

Prostate cancer management in the era of COVID-19: Recommendations from the Hong Kong Urological Association and Hong Kong Society of Uro-oncology

Darren Ming-Chun Poon^{1,2} | Chi-Kwok Chan³ | Tim-Wai Chan⁴ | Foon-Yiu Cheung⁵ | Lap-Yin Ho⁶ | Philip Wai-Kay Kwong⁷ | Eric Ka-Chai Lee⁸ | Angus Kwong-Chuen Leung⁹ | Simon Yiu-Lam Leung¹⁰ | Hing-Shing So¹¹ | Po Chor Tam¹² | Wai-Kit Ma¹²

¹ Department of Clinical Oncology, State Key Laboratory of Translational Oncology, Sir YK Pao Centre for Cancer, Hong Kong Cancer Institute, The Chinese University of Hong Kong, Sha Tin, Hong Kong

² Comprehensive Oncology Centre, Hong Kong Sanatorium & Hospital, Happy Valley, Hong Kong

³ Division of Urology, Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Sha Tin, Hong Kong

⁴ Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong

⁵ Hong Kong Integrated Oncology Centre, Kowloon, Hong Kong

⁶ Asia Clinic, Tsim Sha Tsui, Hong Kong

⁷ Department of Clinical Oncology, Queen Mary Hospital, The University of Hong Kong, Pok Fu Lam, Hong Kong

⁸ Department of Clinical Oncology, Tuen Mun Hospital, Tuen Mun, Hong Kong

⁹ Radiotherapy & Oncology Centre, Hong Kong Baptist Hospital, Kowloon, Hong Kong

¹⁰ Central Urology Clinic, Central, Hong Kong

¹¹ Division of Urology, Department of Surgery, United Christian Hospital, Kowloon, Hong Kong

¹² Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Pok Fu Lam, Hong Kong

Correspondence

Darren Ming-Chun Poon, FRCR, Comprehensive Oncology Centre, Hong Kong Sanatorium & Hospital, Hong Kong.
Email: mc_poon@clo.cuhk.edu.hk

Abstract

Aim: In response to the fast-developing coronavirus disease 2019 (COVID-19) pandemic, special arrangement and coordination are urgently required in the interdisciplinary care of patients across different medical specialties. This article provides recommendations on the management of different stages of localized or metastatic prostate cancer (PC) amid this pandemic.

Methods: The Hong Kong Urological Association and Hong Kong Society of Uro-oncology formed a joint discussion panel, which consisted of six urologists and six clinical oncologists with extensive experience in the public and private sectors. Following an evidence-based approach, the latest relevant publications were searched and reviewed, before proceeding to a structured discussion of relevant clinical issues.

Results: The joint panel provided recommendations for PC management during the pandemic, in terms of general considerations, diagnostic procedures, different disease stages, treatment modules, patient support, and interdisciplinary collaboration. The overall goal was to minimize the risk of infection while avoiding unnecessary delays and compromises in management outcomes. Practical issues during the pandemic were addressed such as the use of invasive diagnostic procedures, robotic-assisted laparoscopic prostatectomy, hypofractionated radiotherapy, and prolonged androgen deprivation therapy. The recommendations were explicated in the context of Hong Kong, a highly populated international city, in relation to the latest international guidelines and evidence.

Conclusion: A range of recommendations on the management of PC patients during the COVID-19 pandemic was developed. Urologists, oncologists, and physicians treating PC patients may refer to them as practical guidance.

KEYWORDS

coronavirus, COVID-19, prostate cancer, prostatectomy, radiotherapy

1 | INTRODUCTION

Since late 2019/early 2020, coronavirus disease 2019 (COVID-19) has quickly emerged from a single-city cluster of cases into a global pandemic, with over 4.5 million cases and 300 000 deaths reported as of May 15, 2020.¹ Largescale antiepidemic measures have been implemented in almost every country, and yet many are struggling to reduce transmission rates that have remained at high levels. It is generally believed that the pandemic will continue for months to years. At this phase, proactive response and coordination are urgently needed not only in terms of case detection, infection control, and antiviral treatment, but also in the interdisciplinary care of patients across medical specialties.

