Prostate cancer management challenges due to COVID-19 in countries with low-to-middle-income economies: A radiation oncology perspective

Desafíos de los países con economías de bajo-a-mediano ingreso para el manejo del cáncer de próstata por la pandemia por COVID-19: La perspectiva del Oncólogo Radioterápico

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Abstract

Description: The COVID-19 pandemic poses an unprecedented challenge for urologic oncology and radiotherapy. Radiation oncology departments and international collaboration groups are sharing their management adaptations made in response to the pandemic. The present narrative review summarizes the current recommendations.

Relevance: There is a need to define which patients are candidates for safe treatment delay until the pandemic is over or controlled, to reduce exposure to the virus in the healthcare personnel and patients.

Conclusions: Telemedicine is recommended for follow-up visits. Active surveillance is the preferred treatment for patients with favorable intermediate risk. In greater risk disease, hormone therapy safely postpones radiotherapy up to 7 months. Radiosurgery is suggested in centers that have the necessary technology and previous experience. A moderately hypofractionated regimen is recommended if radiosurgery/ultra-hypofractionation is not available. Hypofractionation should be implemented if image-guided radiation therapy is already in place. Countries with low and middle-income economies face challenges in adopting the recommendations for prostate cancer management during the pandemic. Postponing treatment may result in the overwhelming of radiation oncology center capacity, after the pandemic.

Keywords:
Developing countries, Radiotherapy, Prostate tumor, COVID-19

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Resumen

Descripción: El COVID-19 representa un desafío para la práctica de la urología oncológica y radioterapia. Departamentos y grupos de colaboración internacional de radio oncología están compartiendo sus adaptaciones de práctica en respuesta a la pandemia. Esta revisión narrativa resume las recomendaciones actuales.

Relevancia: Existe la necesidad de definir qué pacientes son candidatos para un retraso seguro en el tratamiento hasta que la pandemia termine o se controle, de forma que se minimice la exposición del personal de salud y de los pacientes.

Conclusiones: Se recomienda la telemedicina para visitas de seguimiento. La vigilancia activa es el tratamiento preferido para el riesgo intermedio favorable. En enfermedad de mayor riesgo, la hormonoterapia retrasa la radioterapia de forma segura hasta 7 meses. La radiocirugía se sugiere en centros con tecnología y experiencia previa. Se recomienda un régimen de hipofraccionamiento moderado si no se dispone de radiocirugía / ultra hipofraccionamiento. El hipofraccionamiento debe implementarse si las capacidades de IGRT ya están en su lugar. Los países de bajos y medianos ingresos enfrentan desafíos para adaptar las recomendaciones para el manejo del cáncer de próstata durante la pandemia. El aplazamiento del tratamiento puede exceder la capacidad de los centros de oncología radioterápica después de la pandemia.

Palabras clave:
Países en desarrollo, radioterapia, neoplasma prostático, COVID-19

Introduction

From the time the first patient was diagnosed with SARS-CoV-2 in Wuhan, China, incidence rates have risen rapidly in countries all over the world.[1] The current SARS-CoV-2 pandemic poses an unprecedented challenge for cancer management. Cancer patients have become a highly vulnerable population during the pandemic.[2] Oncologists need to ensure a safer approach and direct strategies to prevent the exposure of patients to the virus, while continuing to manage oncologic disease.[3] Of the cancer treatment services, radiotherapy faces a unique challenge in managing cancer patients during the pandemic, given that a majority of treatments need to be delivered daily.

