# Management Recommendations for Prostate Cancer During the COVID-19 Pandemic: A Systematic Review

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## Abstract

**Introduction** The COVID-19 pandemic has delayed screening, diagnostic workup, and treatment in prostate cancer (PCa) patients. Our purpose was to review PCa screening, diagnostic workup, active surveillance (AS), radical prostatectomy (RP), radiotherapy (RT), androgen deprivation therapy (ADT) and systemic therapy during the COVID-19 pandemic.

**Materials and Methods** We performed a systematic literature search of MEDLINE, EMBASE, Scopus, LILACS, and Web of Science, according to Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) statement for relevant material published from December 2019 to February 2021.

**Results** Prostate biopsy can be delayed, except when high-risk PCa is suspected or the patient is symptomatic. Active surveillance is appropriate for patients with very low risk, low risk (LR) and favorable intermediate risk (FIR). RP and RT for high risk and very high risk can be safely postponed up to 3 months. Hypofractionated external beam RT (EBRT) is recommended when RT is employed. ADT should be used according to standard PCa-based indications. Chemotherapy should be postponed until the pandemic is contained.

**Conclusions** The international urological community was not prepared for such an acute and severe pandemic. PCa patients can be adequately managed according to risk stratification. During the COVID-19 pandemic, LR and FIR patients can be followed with active surveillance. Delaying RP and RT in high risk and locally advanced disease is justified.

## Introduction

In December 2019, a series of acute atypical respiratory diseases occurred in Wuhan, China, caused by a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (COVID-19) pandemic[1]. By the end of July 2020, 11.456 million confirmed COVID-19 cases and 530 937 deaths had been reported globally, and by mid-March 2021, 120 million cases and 2.6 million deaths had been reported, according to the COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University[2]. Some studies have suggested that men with COVID-19 have a higher risk than women for SARS-CoV-2-related complications and death[3,4].

Prostate cancer (PCa) is the most frequently diagnosed urogenital neoplasm and is currently the second leading cause of cancer deaths in men in the United States and Europe[5,6].

**Key Words**

Androgen receptor antagonists, adjuvant chemotherapy, prostatic neoplasms, radiotherapy, SARS coronavirus

**Competing Interests**

None declared.

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### Abbreviations

ADT androgen deprivation therapy
ARAT androgen-receptor-axis-targeted therapies
AS active surveillance
BCR biochemical recurrence
ChT chemotherapy
EBRT external beam radiation therapy
FIR favorable intermediate risk
HR high risk
LR low risk
mCRPC metastatic castrate resistant PCa
mpMRI multi-parametric MRI
nmCRPC non-metastatic castration-resistant prostate cancer
PCa prostate cancer
PSADT PSA doubling time
RoB risk of bias
RP radical prostatectomy
RT radiation therapy
UIR unfavorable intermediate risk
VHR very high risk
VLR very low risk

COVID-19 remains a challenge for health care professionals all around the globe. Radical treatment, such as radiotherapy with curative intent and surgical procedures, has been affected by this pandemic. Bhat et al. reported an increase of approximately 22% of PCa patients on the waiting list of radical prostatectomies in a robotic oncological center, revealing the negative effect of COVID-19 on surgical PCa treatment[7]. We performed a systematic review of the best management recommendations for PCa patients during the COVID-19 pandemic, and sought to establish a foundation for PCa management in future pandemics. Our primary aim was to assess the evidence published to date with respect to the management of PCa with surgery, radiotherapy, androgen deprivation and systemic therapy, for all stages and risk stratification categories, since the beginning of COVID-19 pandemic. We also sought to determine whether studies on changes in PCa workup and management made because of the pandemic have provided adequately robust evidence to establish guidelines for PCa management in future pandemics.

## Materials and Methods

### Protocol development and registration

We registered our systematic review protocol in PROSPERO (International Prospective Register of Systematic Reviews, registration number CRD42020193332), following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols) statement[8].

### Eligibility criteria and literature search

We performed a systematic literature search using MEDLINE and EMBASE, Scopus, LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud), and Web of Science, including all indexed publications in English, Spanish, and French. We included recommendations, systematic reviews, clinical trials, and case-control, cohort, and cross-sectional studies related to the workup and management of PCa, patients (such as screening, diagnosis, any modality of treatment, radical prostatectomy (RP), radiation therapy (RT), androgen deprivation therapy (ADT), chemotherapy (ChT) and follow-up), from December 1, 2019, to February 28, 2021. Editorials, letters, and opinion articles were excluded.

### Study selection and data extraction

Two independent investigators (AJMS and JSMA) performed the systematic literature search and screened all identified paper titles and abstracts. The full text of each identified article was reviewed by 3 independent investigators (AJMS, JSMA, INR). Any disagreement about individual study inclusion was resolved by a fourth investigator (EARG).

Information on included studies was entered into an Excel database. Information included the authors, country of research, publication title, date of publication, study design, indexed databases, management options studied in the publication methodology, outcome, and recommendations.

### Risk of bias and quality assessment

Individual study quality assessment was performed using the appropriate tool for the study design and methodology: STROBE (Strengthening the Report of Observational Studies in Epidemiology-II) for cohort, case-control, and cross-sectional studies[9], AGREE II (Appraisal of Guidelines for Research & Evaluation) for guidelines and recommendations[10], and AMSTAR-2 (A Measurement Tool to Assess systematic Reviews) for systematic reviews and meta-analysis[11]. The risk of bias (RoB) was assessed using the ROBINS-I[12] for individual included non-randomized studies, and the ROBIS[13] for systematic reviews. All recommendations based on non-systematic reviews were managed as expert consensus; therefore, no RoB was evaluated for such publications.

### Outcome and synthesis methods

We performed data synthesis for each element of PCa management, including screening and diagnosis, surgical treatment, radiation therapy, androgen deprivation therapy, and systemic therapy. This synthesis was conducted for each PCa risk group in

the National Comprehensive Cancer Network Prostate Cancer Guidelines Risk Stratification as well as for each stage group (localized, locally advanced, and metastatic PCa)[14].