Cancer patients need extra care during this period because many are at an elevated risk of infection,^{2,3} presumably from an immunosuppressive state due to poor performance, treatment-related adverse events, and older age compared with healthy individuals. In this regard, both the disease stage and treatment modalities should be considered. Prostate cancer (PC) patients can be in very different disease stages, from very low-risk localized conditions to high-burden metastatic diseases. Treatments may range from active monitoring to radical prostatectomy (RP) and combination systemic treatments.

With regard to COVID-19, the UK National Institute for Health and Care Excellence (NICE) has published Rapid Guidelines on systemic anticancer therapy and radiotherapy (RT).^{4,5} For robotic surgery and endoscopy during the pandemic, clinicians may refer to the European Association of Urology Robotic Urology Section and Asian Pacific Society for Digestive Endoscopy guidelines.^{6,7} The latest medical literature has also elaborated on various aspects of urological (including cancer) management in COVID-19, including the following: treatment pathways,⁸ surgery triage guidance,⁹ radiation recommendations,¹⁰ and a comprehensive literature review.³

The present article provides a detailed set of recommendations specific to PC management during the COVID-19 pandemic. On April 16, 2020, two professional associations—the Hong Kong Urological Association (HKUA) and Hong Kong Society of Uro-onology (HKSUO)—met via an online conference platform, with the objective of producing a set of recommendations to minimize the risk of infection, while avoiding unnecessary treatment delays or compromised outcomes.

Hong Kong is a city with among the largest urban population and numbers of inbound tourists and air transit passengers in the world. Although the first cases of COVID-19 were reported in January, the rates of transmission and mortality have stayed relatively low, with currently (April 2020) slightly over 1000 cases and four deaths reported. Based on an evidence-based approach, these discussions aimed to combine the specialist expertise of both associations and draw from Hong Kong's experiences in the COVID-19 as well as the 2003 Severe Acute Respiratory Syndrome (SARS) epidemics. It is hoped that these recommendations will be helpful to clinicians both in Asia and globally.

2 | MATERIALS AND METHODS

2.1 | Literature search

To obtain the latest relevant literature on the relationship between PC management and the coronavirus outbreak, a literature search was conducted in multiple medical-related databases, including PubMed, Ovid, ClinicalKey, Proquest, and Google Scholar, using combinations of the following keywords: "COVID-19," "coronavirus," "epidemic," "pandemic," "prostate cancer," "urology," "prostatectomy," "endoscopy," "radiotherapy," "chemotherapy," and "systemic." A total of 53 articles (42 of which were published in 2020) were selected for further discussions.

2.2 | Meeting discussions

A joint meeting of the HKUA and HKSUO was convened on April 16, 2020 to discuss recommendations for PC management during the COVID-19 pandemic. The meeting was cochaired by WKM and DMCP; panel members included a total of six urologists from the HKUA and six clinical oncologists from the HKSUO, who had extensive clinical experience in PC management, both from the public and private sectors. To minimize the risk of infection during the pandemic, the meeting was conducted virtually on the secured web-based GlobalMeet conferencing platform.

3 | RESULTS

The panel provided detailed recommendations for the management of PC patients at different stages, regarding the risks associated with specific procedures. Figure 1 presents a schematic illustration of the framework and highlights some key recommendations. Table 1 contains a comprehensive summary of the recommendations. Further explanations are provided below.

3.1 | General considerations

To prevent deterioration in safety and efficacy during COVID-19, the diagnosis, treatment, and management of PC patients should continue to follow an evidence-based approach. Medical decisions and procedures should be supported by ample scientific evidence and updated guidelines (R1.1). During an epidemic, with the added risks of infection and changing situation, physicians should discuss with the patient regarding any special arrangements to be made, and identify the patient's preferences and concerns¹¹ (R1.2). Because reports suggested that patients with COVID-19 can be asymptomatic but infectious,¹² infection control protocols should be closely followed during the medical procedure. The patient should be assessed for any