There are unique radiotherapeutic considerations in the management of prostate cancer. Overall prognosis is generally favorable, enabling the delay of radiation in a selected population, in times of crisis.[4,5] Prostate cancer is the most common cancer in men. Although countries with high-income economies (HIEs) report higher incidence rates than countries with low and middle-income economies (LMIEs), the latter have higher mortality-to-incidence ratios.[6,7] Because more cases are

diagnosed in the late stage of disease, radiation treatment is fundamental in the management of those patients.[8] There is a pressing demand to define which patients require urgent or no-nurgent treatment (including a 2 to 4-month delay), until the pandemic is over, or at least controlled. [9,10]

The development of novel public health protocols and the consequent modification of cancer centers are both a challenge and an opportunity. Global initiatives to ensure adequate prostate cancer treatment are arising in response to the COVID-19 pandemic.[11,12] Nevertheless, health systems and cancer care facilities in the countries with LMIEs have particularities that need to be considered when providing a recommendation for oncology care, in response to SARS-CoV-2.

We summarize herein the available radiation therapy recommendations for prostate cancer during the pandemic and provide recommendations for their implementation in radiation oncology centers in countries with (LMIEs).

Methods

We conducted a search in the PubMed electronic database (via Medline) on April 11, 2020, that was supplemented by a review of journal articles in the COVID-19 portal of the American Society of Radiation Oncology (available at URL: https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Journal-Articles). No language or publication status restrictions were imposed. Date stipulations included studies published between December 2019 (according to the first diagnosis of the new SARS-CoV-2) and April 11, 2020 (date of the search). The search terms were "COVID-19" OR "SARS-CoV-2" AND "Cancer" OR "Neoplasm" OR "Tumor" AND "Radiotherapy." We included all articles reporting on practice recommendations for prostate cancer during the COVID-19 pandemic, as well as articles that considered multiple types of neoplasms, whenever they had specific prostate cancer recommendations. We excluded studies that did not include radiation therapy considerations and only assessed surgical or chemotherapy recommendations. Two of the authors (MC and SG) carried out the screening of titles and abstracts to minimize selection bias.

Results

Of the 2231 screened titles and abstracts, seven articles were selected. The analyses reviewed included 2 studies from international collaborations (multi-continent),[10,11] 1 national oncology guideline from Spain,[12] 2 national collaborations from Europe (Germany n=1, Italy n=1).[13,14] The remaining articles were institutional recommendations from two European countries (Switzerland and Italy).[15,16] No LMIE-based study met our inclusion criteria. Of the studies included, only two exclusively addressed prostate cancer.[11,12] General recommendations for facing the pandemic were also provided by all studies and are summarized in **Table 1.**

Four of the studies included presented prostate cancer recommendations by stage of the disease. Recommendations are presented in **Table 2** and the hypofractionation schedules in **Table 3**.

Table 1: Summary of recommendations

Author *Publication Date* *Institution* Country	Type of neoplasm	Practice recommendations for prostate cancer	General practice recommendations
Achard V et al. 2020.(16) Geneva University Hospital, Geneva, **Switzerland**	Multiple neoplasms	Hypofractionation, when feasible	Prioritization of treatments Postponement of non-vital procedures Postponement of nonessential visits
Portaluri M et al. 2020.[17] A. Perrino Hospital **Italy**	Multiple neoplasms	Postoperative RT: two-week postponement Prostate cancer under ADT*: two-week postponement	Postponement of control visits Reduction of treatments per day (3 sessions per hour)
Filippi AR et al. 2020.[15] Multiple institutions **Italy**	Multiple neoplasms	Delay RT for low/intermediate risk prostate disease	Adopt hypofractionated schedules Postponement of follow-up visits
Simcock R et al. 2020.[11] Radiation Oncology Journal Club Community **International collaboration**	Multiple neoplasms	Omit RT in low and favorable intermediate risk Omit RT for oligometastatic prostate cancer	Telephone follow-up and/or consultation Prioritization of treatments Postponement of radical treatments when biology permits the delay
Zaorsky NG et al. 2020.[12] International collaboration **United States – United Kingdom**	Prostate	Delay RT for very low, low, and favorable intermediate-risk disease Use ADT to delay RT for 4-6 months in unfavorable intermediate-risk, high-risk, N+, postoperative recurrence, oligometastatic, and low-volume M1 disease.	Remote visits Avoid radiation Postpone radiation Shorten radiation
Combs SE et al. 2020.[14]Multiple institutions **Germany**	Multiple neoplasms	Consider hypofractionated regimens Delay RT with ADT or active surveillance in low risk disease. Delay RT with ADT for 2 to 3 months in intermediate-risk or high-risk disease Consider watchful waiting or ADT in salvage situations	Personnel, patient, and device hygiene Implementation of a management team Division of management team (50% on site, 50% off site) Identify and treat critical cases (ensure triage for SARS-CoV-2)
Gomez-Iturriaga A et al. 2020.[13] URONCOR – SEOR **Spain**	Prostate	Delay RT treatment (3-12 months) for very low, low, and intermediate favorable risk. Consider active surveillance. Use hypofractionated regimen (SBRT or ultra-hypofractionation) † Unfavorable intermediate, high, and very high-risk: start ADT (use as neoadjuvant treatment to delay RT 2 to 6 months)	During the pandemic: Avoid hospital visits (telemedicine for follow-up, in-treatment, and first consultation visits) Delay PSA control for 3-6 months