To determine adequate level of evidence and quality of recommendations for each different PCa management strategy, publication quality of evidence was established, using the SIGN statement for the level of evidence[15]. The priority of management recommendations was based on the European Urological Association Rapid Reaction Group level of priority for COVID-19 pandemic[16]: emergency priority, labeled as black (cannot be postponed > 24 hours because of life-threatening condition); high priority, red (should not be delayed > 6 weeks, since clinical harm such as progression, metastasis, loss of organ function, and death may occur); intermediate priority, yellow (cancel, but reconsider in case of increased capacity; delay of > 3 months may result in clinical harm and should therefore not be recommended); and low priority, green (clinical harm is very unlikely with delay of > 6 months).

## Results

### Literature search and study selection

The literature search identified 349 papers from the different databases. After duplicates and articles not eligible for screening were eliminated, a total of 142 abstracts were screened, and 55 potentially eligible full text articles retrieved. Of these, 27 papers were excluded since outcomes were not documented; therefore, 28 publications were included in our systematic review (Figure 1).

### Study characteristics, quality, and level of evidence

Of the included publications, 4 were systematic reviews, 16 expert opinion and consensus-based recommendations (non-systematic reviews), 1 case-control, and 3 cross-sectional and 4 cohort studies. Regarding quality of evidence, most of the studies complied with more than two-thirds of the corresponding tool items. Table 1 summarizes characteristics, study design, PCa management approached during the COVID-19 pandemic, results and recommendations, and SIGN level of evidence for each publication[15].