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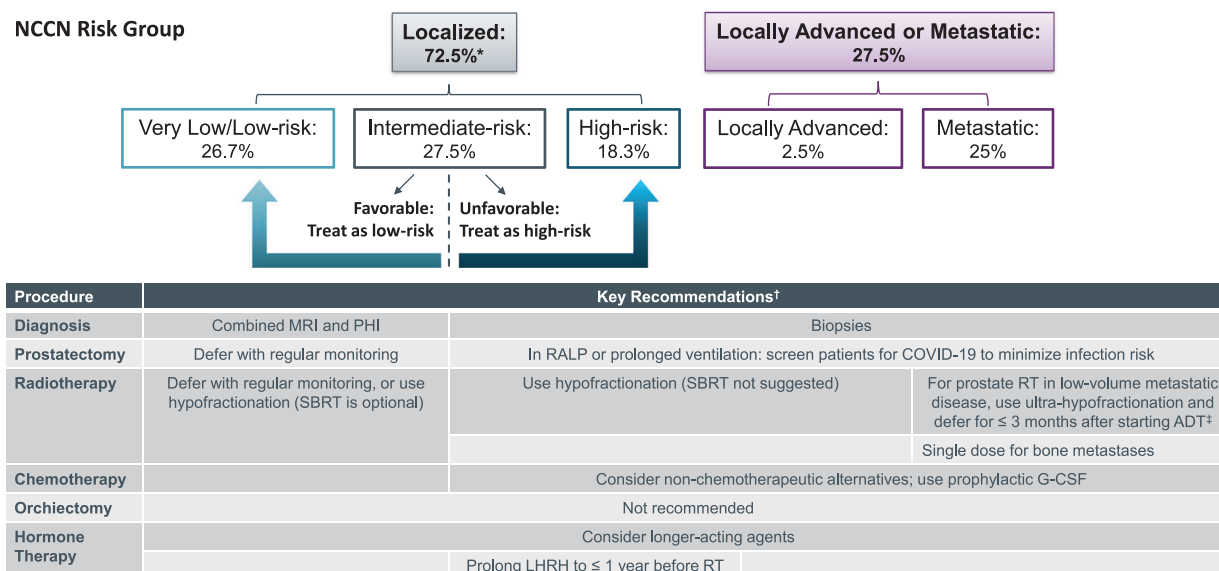


FIGURE 1 Prostate cancer stages and key management recommendations during the COVID-19 pandemic. *Estimated proportions at presentation, adapted from Chan et al.³⁷ †See Table 1 for details. ‡As in the STAMPEDE protocol.²⁷ Abbreviations: ADT, androgen deprivation therapy; COVID-19, coronavirus disease 2019; G-CSF, granulocyte colony-stimulating factor; LHRH, luteinizing hormone-releasing hormone; MRI, magnetic resonance imaging; NCCN, National Cancer Comprehensive Network; PHI, Prostate Health Index; RT, radiotherapy; RALP, robotic-assisted laparoscopic prostatectomy; SBRT, stereotactic body radiotherapy

contact with infected or suspected cases, travel history, and symptomatology beforehand (R1.3).

3.2 | Diagnostic procedures

During the COVID-19 pandemic, many places are currently experiencing shortages of medical and laboratory resources and supplies. Priority for diagnostic procedures should be given to patients who may be more urgently in need of starting treatment, which would also help to reduce infection risks.⁸ For PC, these are generally patients with suspected metastatic, locally advanced, or high-risk disease (R2.1).

The panel also came to a general agreement to reserve the use of invasive diagnostic procedures for patients with highly suspicious conditions,¹³ which are reflected by either a prostate-specific antigen (PSA) level of ≥ 20 ng/mL, a high PSA density, and/or an abnormal digital rectal examination result (R2.2). For patients whose PSA level is below 20 ng/mL,¹⁴ physicians may employ noninvasive diagnostic methods first, for example, using both magnetic resonance imaging (MRI) and the Prostate Health Index (PHI) (R2.3). If these do not provide clear results, further assessments, such as a urinary RNA analysis, may be undertaken before considering biopsy.¹⁵

3.3 | Localized PC

Most guidelines stratify localized PCs into low-, intermediate-, and high-risk categories.¹⁶ In low-risk patients (those with PSA < 10 ng/mL, Gleason score ≤ 6 , staged T1/T2), treatment may be temporarily deferred during the epidemic, when accompanied by regular monitoring¹⁷ (R3.1). PSA testing may be performed every 3 months; MRI scanning may be conducted yearly. Physicians are reminded that active surveillance plays an important role in the management of low-risk patients,¹⁸ and is highly recommended.