ADT: Antigen Deprivation Therapy, AS: Active Surveillance, Fx: Fraction. PSA: Prostate-Specific Antigen. RT: Radiation Therapy. SBRT: Stereotactic Body Radiation Therapy.
*No other specification
† If previous experience and available technology

Table 2: Treatment modality by disease status

Disease status	*Recommended treatment during the pandemic*				*Evidence/guidelines cited*
	AS	*WW*	*ADT*	*EBRT*	
Very low and low risk					
Combs SE *et al*. 2020	Recommended treatment	Life expectancy <10 years T1- 4 GS=7	Recommended	Delay	NCCN prostate cancer guidelines.[18]
Gómez-Iturriaga A *et al*. 2020		Not recommended	Not recommended	Delay (3 to 12 months)	
Zaorksy NG *et al*. 2020				Not recommended	
Simcock R *et al*. 2020				Not recommended	
Favorable intermediate risk					
Gómez-Iturriaga A *et al*. 2020	Recommended	Not recommended	Not recommended	Delay	
Zaorksy NG *et al*. 2020	Recommended			Delay	
Simcock R *et al*. 2020	Recommended (3-6 months PSA testing)		ADT if RT indicated*	Delay (3 to 6 months)	ProtecT trial - Neal DE *et al.*[19]
Unfavorable intermediate risk					
Gómez-Iturriaga A *et al*. 2020	Not recommended	Not recommended	ADT+RT (can delay RT for 2-6 m)	Delay	DART01/05 GICOR- Lancet Oncol–2015.[20]
Zaorksy NG *et al*. 2020			ADT + RT (can delay RT for 6 m)	36.25-40 Gy / 5 Fx † or 60 Gy/20 Fx	
High and very high risk					
Combs SE *et al*. 2020 IR - HR	Not recommended	Not recommended	RT+ADT (can delay RT for 2-3 m)	60 Gy / 20 Fx Or 42.7 Gy/ 7 Fx every other day (if age < 75 y)	EORTC 22991-JCO 2016.[21] CHHiP 2016-2017.[22] HYPO-RT-PC.[23]
Zaorksy NG *et al*. 2020			RT+ADT (can delay RT 4-6 m)	36.25-40 Gy / 5 Fx † or 60 Gy/20 Fx	Morris–ASCENDE-RT- Int J Radiat Oncol Biol Phys–2017 Pisansky Tm–JCO-2015
Simcock R *et al*. 2020			RT+ADT (can delay RT 2-4 m)	Delay treatment	DART01/05 GICOR - Lancet Oncol 2015.[20]
N+					
Gomez-Iturriaga A *et al*. 2020	Not recommended	Not recommended	ADT+RT (can delay RT for 2-6 m)	60 Gy/20 Fx (daily)	Abdollah F - Eur Urol. 2018.[24] Lieng H-Radiother Oncol–2019.[25]
Zaorksy NG *et al*. 2020			ADT + RT (Can delay RT 4-6 m)	36.25-40 Gy/5 Fx or 60 Gy/20 Fx	
Post-prostatectomy/salvage					
Combs SE *et al*. 2020	Not recommended	Recommended (or ADT)	Recommended (or WW)	52.5 Gy/20 Fx	NCCN Guidelines.[18] Chin –RED Journal -2020.[26]
Gomez-Iturriaga A *et al*. 2020		Not recommended	ADT+RT		Gonzalez San Segundo C – Eur Urol- 2019.[27] RADICALS Chin –RED Journal -2020.[26]
Zaorksy NG *et al*. 2020			RT+/-ADT (can delay RT 4-6 m)		Chin et al. RED Journal 2020.[26]
Simcock R *et al*. 2020			Recommended (2-4 m)	Delay treatment	Ghadjar P-Strahlenther Onkol–2018.[28]