**FIGURE 1.**
PRISMA Flow Diagram

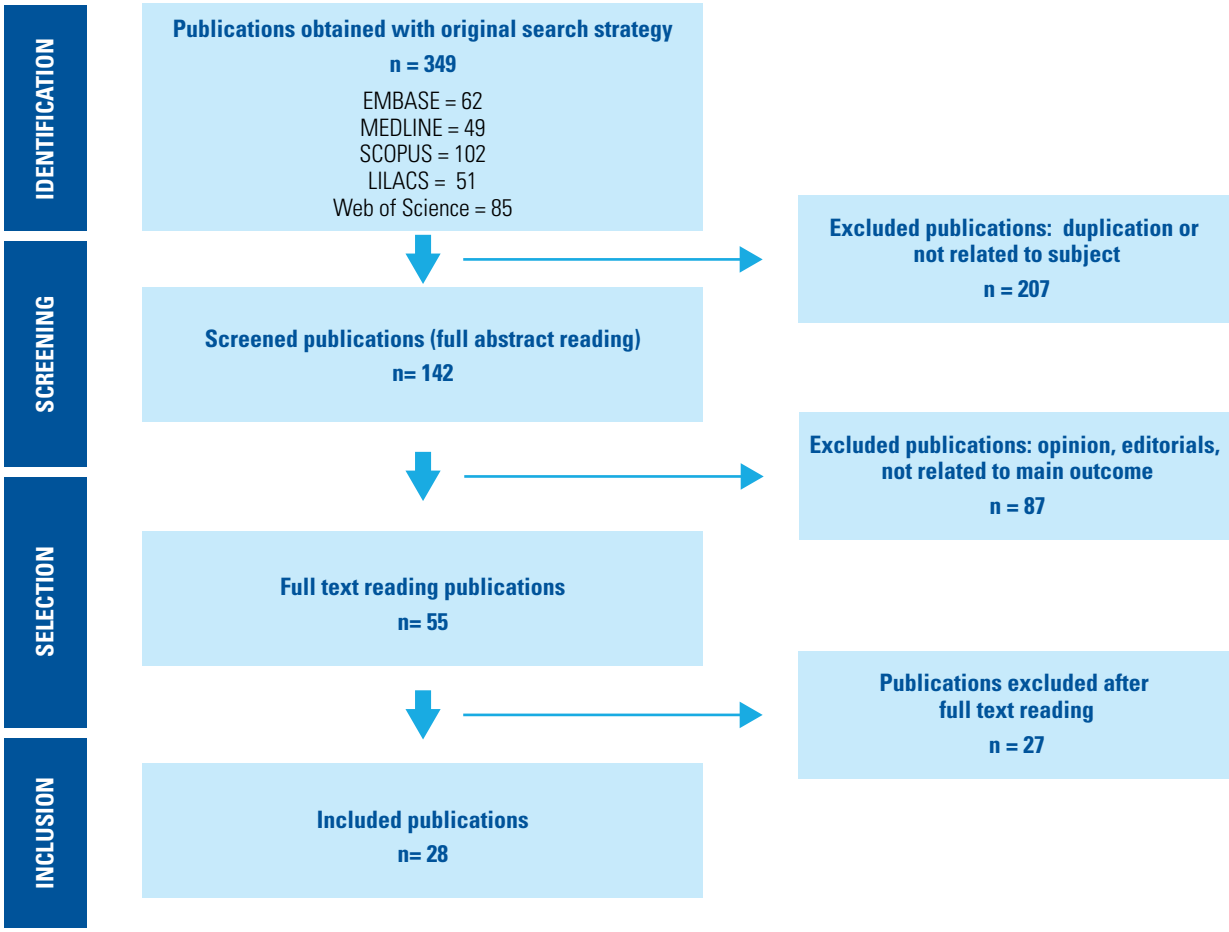

**TABLE 1.**

Characteristics of included publications

| Publication | Country | Date of Publication | Methodology | PCa management | Level of evidence [15] | RoB assessment |
|---|---|---|---|---|---|---|
| Kokorovic et al.[20] | Canada | June 2020 | Expert/consensus-based recommendations | Screening/diagnosis, AS, RP, RT, ADT | 4 | NA |
| Heldwein et al.[34] | International | September 2020 | Systematic review | Screening/diagnosis, RP, RT, ADT, ChT | 2 ++ | Low[a] |
| Montopoli et al.[43] | Italy | August 2020 | Case/control | ADT | 2 - | Moderate[b] |
| Gómez Rivas et al.[21] | Spain | February 2020 | Expert/consensus-based recommendations | Screening/diagnosis, RP, RT, ADT, ChT | 4 | NA |
| Larrea et al.[41] | Spain | May 2020 | Cross-sectional | RT | 3 | NA |
| Simcock et al.[29] | International | March 2020 | Expert/consensus-based recommendations | AS, RT | 4 | NA |
| Amparore et al.[18] | Italy | May 2020 | Systematic review | Screening/diagnosis, RP, RT, ADT, ChT | 2 ++ | High[a] |
| Würnschimmel et al.[32] | Germany | May 2020 | Cross-sectional | RP | 2 - | NA |
| Popert et al.[17] | United Kingdom | May 2020 | Cross-sectional | Screening/diagnosis | 2 - | NA |
| Zaorky et al.[42] | United States/ United Kingdom | March 2020 | Systematic review | RT | 2 ++ | Low[a] |
| Méjean et al.[22] | France | March 2020 | Expert/consensus-based recommendations | Screening/diagnosis, RP, RT, ADT, ChT | 4 | NA |
| Wallis et al.[39] | International | April 2020 | Expert/consensus-based recommendations | RP, RT, ADT | 4 | NA |
| Narain et al.[23] | India | April 2020 | Expert/consensus-based recommendations | Screening/diagnosis, RP, RT, ADT | 4 | NA |
| Dovey et al.[24] | International | May 2020 | Expert/consensus-based recommendations | Screening/diagnosis, AS, RP, RT, ADT, ChT | 4 | NA |
| Katims et al.[36] | United States | June 2020 | Systematic review | RP | 2++ | High[a] |
| Obek et al.[25] | Turkey | July 2020 | Narrative review/ recommendations | Screening/diagnosis, RP, RT, ADT | 4 | NA |
| Tachibana et al.[40] | United States | November 2020 | Narrative review/ recommendations | RP, RT, ADT, ChT | 4 | NA |
| Tan et al.[31] | United Kingdom | January 2021 | Cohort | RP | 2+ | Moderate[a] |
| Madan et al.[26] | United States | August 2020 | Narrative review/ Recommendations | Screening/diagnosis, RP, RT, ADT | 4 | NA |
| Caffo et al.[45] | Italy | September 2020 | Cohort | ADT | 2+ | High[a] |

*[a] ROBIS assessment tool[13] [b] ROBINS-I assessment tool[12]*
*ADT: androgen deprivation therapy; AS: active surveillance; NA: not applicable; PCa: prostate cancer; RoB: risk of bias; RP: radical prostatectomy; RT: radiation therapy.*

*continued on* ***page 244***

**TABLE 1.**

Characteristics of included publications, *Cont'd*

| Publication | Country | Date of Publication | Methodology | PCa management | Level of evidence [15] | RoB assessment |
|---|---|---|---|---|---|---|
| Rodriguez-Sanchez et al.[27] | International | July 2020 | Narrative Review/ recommendations | Screening/diagnosis, AS, RP, RT, ADT | 4 | NA |
| Barthwal et al.[44] | India | July 2020 | Narrative review/ recommendations | RT | 4 | NA |
| Caicedo-Martinez et al.[30] | Colombia | July 2020 | Narrative review/ recommendations | Screening/diagnosis, AS, RP, RT, ADT | 4 | NA |
| Detti et al.[28] | Italy | February 2021 | Expert/consensus-based recommendations | Screening/diagnosis, AS, RP, RT, ADT | 4 | NA |
| Diamand et al.[37] | International | June 2020 | Cohort | RP | 2++ | Low[a] |
| Lalani et al.[46] | Canada | April 2020 | Expert/consensus-based recommendations | ADT, ChT | 4 | NA |
| Shinder et al.[35] | United States | May 2020 | Expert/consensus-based recommendations | RP, ADT | 4 | NA |
| Ginsburg et al.[38] | United States | October 2020 | Cohort | RP | 2++ | Low[b] |

[a] *ROBIS assessment tool[13]* [b] *ROBINS-I assessment tool[12]*
*ADT: androgen deprivation therapy; AS: active surveillance; NA: not applicable; PCa: prostate cancer; RoB: risk of bias; RP: radical prostatectomy; RT: radiation therapy.*

## Screening and diagnosis of PCa

Popert et al.[17] undertook a prospective cohort study of patients managed with prostate biopsy during the pandemic (April 2020) in the United Kingdom. They established a 3-level risk stratification:

- High risk (red): PSA density > 0.2ng/mL/cc and MRI suspicious lesions (Likert/PI-RADS 3, 4 and 5); biopsy should be performed within a month.
- Intermediate risk (amber): PSA density < 0.2 and suspicious lesions; biopsy within 3 months.
- Low risk (green): PSA density < 0.2 and no suspicious lesion; biopsy safely postponed indefinitely.

Amparore et al.[18] performed a systematic search of all urological association and society websites between April 8, and April 18, 2020, for guidelines on the management of urological pathologies during the pandemic. They concluded that prostate biopsies should be performed in men with suspected high-risk, locally advanced, or symptomatic PCa and this should be done without preceding MRI[19]. The remaining publications related to prostate biopsy are expert consensus recommendations[20–28]; most authors recommend that new PSA screening and continuation of diagnostic workup should not be performed until the pandemic is contained and suggest delaying prostate biopsy except in symptomatic patients[21–23], PSA > 10ng/mL[31,34,39], suspicion of cT3 disease, PSA doubling time (PSADT) < 6 months[24,27], or in case of medullary compression or obstructive renal failure secondary to PCa suspicion[22,27]. A summary of recommendations for screening and diagnosis is provided in **Table 2**.