Treatment should not be delayed in high-risk patients, because their conditions require more immediate attention and they would most likely benefit from treatment (R3.2). Previous trials demonstrated that the efficacy was similar for short versus long courses of neoadjuvant androgen deprivation therapy (ADT),^{19,20} and a retrospective analysis suggested that high-risk PC patients who received > 24 months of ADT concurrent with RT had a lower risk of PSA failure.²¹ During this epidemic period, to defer the start of RT, the panelists suggested that before starting RT, ADT may be prolonged for up to 1 year. Surgeries should proceed while resources are adequate (eg, staffing and personal protective equipment).¹³

For intermediate-risk patients, to support clinical decision making during this period, the panel suggested adopting the US National

TABLE 1 Panel recommendations on prostate cancer management during the COVID-19 pandemic

Recommendation		Ref.
1. General considerations		
R1.1	In principle, PC diagnosis, treatment and management should continue to follow an evidence-based approach.	-
R1.2	Physicians should discuss with the patient any special medical arrangements made during the pandemic such as whether the patient would be willing to defer treatment.	[11]
R1.3	Because COVID-19 can be asymptomatic, infection control protocols should be closely followed during any diagnostic or therapeutic procedure, and the patient should be assessed for travel history and symptomatology beforehand.	[12]
2. Diagnostic procedures		
R2.1	Priority should be given to patients with suspected high-risk, locally advanced, or metastatic diseases.	[8]
R2.2	Invasive diagnostic procedures should be reserved for patients with highly suspicious conditions, that is, a PSA level of ≥ 20 ng/mL, high PSA density, and/or abnormal DRE results.	[13]
R2.3	For patients with PSA levels < 20 ng/mL, combined radiological (eg, MRI) and serological (eg, PHI) assessment is preferred. In case of uncertainty, further assessments, such as urinary RNA analysis, may also be undertaken before biopsy is considered.	[14]
3. Localized PC		
R3.1	For low-risk localized PC (PSA < 10 ng/mL, Gleason score ≤ 6 , staged T1/T2), treatment may be temporarily deferred and accompanied by regular monitoring such as PSA testing every 3 months and MRI scanning every year. As usual, active surveillance is important and highly recommended.	[17,18]
R3.2	In high-risk patients, treatment should not be delayed. When combining RT with ADT, the latter may be prolonged for up to 1 year before the commencement of RT. Surgeries should proceed while resources allow (eg, staffing and personal protective equipment).	[13,19–21]
R3.3	Intermediate-risk patients may be subdivided into those with favorable and unfavorable intermediate risks, as in the NCCN guideline, and managed as low- and high-risk patients, accordingly.	[18]
4. Metastatic PC		
R4.1	To reduce the infection risks associated with operative procedures, medical castration is preferred over surgical castration (orchiectomy). The pros and cons of LHRH agonists and antagonists should be discussed with the patient. Longer-acting agents may help to reduce the number of required hospital visits.	[22]
R4.2	Immunosuppression from chemotherapy may increase the risks of fever and infection. While chemotherapy can produce significant survival benefits in mHSPC patients, nonchemotherapeutic alternatives (eg, abiraterone and enzalutamide) should be considered. When administering chemotherapy, prophylactic G-CSF should be given to reduce the risk of febrile neutropenia.	[4,23,25,26]
R4.3	Ultrahypofractionated prostate RT (6 Gy in 6 weekly fractions) as in the STAMPEDE M1 RT protocol may be adopted for low-burden metastatic disease (see also R6.1).	[27]
5. Prostatectomy		
R5.1	Patients may be screened for COVID-19 before undergoing prostatectomy that involves prolonged ventilation or robotic-assisted laparoscopy, to minimize any added risk of respiratory and aerosol transmission.	[6,7,28,29]
6. Radiotherapy		
R6.1	Hypofractionation can reduce the frequency of patient visits and amount of hospital resources required. Ultrahypofractionation (ie, SBRT) may be used in patients with low- or intermediate-risk localized disease, or low-burden metastatic disease (see also R4.3 above).	[10,18,30]
R6.2	For palliative RT to bone metastases, single dose is preferred over fractionation.	[18]
R6.3	When using immobilization devices (eg, rectal balloons) and image-guiding implants (eg, fiducial markers), any potential for an increased risk of SARS-CoV-2 infection (eg, from contact and prolonged visits) should be considered.	[10]
7. Patient support		
R7.1	To ensure accessibility and responsiveness, some supplementary care services may be provided over the phone including follow-up calls, explanation of testing results, and treatment reminders.	[31]

(Continues)

TABLE 1 (Continued)