ADT: Antigen Deprivation Therapy, AS: Active Surveillance, ASTRO: American Society of Radiation Oncology, EBRT: External Beam Radiation Therapy, FIR: Favorable Intermediate Risk, Fx: Fraction, GS: Gleason Score, HR: High Risk, m: months, N+: regional lymph node involvement, PSA: Prostate Specific Antigen, RT: Radiation Therapy, UIR: Unfavorable Intermediate Risk, VLR: Very Low Risk, WW: Watchful Waiting, y: years.

1Published on behalf of the European Society of Radiation Oncology.
2Published on behalf of the American Society of Radiation Oncology
*: For patients requiring RT: delay initiation of ADT for 2-3 months (can extend ADT up to 8 months) can safely delay RT for 4-5 months.
†: Preferred (for centers not able to perform image guidance (cone-beam CT with or without fiducial markers), a 20-fraction regimen can be utilized from 60 to 62 Gy).

Table 3: Summary of hypofractionation regimen recommendations

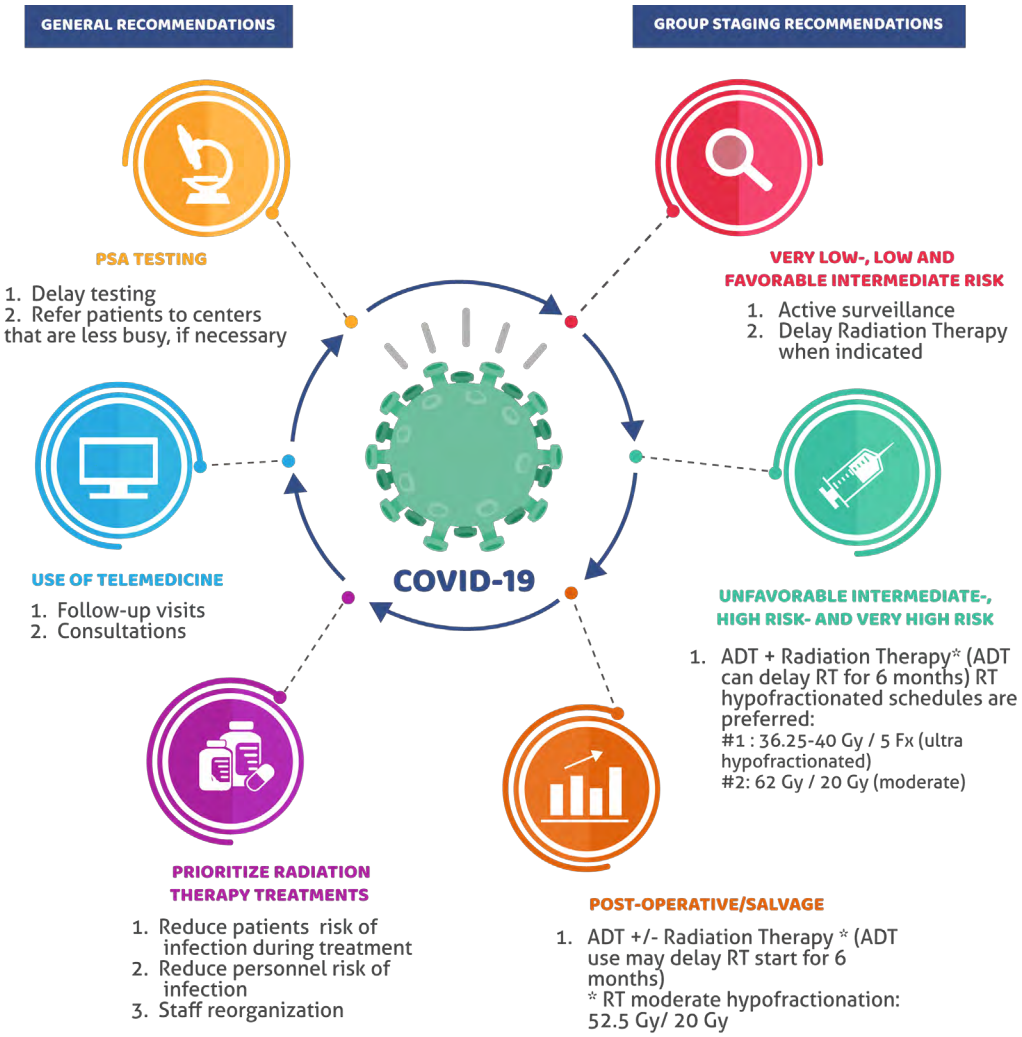
Schedule	*Dose / Fraction*	*Risk*						
		Low	*Intermediate*	*High*	*N+*	*Low volume M1*	*Adjuvant /Salvage*	*Evidence*
Moderate hypofractionation								
Combs SE *et al*. 2020	60 Gy/20 Fx (daily)	-	Yes	Yes	-	-	-	