## Active surveillance in PCa

Six papers (all of them being either narrative reviews or consensus-based recommendations) addressed the role of active surveillance (AS) in PCa patients and concluded that in very low risk (VLR), low risk (LR), and favorable intermediate risk (FIR) PCa patients, AS is an adequate management strategy[20,24,27,29,30]. For LR and FIR patients, Rodriguez-Sanchez et al. and Caicedo-Martinez et al. suggest implementation of AS while delaying RP and RT until the pandemic is controlled[27,30], and Kokorovic et al. suggest either AS or delaying RP up to 12 months[20]. Detti et al. recommend multi-parametric MRI (mpMRI) of the prostate instead of re-biopsy in patients on AS[28]. A summary of recommendations for AS is provided in **Table 3**.

**TABLE 2.**

Summary of prostate cancer screening and diagnostic evaluation recommendations during the COVID-19 pandemic

| Paper | Screening and diagnostic evaluation | |
|---|---|---|
| | New PCa screening | Symptomatic or mPCa suspicion |
| Kokorovic et al.[20] | New PSA screening and diagnostic workup should be delayed | |
| Heldwein et al.[34] | Individual patient- based decision. Postpone until pandemic control; perform without MRI if suspicion of advanced disease | |
| Gómez Rivas et al.[21] | New PSA screening and diagnostic workup should be delayed | In symptomatic disease perform biopsy |
| Amparore et al.[18] | Delay until pandemic control | Biopsy without previous MRI |
| Popert et al.[17] | PSA density ≥ 0.2 ng/mL/cc and MRI Likert/PI-RADS 3, 4, 5 biopsy within 3 months, otherwise defer indefinitely | |
| Méjean et al.[22] | New PSA screening and diagnostic workup should be delayed | Biopsy in case of medullary compression |
| Narain et al.[23] | New PSA screening and diagnostic workup should be delayed | Symptomatic disease or PSA ≥ 10 ng/mL perform biopsy |
| Obek et al.[25] | New PSA screening and diagnostic workup should be delayed | Do not delay biopsy ≥ 3 months in: PSA ≥ 20ng/mL, DRE cT3 and PSADT ≤ 6 months<br>If suspicion of mPCa, perform first imaging studies, if confirmed initiate ADT, biopsy may be postponed |
| Madan et al.[26] | Delay diagnostic workup until pandemic control, no time specified | |
| Rodriguez-Sanchez et al.[27] | Delay biopsy unless PSA ≥ 20 ng/mL, PSADT ≤ 6 months, T3 or symptomatic | |
| **EAU Rapid Response Priority Level** | Low priority | Intermediate priority |
| **Recommendation summary** | PCa screening and workup with PSA and MRI can be safely delayed until pandemic control; if suspicion of advanced, mPCa, or symptomatic, consider biopsy without MRI; if suspicion of mPCa, perform imaging studies first | |

*DRE: digital rectal examination; EAU: European Association of Urology; mPCa: metastatic prostate cancer; MRI: magnetic resonance imaging; PCa: prostate cancer; PSA: prostate specific antigen; PSADT: PSA doubling time.*

## Surgical management of PCa

Tan et al. performed a retrospective analysis of 282 patients who underwent RP between March and May 2020, 99% by robotic surgery, and none of the patients had developed SARS-CoV-2 infection at the 30-day follow-up after surgery[31].

In Germany, Würnschimmel et al. performed a retrospective analysis of all surgically treated PCa patients, reporting a total of 784 patients, 447 (57%) patients before the pandemic (January and February 2020) and 337 (43%) patients in the first month and a half of the pandemic before operating room shutdown (March and April 2020)[32]. Of a total of 784 patients, 623 (79%) patients were ISUP (International Society of Urological Pathology) grades group 1, 2, and 3[33], corresponding to very low risk, low risk, favorable intermediate risk, and unfavorable intermediate risk.

**TABLE 3.**

Summary of active surveillance recommendations during the COVID-19 pandemic

| Paper | Active surveillance |
|---|---|
| | VLR LR FIR |
| Kokorovic et al.[20] | Delay RP up to 12 months or AS |
| Simcock et al.[29] | AS |
| Dovey et al.[24] | AS should be managed by telemedicine according to PSA, genomic testing, and MRI |
| Rodriguez-Sanchez et al.[27] | Consider AS, no RP or RT should be considered during the pandemic, PSA testing may be postponed 3–6 months |
| Caicedo-Martinez et al.[30] | AS indicated, delay RT until pandemic control |
| Detti et al.[28] | AS is preferred, consultation visits deferred by 6 months; if re-biopsy indicated during AS, consider mpMRI instead |
| **EAU Rapid Response Priority Level** | Low priority |
| **Recommendation summary** | In VLR, LR and FIR AS is an adequate management strategy |

*AS: active surveillance; EAU: European Association of Urology; FIR: favorable intermediate risk; LR: low risk; mpMRI: multi-parametric MRI; MRI: magnetic resonance imaging; PSA: prostate specific antigen; RP: radical prostatectomy; RT: radiation therapy; VLR: very low risk.*

Of these, 352 patients were treated before the pandemic, and 271 during the first month of the outbreak. The authors reported no statistical difference related to complications and outcomes and no COVID-19 infection amongst the patients treated during the pandemic, and therefore concluded that performing surgery in these patients is feasible when adequate safety measures are in place[32].

Heldwein et al. performed a systematic review of all urological management recommendations issued during the first months of the pandemic, including both consensus-based recommendations and opinion-based recommendations. On the basis of a previous European Association of Urology (EAU) rapid reaction group statement[16], they proposed a 5-level, color-based triage for urological procedures priority: zero (red) for emergency: survivorship compromised if surgery not performed within hours; 1 (brown) proceed as planned, do not postpone: survivorship compromised if surgery nor performed within days; 2 (yellow), consider delaying up to 1 month: patient condition can deteriorate or survivorship be compromised if surgery not performed within 30 days or proceed as planned if COVID-19 trajectory not in rapid escalation phase; 3 (green) safe delay 1 to 3 months: proceed as planned if COVID-19 not in rapid escalation phase; 4 (blue) safe to delay > 3 months. For VLR, LR, FIR, and UIR prostate cancer, radical prostatectomy was considered blue level priority; therefore, delaying > 6 months is justified[34].