Recommendation		Ref.
8. Interdisciplinary collaboration		
R8.1	Interdisciplinary collaboration (urologists, oncologists, pathologists, anesthesiologists, etc.) remains vital during an epidemic, as diverse expertise is often needed for an effective response, and resources can be limited. To minimize the risk of infection, regular interdisciplinary meetings may be conducted through a secured web-based platform.	[32]

Abbreviations: ADT, androgen deprivation therapy; COVID-19, coronavirus disease 2019; DRE, digital rectal examination; G-CSF, granulocyte colony-stimulating factor; LHRH, luteinizing hormone-releasing hormone; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PC, prostate cancer; PHI, Prostate Health Index; PSA, prostate-specific antigen; RT, radiation therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBRT, stereotactic body radiotherapy.

Comprehensive Cancer Network distinction between favorable intermediate-risk and unfavorable intermediate-risk groups: favorable intermediate-risk patients are those with ≤ 1 intermediate-risk factor, Histological Grade Group ≤ 2 , and $< 50\%$ of biopsy cores that are positive; otherwise, intermediate-risk patients are in the unfavorable group.¹⁸ Favorable intermediate-risk patients may receive COVID-19 arrangements similar to those for low-risk patients, whereas unfavorable intermediate-risk patients may be treated more like high-risk patients (R3.3).

3.4 | Metastatic PC

The panel recommended medical over surgical castration during the epidemic, because they are associated with similar survival rates,²² but medical castration is noninvasive and provided on an outpatient basis (R4.1). The use of longer-acting medical castration agents may help to reduce the number of required hospital visits. The physician should discuss with the patient the pros and cons of the luteinizing hormone-releasing hormone agonists and antagonists, which will also help to address patient needs and concerns.

Chemotherapeutic agents are generally associated with high rates of hematological toxicity, such as neutropenia,²³ which may increase the risk of infection. While chemotherapy may provide significant survival benefits in patients with metastatic hormone-sensitive PC,²⁴ nonchemotherapeutic alternatives, including abiraterone and enzalutamide, are available and should be considered (R4.2). The prioritizing system for systemic anticancer treatments published by NICE may be helpful for assessing the risks and benefits of different options.⁴ Prophylactic granulocyte colony-stimulating factors can reduce the risk of developing chemotherapy-induced febrile neutropenia,²⁵ including in Chinese patients,²⁶ and should be prescribed during this period.

For low-volume metastatic PC, the latest STAMPEDE M1|RT results showed that prostate RT significantly prolonged overall survival.²⁷ During the COVID-19 epidemic, in these cases, ultrahypofractionation (6 Gy in 6 weekly fractions) may be used, and lifelong ADT may be started up to 3 months before RT, according to the STAMPEDE protocol (R4.3; see also section 3.6).

3.5 | Prostatectomy

While it is good clinical practice to apply a high level of infection control to surgery, the panelists noted two aspects of prostatectomy that may increase the risk of SARS-coronavirus-2 (SARS-CoV-2) infection within the operating theater or patient ward: prolonged ventilation and robotic-assisted laparoscopy. Prolonged ventilation may be required in patients suffering from certain respiratory conditions such as sleep apnea. There might be an increased risk of infection through contamination in the ventilation system or during intubation.²⁸ Second, robotic-assisted laparoscopy makes use of an artificial pneumoperitoneum, which is aerosol generating.^{6,7,28} Because SARS-CoV-2 is likely capable of airborne transmission,²⁹ caution should be exercised. When a prostatectomy involves any of these two aspects, the patient should be screened for COVID-19 beforehand (R5.1).

3.6 | Radiotherapy

Hypofractionated RT can be helpful for reducing the number of hospital visits. There has been growing evidence on the comparable efficacy and safety of hypofractionated versus traditional RT in localized PC.³⁰ Ultrahypofractionation (ie, stereotactic body RT) may be used in patients with low- or intermediate-risk localized or low-burden metastatic disease (R6.1; see section 3.4 above). Data on the use of ultrahypofractionation in high-risk patients are still lacking.^{10,30} For palliative RT to bone metastases, single dose is preferred over fractionation (R6.2), because of the comparable efficacies and reduced number of visits in the former.¹⁸

The use of immobilization devices (eg, endorectal balloons) and image-guiding implants (eg, gold seed fiducial markers) may require invasive procedures and extended hospital stays.¹⁰ The potential increased risk of SARS-CoV-2 infection should be considered (R6.3).