Zaorsky NG *et al*. 2020		-	Yes	Yes	Yes	-	-	
Gomez- Iturriaga A *et al*. 2020		Yes	Yes	Yes	Yes	Yes	-	
Simcock R *et al*. 2020		Yes	Yes	Yes	-	-	-	CHHiP 2016–2017.[22] PROFIT
Combs E *et al*. 2020	52.5 Gy/20 Fx (daily)	-	-	-	-	-	Yes	Chin *et al*–Red Journal–2020.[26] RADICALS
Zaorsky NG *et al*. 2020		-	-	-	-	-	Yes	
Gomez- Iturriaga A *et al*. 2020		-	-	-	-	-	-	
Simcock R *et al*. 2020		-	-	-	-	-	Yes*	
Ultra-hypofractionation								
Combs SE *et al*. 2020	42.7 Gy/7 Fx (every other day)	-	Yes (Age <75 y)	Yes (Age <75y)	-	-	-	
Zaorsky NG *et al*. 2020		-	-	-	-	-	-	
Gomez- Iturriaga A *et al*. 2020		Yes	Yes	Yes				
Simcock R *et al*. 2020			Yes (T1c-3a, PSA 20 or less)	Yes (T1c-3a, PSA 20 or less)	-	-	-	
Zaorsky NG *et al*. 2020	36 Gy/6 Fx (1 Fx per week)	-	-	-	-	Yes	-	STAMPEDE.[29]
Simcock R *et al*. 2020		-	-	Yes (Age >75, or >70 with moderate comorbidity)	-	Yes	-	
SBRT								
Zaorsky NG *et al*. 2020		-	Yes	Yes	Yes	-	-	
Gomez- Iturriaga A *et al*. 2020		Yes	Yes	Yes	-	-	-	
Simcock R *et al*. 2020	36.25–40 Gy/5 Fx (alternate days)	Yes	Yes	Yes	-	-	-	MSKCC NRG GU005 (Phase III ongoing) NCCN.[30]

Fx: Fraction, N+, regional lymph node involvement, PSA: Prostate-Specific Antigen.