In a systematic search of rapid response recommendations and guidelines issued by European urological associations and societies, Amparore et al. found that all recommended delaying surgical management for low- and intermediate-risk prostate cancer[18]. Méjean et al. recommend delaying of RP in low- and intermediate-risk PCa for at least 2 months[22], Narain et al. and Shinder et al. recommend delaying for up to 6 months[23,35], and 3 consensus-based recommendations state non-specific time delay of surgical treatment on LR and FIR PCa until the COVID-19 pandemic is controlled[21,27,36].

In 2020, Diamand et al. and Ginsburg et al. published retrospective cohort studies of intermediate- and high-risk PCa patients who underwent RP before the COVID-19 pandemic[37,38]. Diamand et al. performed a European multicenter study of 926 patients who had a delay of surgical treatment after PCa diagnosis and found no upgrading, lymph node involvement, or biochemical

recurrence (BCR) associated with a 3-month delay of RP in intermediate- and high-risk PCa[37]. Ginsburg et al. studied 129 062 patients with the same characteristics and found no increase in adverse oncological outcomes after RP (upgrading, positive lymph nodes or need of adjuvant therapies) even after a 12-month delay[38].

For high-risk (HR) and very high-risk (VHR) PCa patients, Würnschimmel et al., included 148 (19%) high-risk patients (ISUP 4 and 5) managed with radical prostatectomy, 83 (56%) before the pandemic and 65 (44%) during the first month of the pandemic. They reported no COVID-19 infections, and therefore suggested continuation of RP in high-risk patients with adequate COVID-19 safety measures[32]. Amparore et al. suggest not to continue RP for HR and locally advanced disease if possible[18]. Heldwein et al. concluded that RP for high-risk patients can be safely delayed between 1 and 3 months. If there is a delay of more than 3 months because of the pandemic, or if there is suspicion of lymph node involvement, ADT with or without RT can be initiated[34]. Most expert consensus-based published recommendations conclude that RP for high-risk patients can be safely delayed for between 2 and 6 months[21–28,35,39,40]. If further delay is expected, ADT should be considered until surgical management can be undertaken[21–26,40]. Katims et al., however, report that in high-risk patients there may be an increased risk of biochemical recurrence (HR 2.19; CI 95% 1.24 to 3.87; $P = 0.007$) and positive surgical margins (OR 4.08; CI 95% 1.52 to 10.9; $P = 0.005$) in case of > 9-month delay[36]. Summary of recommendations for surgical management is provided in **Table 4**.

## Radiation therapy in PCa

Larrea et al. retrospectively reported on 100 oncology patients treated with external beam radiation therapy (EBRT). Only 9 had PCa. No stage or risk stratification of these patients is specified; however, 7 were treated with hypofractionated EBRT with curative intent, and the remaining 2 because of BCR, with no reports of COVID-19 infection in these patients[41].

For low- and intermediate-risk PCa patients, all publications agree on active surveillance and delay of any modality of treatment[18,20–30,34,39,40]. For high-risk patients and locally advanced disease, 3 systematic reviews[18,34,42] conclude that if primary curative RT is planned, delay between 1 and 3 months is feasible. However, initiation of ADT should be immediate or as soon as possible: according to EAU priority, RT is considered level 2 (yellow)[34]. Three expert consensus-based recommendations suggest the use of RT with ADT in HR localized and locally advanced disease for patients not eligible for RP, with immediate initiation of long deposit ADT[20,21]. A delay of up to 3 months is considered safe and feasible[16]; however, most expert consensus documents recommend delays of up to 6 months, with initiation of ADT while waiting for RT[25–28,30,41]. For postprostatectomy RT, adjuvant RT should not be initiated; instead, salvage RT is recommended[18,20,22,28,29,34,39,42,43]. Metastatic disease requiring palliative RT management should be undertaken as soon as possible on the basis of symptomatic disease or risk of fracture and medullary compression[20,21,28]. Regardless of PCa risk and stage, brachytherapy is not recommended, and the ideal EBRT treatment should be either hypofractionated or ultra-hypofractionated[18,20-22,25-30,34,39,41,44]. Follow-up with PSA testing after RT may be at 6-month intervals to reduce hospital exposure[27,30]. A summary of recommendations is provided in **Table 5**.

## Androgen deprivation therapy in PCa

Montopoli et al.[43] performed a retrospective analytical study of all prostate cancer patients in Veneto, Italy, reporting a total of 118 SARS-CoV-2-positive cases: 4 were on ADT, and the remaining 114 were not. No PCa risk or stage was specified, but the authors concluded that PCa patients on ADT have a significantly lower risk of COVID-19 infection (OR 4.05; 95% CI 1.55 to 10.59). Caffo et al.[45] performed a multicenter retrospective study in Italy (20 oncological centers), including 1433 men with metastatic castration-resistant PCa (mCRPC), who continued oncological consultation during the pandemic (February to June 2020); 34 (2.3%) developed SARS-CoV-2 infection, all of them with ADT, 9 with concomitant chemotherapy, and 19 with concomitant androgen-receptor-axis-targeted therapies (ARAT). Thirteen patients (38.2%) died, 85.7% of whom had previously received 2 or more mCRPC therapies. The authors therefore concluded that mCRPC patients were at increased risk of SARS-CoV-2 infection and mortality, regardless of ADT[38]. All included recommendations and systematic reviews conclude that ADT in VLR, LR, and FIR prostate cancer is not recommended[18,20–30,34,35,39,42,43,46]. For UIR and HR, as well as for locally advanced disease (N1) eligible for radical curative treatment, when RP is delayed, ADT can be safely initiated when pandemic-related delay is expected to surpass 3 to 6 months and in cases of patient cancer-related anxiety[18,20–30,34,35,39,42,43,46]. Immediate ADT, preferably a long depot (3- or 6-month duration) formulation, is recommended for hormone sensitive metastatic prostate cancer (mHSPC) [18,20–23,28,29,34,39,42,43,46]. For non-metastatic castration-resistant prostate cancer (nmCRPC), ADT plus ARAT, such as abiraterone, enzalutamide, apalutamide, or darolutamide is recommended. Madan et al. recommend enzalutamide, since no concomitant steroid is needed[26]. For mCRPC, when no previous second-generation hormone therapy has been used, ARAT (except abiraterone) is recommended. In both