3.7 | Patient support

While there may be an infection risk associated with hospital visits, and patients may not find it convenient or safe to leave home in this

period, some supplementary care services may be provided to improve accessibility to healthcare.³¹ A simple way is to provide some services over the phone including follow-up calls, explanations of testing results, and treatment reminders (R7.1).

3.8 | Interdisciplinary collaboration

The epidemic can affect PC management in various ways and strain overall healthcare resources. Interdisciplinary expertise remains vital for developing comprehensive response strategies, accurate risk assessments, and effective workflow coordination (R8.1). To minimize the risk of infection, regular interdisciplinary meetings may be conducted through secured online platforms.³²

4 | DISCUSSION

It is worth noting that an evidence-based approach to medicine may become obscure during an epidemic. On the one hand, little is known about the severity and mortality of COVID-19 among cancer patients,³³ and there is no study evidence for treating suspected, infected, or discharged COVID-19 patients with PC. Our panel suggested following standard infection control protocols closely. Where there are preliminary data suggesting additional risks, such as the possibility of airborne SARS-CoV-2 transmission, extra caution may be taken. Cancer patients, if positive for COVID-19, should at least be treated with regard to their baseline characteristics including performance and immune statuses, demographics, and comorbidities. On the other hand, while following an evidence-based approach may not suffice for solving some present dilemmas, justification may be lacking if management deviates from usual practice. Our panel noted that, coincidentally, adopting the latest evidence-based medicine may itself be helpful toward optimizing a balance between infection risks and treatment outcomes. For example, adopting recent hypofractionation techniques for RT can reduce hospital visits, with similar efficacy and safety compared to conventional fractionation.

One important consideration during the pandemic for most PC patients after diagnosis is whether to defer surgery. Stensland et al.⁹ recommended that most prostatectomies should be delayed including up to 12 months for selected high-risk disease patients. The rationale was partly based on a retrospective analysis of 2653 patients,³⁴ which observed a small significant overall increase in biochemical recurrence at 5 years in patients who delayed RP; hazard ratio [HR] = 1.02; 95% confidence interval [CI]: 1.01-1.03, $P = .0005$). Nonparametric curve fitting suggested that the apparent worsened biochemical control was concentrated in high-risk patients who postponed RP beyond 12 months. Therefore, our panel recommended that prostatectomy for high-risk patients (including unfavorable intermediate-risk patients during this period) should proceed wherever possible.

There may be a concern that the selection of certain management modules over others will transfer the risk of infection from one team of healthcare professionals to another. For example, the choice of combined MRI scan and PHI test over biopsy may transfer the risk from the urology to the radiology team. Our panel agreed that biopsy is more invasive than MRI scan and PHI test, requires closer physical contact, and involves a longer hospital stay. However, it is possible that the radiology laboratory may be at an elevated risk of contamination from suspected COVID-19 patients undergoing chest imaging. Thus, some further risk assessments and discussions may still be needed, which highlights the importance of interdisciplinary collaboration during the epidemic.

These recommendations have some limitations. First, they apply to an urban setting where tertiary medical care is routinely available. It was assumed that resources have become constrained during the epidemic, but not severely deficient. If a worst-case scenario were to happen, these recommendations will provide a basis for action, but further adaptations will be needed. For example, if operating theaters become excessively contaminated, surgeries might need to be further deferred. Conversely, our panelists noted that infection control may be less difficult in privately operated hospitals than public ones due to a lower patient-to-staff ratio. Thus, some medical procedures may be somewhat less risky to perform in the private setting. Second, as our understanding of COVID-19 deepens, these recommendations can be further refined. For example, numerous reports have documented viral transmission through asymptomatic individuals,³⁵ as well as renewed viral positivity in the throat swabs of discharged patients.³⁶ When we understand these phenomena more clearly, our practices may need to change accordingly. Another possibility to consider is the development of a SARS-CoV-2 vaccine. If a vaccine becomes available, the suitability of vaccination in PC patients will also need to be determined.

5 | CONCLUSIONS

These practical recommendations cover various management modules for patients at different stages of PC during the COVID-19 pandemic. Clinicians working with PC patients may follow these recommendations, to minimize the risk of infection while avoiding unnecessary delays and compromises in management outcomes.

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AUTHOR CONTRIBUTIONS

The panel meeting was cochaired by WKM and DMCP. All authors participated in the panel meeting and read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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