* Post-prostatectomy, fossa only

Finally, we presented a summary of treatment recommendations focusing on LMIE populations (**Figure 1**). It includes general recommendations, stage group-specific recommendations, and follow-up consultation guidance (Telemedicine).

Figure 1: Summary of recommendations for prostate cancer management during COVID-19



ADT: Androgen Deprivation Therapy, PSA: Prostate-Specific Antigen. *SBRT/Ultra-hypofractionation schedules should be performed only in centers with previous experience and available technology.

Discussion

As the coronavirus pandemic continues to rise, new recommendations for the delivery of radiation therapy in prostate cancer are being developed. Radiation oncology departments in countries highly affected by SARS-CoV-2, such as Italy, are sharing their practice adaptations,[16,17] and international radiation therapy collaboration groups and societies are providing new guidelines.[11–13] Recommendations have been modeled after North American and European standards, but countries with LMIEs have had no significant representation in their development. To the best of our knowledge, no radiation oncology guidelines in countries with LMIEs have yet been issued. In this brief review, we have summarized recommendations and provided considerations for their implementation in LMIEs (**Figure 1**). In response to the unique and highly contagious behavior of COVID-19, most articles have included general recommendations for facing the pandemic, which include consultation/follow-up and unique treatment recommendations.

Overall, telemedicine for follow-up and in-treatment visits is being implemented.[11,15] Telemedicine has previously been described as an effective alternative in prostate cancer for follow-up visits[31] and it is crucial during the COVID-19 pandemic. To ensure its implementation, insurance services are including teleconsulting in their coverage (i.e., Medicare in the US). Concerns in countries with LMIEs arise, given the weaker health systems and lack of national and international guidelines with telemedicine regulations.[32,33] Previous studies on mobile health for cancer in countries with LMIEs have not shown the promising results observed in HIE settings, and so additional efforts will need to be taken by the radiation oncologist to implement telemedicine in those LMIEs.[33,34] Remote treatment planning is a safe strategy for reducing exposure of the medical staff (radiation oncologists, medical physicists, nurses) to the virus. However, the lack of software for remote treatment planning in countries with LMIEs lowers its feasibility during the pandemic, and radiotherapy administrators must try to provide and enhance the capacity of their centers to work remotely.

Prioritizing treatments as a critical strategy to reduce the number of patients and daily treatments per machine is being applied to other neoplasia in general radiation oncology practice.[9,11,15,35] Prostate cancer is unique, as its usual progression permits safe treatment delay. Disease staging (risk groups) is critical for defining the suitability of the patient for treatment delay or postponement that will not compromise the oncologic outcome. In early-stage disease, current practice promotes active surveillance as the preferred treatment in very low and low-risk disease (Table 2).[18] Although current guidelines do not have a preferred treatment during the pandemic in relation to favorable intermediate-risk disease, active surveillance is being adopted as the recommended modality, given that it has previously been shown to be a safe approach.[11–13,19] Because active surveillance requires periodic prostate-specific antigen (PSA) testing, patients should be referred to laboratories and centers that are less busy, to minimize their risks for exposure and infection.

Recommendations for advanced disease are particularly relevant in countries with LMIEs, where most patients are diagnosed in later disease stages and radical treatment is almost always imperative.[7,36] For unfavorable

and high-risk disease, radical treatment with radical prostatectomy or radiotherapy is usually required. Androgen deprivation therapy can be used to delay the start of said treatment. Recommendations for the duration of neoadjuvant ADT vary, with a maximum acceptable delay of 6 to 7 months, based on the previously published RTOG 9910 trial.[37] Because a delay of 7 months is safe, schedules that reduce the number of hospital visits, such as 6-month subcutaneous delivery systems, are preferred.[38,39] The availability of ADT could be more challenging in low-resource settings. We recommend that professionals keep a record of postponed treatments and ensure that all patients are safely getting the proper ADT doses.