**TABLE 4.**

Summary of radical prostatectomy recommendations during the COVID-19 pandemic

| Paper | Radical prostatectomy | |
|---|---|---|
| | VLR LR FIR | UIR HR VHR |
| Kokorovic et al.[20] | Delay up to 12 months or AS | Delay 3 months |
| Heldwein et al.[34] | Delay ≥ 6 months | Delay 1–3 months |
| Gómez Rivas et al.[21] | Delay, time not specified | Delay 2–6 months; consider ADT if locally advanced |
| Amparore et al.[18] | Delay indefinitely | Delay 1–3 months, before if control of pandemic |
| Würnschimmel et al.[32] | Safe to continue surgery planning, no infection among RP patients | |
| Méjean et al.[22] | Delay ≥ 2 months | Delay 2 months |
| Wallis et al.[39] | Delay, time not specified | Delay 3–6 months |
| Narain et al.[23] | Delay 6 months | Delay, time not specified |
| Katims et al.[36] | Delay ≥ 9 months | Delay of up to 3 months does not increase the risk of BCR nor negative oncological outcomes |
| Obek et al.[25] | Delay between 6 and 12 months is safe | Delay of up to 6 months is safe for UIR and HR; consider ADT if further delay expected |
| Tachibana et al.[40] | – | Delay between 60 days and 12 months is safe |
| Tan et al.[31] | RP was safe despite pandemic scenario, no patient developed COVID-19 on 30-day follow-up | |
| Madan et al.[26] | Delay until pandemic control, no time specified | Delay up to 6 months, consider neoadjuvant ADT for up to 6 months |
| Rodriguez-Sanchez et al.[27] | RP should not be considered during the pandemic | Delay unless PSADT ≤ 3 months, alternative for HR consider ADT |
| Detti et al.[28] | If RP is planned, delay between 6 and 12 months | Delay 6 months, neoadjuvant ADT is not recommended |
| Diamand et al.[37] | A delay of RP up to 3 months has no impact on oncological outcomes in IR and HR | |
| Shinder et al.[35] | Delay ≥ 3 months | Delay of 3 months adequate cut-off in most HR; HR already on 6-month delay should be managed as high priority, RP as soon as possible |
| Ginsburg et al.[38] | RP can be safely postponed up to 12 months in IR and HR | |
| **EAU Rapid Response Priority Level** | Low priority | Intermediate priority<br>High priority |
| **Recommendation summary** | RP in VLR, LR and FIR can be safely delayed ≥ 6 months; HR and VHR delay should be based on individual patient case | |

*ADT: androgen deprivation therapy; AS: active surveillance; BCR: biochemical recurrence; EAU: European Association of Urology; FIR: favorable intermediate risk; HR: high risk; LR: low risk; RP: radical prostatectomy; PSADT: PSA doubling time; UIR: unfavorable intermediate risk; VHR: very high risk; VLR: very low risk.*

**TABLE 5.**

Summary of radiation therapy recommendations during the COVID-19 pandemic

| Paper | Radiation therapy | | |
|---|---|---|---|
| | VLR LR FIR | UIR HR VHR | mPCa |
| Kokorovic et al.[20] | Delay, time not specified | Hypofractionated, delay, time not specified, initiate ADT immediately; short course RT in painful bone metastasis | |
| Heldwein et al.[34] | – | Delay 3 months, initiate ADT in HR | Delay indefinitely, initiate ADT |
| Gómez Rivas et al.[21] | – | Salvage RT is preferred | In case of symptomatic oligometastasis palliative RT can be used |
| Larrea et al.[41] | RT is safe in hypofractionated ERBT modalities | | |
| Simcock et al.[29] | AS | Delay 3–4 months with ADT initiation, hypofractionated | Delay, initiate instead ADT for mPCa, even if symptomatic |
| Amparore et al.[18] | – | If patient anxiety, hypofractionated ERBT + ADT | - |
| Zaorky et al.[42] | Delay until pandemic control | Delay up to 3 months, immediate ADT initiation | Delay, initiate ADT; in case of PSADT ≤ 3 months and RT beneficial, do not delay |
| Méjean et al.[22] | – | Follow national guidelines | Delay, time not specified |
| Wallis et al.[39] | – | Delay 3 months; hypofractionated | – |
| Narain et al.[23] | – | PSA ≥ 20 ng/mL and locally advanced consider RT + ADT | – |
| Obek et al.[25] | Delay between 6 and 12 months | Delay up to 6 months; consider ADT if further delay is expected; initiate within 6 weeks ADT + EBRT as curative treatment for locally advanced disease | – |
| Madan et al.[26] | Delay until pandemic control, no time specified | Delay up to 6 months, consider neoadjuvant ADT for up to 6 months | – |
| Rodriguez-Sanchez et al.[27] | RT should not be considered during the pandemic | Delay RT unless PSADT ≤ 3 months, alternative for HR consider ADT | – |
| Barthwal et al.[44] | Brachytherapy should be avoided and converted to EBRT or ADT | | – |
| Caicedo-Martinez et al.[30] | If RT indicated delay, time not specified | ADT alone to delay RT for 6 months regardless of risk or stage | – |
| Detti et al.[28] | – | For UIR, initiate ADT and delay EBRT 6 months; for HR consider ADT + EBRT, delaying RT for 3–6 months while on ADT, hypofractionated | For low volume, initiate ADT; for high volume consider ADT or systemic therapy and single dose EBRT for symptomatic bone metastasis |
| **EAU Rapid Response Priority Level** | Low priority | Intermediate priority | |
| **Recommendation summary** | RT should not be used in VLR, LR and FIR; for HR and VHR eligible for RT, initiate ADT and safely postpone ≤ 3 months; hypofractionated ERBT is recommended; salvage RT is preferred | | |

