemic. Furthermore, we conducted a review on topics recently being highlighted such as the protective role of androgen deprivation therapy on SARS-CoV-2 infection, vaccination and immune response in patients with prostate cancer, and the outcomes of altered treatment plans. Identifying the changes in research and clinical

practice of patients with prostate cancer worldwide is essential in providing appropriate patient care in today's rapidly changing circumstances.

Capsule Summary

This review summarizes cutting-edge topics being highlighted which include the protective role of androgen deprivation therapy on SARS-CoV-2 infection, vaccination and immune response in patients with prostate cancer, and the outcomes of altered treatment plans.

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Author Contribution

All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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