Even before the current pandemic, radiotherapy for prostate cancer was developing towards hypofractionated schedules.[40,41] During the SARS-CoV2 pandemic, that has become more relevant, so that the exposure of patients and medical staff to the virus can be reduced.[11–14,16] Ultra-hypofractionated radiotherapy is preferred for localized disease in the new recommendations (Table 3).[11–14] Only two of the authors included in the review assessed the possible lack of technology and considered a 20-fraction regimen that could be used in centers with no image-guided radiation therapy (IGRT) or previous experience in ultra-hypofractionation.[12,13] Very few radiotherapy centers in countries with LMIEs have the technologic capacity and the necessary devices to administer ultra-hypofractionation in prostate cancer.[42] Furthermore, the use of non-modulated three-dimensional conformal radiation therapy (3D-CRT) is not supported for the delivery of moderate hypofractionation. We believe hypofractionated schedules should be started if IGRT capacities are already in place,[43] but even though hypofractionation is beneficial in reducing the number of hospital visits, it should not be implemented in centers that do not have previous experience or when high treatment conformation cannot be guaranteed.[12,13]

If IGRT is available, moderate hypofractionation is now more feasible in radiation oncology centers in countries with LMIEs. Hypofractionation should be a priority in those countries, not only during the present situation but afterwards, as well, because it enables broader machine availability and increases the capacity of the radiation oncology services.[44] The adoption of the recommendations presented herein involves treatment postponement for most prostate cancer patients. Thus, after the crisis, the capacity of radiation therapy facilities may be overwhelmed.[11,45] That situation becomes even more challenging in LMIE settings that have lower machine capacity and human workforce per capita, with one linear accelerator for 5 million inhabitants, compared with one for every 120,000 inhabitants in countries with HIEs.[44,46]

We suggest the following key points for implementing the newly formulated recommendations for prostate cancer during the pandemic in countries with LMIEs:

1. Consider hypofractionation regimens in intermediate and high-risk patients that require treatment. In centers with experience, stereotactic body radiation therapy (SBRT) can be considered. If available, we suggest the use of IGRT with daily cone beam imaging or daily kV imaging (with larger planning target volume (PTV) margins and no fiducials, to reduce invasive procedures during the pandemic).

2. Remote treatment planning is a safe strategy for reducing exposure of the medical staff to the virus. Lack of software for remote treatment planning in countries with LMIEs lowers its feasibility. Radiotherapy administrators must make further efforts to provide and enhance the capacity of their centers to work remotely.
3. Stay updated on local data, estimating the peak of the pandemic, to decide when to delay or postpone treatment.
4. Keep a strict record of patients that are candidates for treatment postponement.
5. Provide a special informed consent statement, in which patients understand the risk and benefits of treatment postponement.
6. Make sure the patients have access to ADT. The availability of ADT could be more challenging in countries with LMIEs. Employ administration schedules that reduce the number of hospital visits.
7. Establish communication and work strategies with other local or national centers. Collaboration between centers can help in the response to staff reorganization or medical staff illness.

The aim of the present narrative review was not to change clinical practice, given that it does not follow a systematic review or clinical practice guideline methodology that evaluates quality and strength of recommendations (the GRADE system), but rather to provide radiation oncologists with a broad picture of the current recommendations and our own considerations for their implementation in low-to-middle-income economic settings.

Conclusion

Countries with LMIEs face significant challenges for adopting the present recommendations in relation to prostate cancer management during the SARS-CoV-2 pandemic. Of those recommendations, moderate hypofractionation is now more feasible, but it should only be implemented if IGRT capacities are already in place. Major challenges await due to the fact that treatment postponement could lead to the overwhelming of radiation oncology center capacity, once the pandemic has been controlled.

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