*ADT: androgen deprivation therapy; AS: active surveillance; EAU: European Association of Urology; EBRT: external beam radiation therapy; FIR: favorable intermediate risk; HR: high risk; LR: low risk; mPCa: metastatic prostate cancer; PSA: prostate specific antigen; PSADT: PSA doubling time; RT: radiation therapy; UIR: unfavorable intermediate risk; VHR: very high risk; VLR: very low risk.*

cases (nmCRPC and mCRPC), ARAT should be initiated as soon as possible[18,20–23,29,34,39,42,43,46]. The use of corticosteroids is controversial, and Méjean et al. do not recommend it[22]. If indicated, the lowest possible dose should be used: prednisone 5 mg twice daily, decreasing to once daily if there are individual concerns, has been suggested[23,46]. A summary of recommendations for ADT is provided in **Table 6**.

### Chemotherapy in PCa

Five publications broached the subject of ChT in PCa patients during the COVID-19 pandemic, all of them consensus-based recommendations, advising against the use of docetaxel in metastatic disease. Méjean et al. recommend that in case of mCRPC, docetaxel or cabazitaxel may be used, but at a reduced dosage and with the concomitant use of granulocyte-colony stimulating factor (G-CSF)[20–22,26]. Lalani et al. recommend the use docetaxel in case of mCRPC patients who have previously received ADT + ARAT with inadequate response, and in case of bone metastasis prefer only the use of Radium-223[46]. A summary of recommendations is provided in **Table 7**.

## Discussion

At the beginning of the pandemic, most institutions and countries issued non-specific and rapid response recommendations; however, as the pandemic continued, new evidence and complete reviews and recommendations were published. The main objective of each country and individual health system during the COVID-19 pandemic has been to limit the spread of SARS-CoV-2 infection. Despite this, however, it is still necessary to provide individual management for urological oncology patients. Although Popert et al. reported no COVID-19-related infection in prostate biopsy patients, all systematic reviews and recommendations support delaying biopsy and diagnostic workup in PCa until the pandemic is contained[17]. Würnschimmel et al. and Tan et al. published studies about RP during the pandemic, and even though no SARS-CoV-2 infection occurred, it is evident that at least for patients with low- or intermediate-risk PCa, active surveillance can be an adequate and safe alternative[32,31]. For high-risk patients, a delay of 6 months may be safe. In cases of patient anxiety or symptomatic PCa, treatment may be indicated, either ADT alone or ADT + RT. For mHSPC, ADT is also recommended, while in nmCRPC and mCRPC, immediate ARAT is the treatment of choice.

The PIVOT and ProtecT trials proved that in localized PCa, particularly in low- and intermediate-risk disease, curative treatment does not affect long-term mortality and survival on localized PCa, yet the ProtecT trial did find that active surveillance was associated with a higher incidence of biochemical recurrence and metastasis[47,48]. Although these studies report good outcomes in patients with non-metastatic PCa, oncological curative treatment in cases of UIR, HR and VHR, continues to be the desired treatment but the SARS-CoV-2 pandemic has in many cases delayed its provision. We can conclude from this systematic review that all modalities of radical treatment for non-metastatic PCa can be safely delayed, and that ADT can be used as an alternative treatment during the pandemic in order to prevent SARS-CoV-2 infection.

The sudden onset of the COVID-19 pandemic led to the rapid publication of papers and recommendations, sometimes with inadequate methodology and low levels of evidence, as well as expert consensus-based recommendations. Because of this, few papers met our criteria, leaving a fairly small sample. The main limitation of our study is the lack of RoB analysis of expert consensus-based recommendations. This is due to absence of an adequate tool, as well as the absence of clinical trials and the impossibility of performing any meta-analysis because of the scarce information in each study.

## Conclusions

The international urological community was not prepared for such a sudden and unprecedented global pandemic. Evidently an immediate emergency response was necessary to prevent and control SARS-CoV-2 infections in patients with urological comorbidities needing treatment, such as prostate cancer patients; however, COVID-19 paralyzed urologic oncology departments in most countries. This systematic review suggested that low-risk and intermediate-risk PCa patients can be managed with active surveillance, that delaying surgical and radiation therapy treatment in high-risk and locally advanced disease is justified, and that ADT is an adequate treatment option for HR and metastatic disease.

It is very likely that there will be new pandemics with implications, effects, and long-term outcomes similar to those of COVID-19. We hope that the present review will establish a foundation for the management of prostate cancer in future emergency scenarios and pandemics.

**TABLE 6.**

Summary of androgen deprivation therapy recommendations during the COVID-19 pandemic

| Paper | Androgen deprivation therapy | |
|---|---|---|
| | UIR HR VHR | mPca |
| Kokorovic et al.[20] | RT + ADT in locally advanced; hypofractionated | Oligometastatic HSPC ADT while delay RT; nmCRPC and mCRPC initiate ARAT |
| Heldwein et al.[34] | If significant RP delay or RT is planned, initiate immediately | Initiate ADT as soon as possible |
| Montopoli et al.[43] | PCa patients on ADT have lower risk for SARS-CoV-2 infection (OR 4.05; 95% CI 1.55 to 10.59) | |
| Gómez Rivas et al.[21] | ADT if RP is further delayed by uncontrolled pandemic | mHSPC initiate ADT; nmCRPC and mCRPC initiate ADT + ARAT |
| Simcock et al.[29] | Initiate ADT even if RT delay | |
| Amparore et al.[18] | – | Consider ADT if patient anxious about outcome |
| Zaorky et al.[42] | Initiate ADT immediately if RT delay is planned | |
| Méjean et al.[22] | ADT if RT or RP delay is foreseen in HR and locally advanced | HSPC initiate ADT; nmCRPC and mCRPC initiate ADT + ARAT |
| Wallis et al.[39] | ADT if RT or RP is planned to be delayed | ADT as soon as possible, mCRPC and nmCRPC along with ARAT |
| Narain et al.[23] | Consider ADT if RP delay when risk of progression is suspected | ADT + ARAT if high volume mHSPC or CRPC |
| Obek et al.[25] | For locally advanced disease, encourage ADT + EBRT as curative treatment and initiate within 6 weeks | – |
| Tachibana et al.[40] | Consider ADT for a 3-month duration when RP delays ≥ 3 months in HR | – |
| Madan et al.[26] | – | Long depot ADT should be used, if ARAT, enzalutamide is preferred |
| Caffo et al.[45] | – | mCRPC seem to have higher risk of SARS-CoV-2 and poor prognosis |
| Rodriguez-Sanchez et al.[27] | RP and RT should be deferred unless PSADT ≤ 3 months, consider ADT as an alternative for HR | – |
| Caicedo-Martinez et al.[30] | ADT alone to delay RT for 6 months is recommended regardless of risk stratification or stage | – |
| Detti et al.[28] | – | For low volume, initiate ADT; for high volume consider ADT or ARAT and single dose EBRT for symptomatic bone metastasis |
| Lalani et al.[46] | – | In mHSPC and mCRPC docetaxel should be avoided as possible, ARAT + ADT should be used instead |
| **EAU Rapid Response Priority Level** | High priority | |
| **Recommendation summary** | PCa patients on ADT seem to have a lower risk of SARS-CoV-2 infection; ADT should be immediately initiated when PCa-based indication exists; CRPC should also be managed with ARAT as soon as possible | |

*ADT: androgen deprivation therapy; ARAT: androgen-receptor-axis-targeted; CRPC: castration-resistant prostate cancer; EAU: European Association of Urology; HR: high risk; HSPC: hormone sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; mPCa: metastatic prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; PSADT: PSA doubling time; RP: radical prostatectomy; RT: radiation therapy; UIR: unfavorable intermediate risk; VHR: very high risk.*

**TABLE 7.**

Summary of chemotherapy recommendations during the COVID-19 pandemic

| Paper | Chemotherapy |
|---|---|
| | mPca |
| Kokorovic et al.[20] | ChT during the pandemic is not encouraged |
| Gómez Rivas et al.[21] | ChT during the pandemic is not encouraged |
| Méjean et al.[22] | Preferably avoid, if used, cabazitaxel is preferred with concomitant G-CSF use |
| Madan et al.[26] | Chemotherapy should not be recommended |
| Detti et al.[28] | For high volume consider ADT + systemic therapy other than ChT; for symptomatic bone metastasis consider single dose EBRT |
| Lalani et al.[46] | In mHSPC and mCRPC docetaxel should be avoided as possible, ARAT + ADT should be used instead |
| **EAU Rapid Response Priority Level** | Low priority |
| **Recommendation summary** | ChT is not recommended during the pandemic because of high infection risk |

*ADT: androgen deprivation therapy; ARAT: androgen-receptor-axis-targeted; ChT: chemotherapy; EAU: European Association of Urology; G-CSF: granulocyte-colony stimulating factor; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; mPCa: metastatic prostate cancer.*

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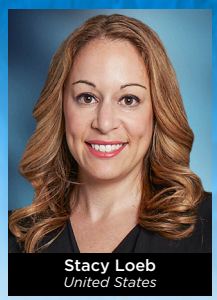
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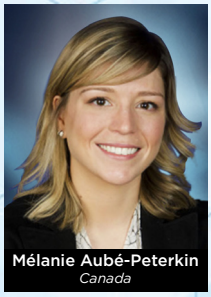
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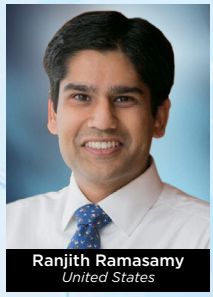
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# Effect of Metallic Ureteric Stents on Magnetic Resonance Imaging: Implications for Malignant Ureteral Obstruction

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## Abstract

Metallic ureteric stents are increasingly used for the management of malignant ureteric obstruction, a commonly encountered complication in urological and other malignancies. However, there has been limited evaluation of complications associated with these stents, including those that might arise from the use of magnetic resonance imaging (MRI). While most devices are deemed nominally "MRI-safe," their implication on the quality of imaging produced has not been evaluated in clinical trials, and in our practice, significant artefact has been encountered with some ureteric stents—specifically, the Teleflex Rüsch DD tumour stent—compromising image quality and diagnostic certainty.

In managing malignant ureteric obstruction, metal or metal-incorporating stents are an increasingly popular option, owing to evidence suggesting improved patency compared with conventional polymeric stents[1]. In our practice, 44% of patients undergoing ureteral stenting between March 2017 and March 2018 (n = 77) had one or more metallic stents inserted.

Depending on the malignancy, a significant proportion of patients undergoing stenting will require further pelvic magnetic resonance imaging (MRI) for staging or re-staging. This is particularly the case in the management of rectal cancer. While all the stents are certified MRI-safe, their effect on the quality of MRI images produced has not been fully elucidated. MRI compatibility has largely focused on energy absorption and safety within MRI systems; however, their effect on the quality of diagnostic imaging has received limited mention.

Metals produce aberrancy within MRI images through several mechanisms[2,3]:

- Inhomogeneities in the strong magnetic field, produced by paramagnetic/ferromagnetic components.
- Frequency-encoding misregistration, due to changes in frequency of dephasing.
- Signal loss, due to increase in the rate of T2 phase decay.
- Failure of fat suppression, owing to the effect of metallic implants on the resonance frequency of nearby fat.

The following factors contribute to the extent of artefact formed[3]:

- The size of metallic implant.
- Specific composition of the implant.
  - Artefact worsens with ferromagnetic implants (steel, iron) compared with those of paramagnetic or diamagnetic metals (titanium, platinum, copper).

## Key Words

Ureteric stents, metallic stents, magnetic resonance imaging, malignant ureteric obstruction

## Competing Interests

None declared.

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