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## Management of prostate cancer radiotherapy during the COVID-19 pandemic: A necessary paradigm change

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### ABSTRACT

**Purpose:** To adapt the management of prostate malignancy in response to the COVID-19 pandemic.

**Methods:** In according to the recommendations of the European Association of Urology, we have developed practical additional document on the treatment of prostate cancer.

**Results:** *Low-Risk Group* Watchful Waiting should be offered to patients >75 years old, with a limited life expectancy and unfit for local treatment. In Active Surveillance (AS) patients re-biopsy, PSA evaluation and visits should be deferred for up to 6 months, preferring non-invasive multiparametric-MRI. The active treatment should be delayed for 6–12 months. *Intermediate-Risk Group* AS should be offered in favorable-risk patients. Short-course neoadjuvant androgen deprivation therapy (ADT) combined with ultra-hypo-fractionation radiotherapy should be used in unfavorable-risk patients. *High-Risk Group* Neoadjuvant ADT combined with moderate hypofractionation should be preferred. Whole-pelvis irradiation should be offered to patients with positive lymph nodes in locally advanced setting. ADT should be initiated if PSA doubling time is < 12 months in radio-recurrent patients, as well as in low priority/low volume of metastatic hormone sensitive prostate cancer. If radiotherapy cannot be delayed, hypo-fractionated regimens should be preferred. In high priority class metastatic disease, treatment with androgen receptor-targeted agents should be offered. When palliative radiotherapy for painful bone metastasis is required, single fraction of 8 Gy should be offered.

**Conclusions:** In Covid-19 Era, the challenge should concern a correct management of the oncologic patient, reducing the risk of spreading the virus without worsening tumor prognosis.

### Introduction

The COVID-19 pandemic is unlike anything seen before by modern science-based medicine. In order to treat patients safely while protecting medical teams, the entire health care system must optimize the way it approaches prevention and treatment at a time when social distancing is the key player to fight against COVID-19 pandemic.

Prostate cancer (PCa), which is frequently treated with radiation, is the most common solid tumor in men; it is a heterogeneous disease where timely therapy is indicated for some cases, and where watchful

waiting, active surveillance, or deferral of treatment could be acceptable for others [1–3].

We have a duty to avoid unnecessary outpatient visits and in doing so reduce the chance of virus transmission. All indications and treatment modalities must be re-discussed. Increasing use of Telehealth with video visits or phone calls may be an important way to continue to support patients and their careers during this crisis. This approach allows to reduce hospital admissions and risk of infections using a RADS framework (Remote visits, and Avoidance, Deferment and Shortening of radiation therapy) but it cannot be applied to all patients. Those with

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LOW PRIORITY	INTERMEDIATE PRIORITY	HIGH PRIORITY	EMERGENCY
Clinical harm very unlikely if postponed 6 months	Clinical harm possible if postponed 3-4 months but unlikely	Clinical harm very likely if postponed > 6 weeks	Life threatening situation.

Fig. 1. Levels of priority.

Modified from EAU recommendations [4]

unfavorable risk class or with metastatic disease presenting new symptoms may need a physical evaluation.

Our goal is to minimize the risks of infection for both patients and health professionals delivering urological care whenever possible, although it is not always possible to mitigate it entirely. It should be understood that there may not be high quality evidence for the compromises proposed, but we hope this document will function as an important additional guide, to the management of urological conditions during the current COVID-19 (Coronavirus disease 2020) pandemic.

## Methodology

The European Association of Urology (EAU) recently published recommendations on possible modification to latest Guidelines 2020 [4], we utilize same levels of priority to adapt our treatment flowchart; this classification is resumed in a color-coded risk stratification tool (Fig. 1).

As PCa is a heterogeneous disease and most hospitals worldwide are affected by COVID-19, prioritization of cases could take advantage of stratification into risk classes.

## Localized prostate cancer

### Low risk

According to 2009 TNM classification for staging PCa and to EAU risk group classification, low risk PCa is defined as a disease characterized by cT1–2a and GS < 7 and PSA < 10 ng/ml.

For low risk PCa the therapeutic strategies can include Watchful Waiting (WW), Active Surveillance (AS) or active treatment which can consist of Radical Prostatectomy (RP) or Radiation Therapy (RT). WW aim is to avoid an active treatment and can be considered for those patients with a limited life expectancy (< 10 years). Patients on WW are treated only when symptoms appear, with a palliative purpose. Two randomized trials, the SPCG-4 and the PIVOT trial [5,6], compared WW and RP for low risk patients, defined as patients >75 years, affected by cT1–2 PCa and with PSA levels < 50 ng/ml. An important limit of these trials is that 50% and 35% of patients, respectively, have an intermediate or high-risk disease, according to the new system of classification. Even with this limitation, both trials show no significant difference between the two arms of treatment, in terms of overall survival (OS) and cancer specific survival (CSS).

Therefore, during the Covid pandemic, WW seems the best therapeutic option to offer to patients >75 years old, with a limited life expectancy and unfit for local treatment, considering the need to reduce the hospital access.

AS is a well-established approach which allows the deferment of surgery or radiotherapy, and is characterized by a low risk of PCa mortality [7]. The ProtecT trial, at 10 years of follow-up, demonstrates that PCa death in patients affected by clinically localized disease and randomized to AS, surgery or radiotherapy was about 1% irrespective of the treatment assigned [3], although in a recent pooled analysis those in AS showed a modest increased risk of dying for PCa [8]. The EAU strongly recommends AS for low risk patients with a life expectancy > 10 years [4]. In order to better identify baseline risk allocation of PCa patients, multiparametric-MRI (mp-MRI) is being introduced in AS protocols [9]. During the follow-up, mp-MRI might reduce the number

for serial biopsies [10]. In 2019, the UK National Institute for Care and Clinical Excellence (NICE) recommended mp-MRI for all patients inactive surveillance as well as the EAU, which specify that in case of negative follow-up mp-MRI with long PSA doubling time, repeated biopsy could be omitted.

According to EAU COVID-19 recommendations [11], re-biopsy, PSA evaluation and follow-up visits should be deferred for up to 6 months in AS patients, to reduce the risk of virus transmission. We believe that follow-up mp-MRI should be used in this setting during the COVID-19 pandemic: it is a non-invasive and cost-effective procedure, which allows the whole-gland evaluation detecting disease progression and overcoming the anxiety experienced by PCa patients, caused by their state of neoplastic disease during this world pandemic crisis [12]. Moreover, mp-MRI instead of repeated biopsy could reduce the risk of COVID-19 transmission.

In addition to the ProtecT trial, many other studies compared AS to active treatment (surgery or radiotherapy). PIVOT is one of several randomized trials evaluating active versus conservative strategies for localized prostate cancer [1]. These trials demonstrated that among men with low-risk disease, there is an absolute small reduction in terms of all-cause mortality (< 5 months) for patients undergone active treatment. Dell'Oglio et al. confirmed no advantage in terms of OS for well differentiated localized prostate cancer patients, identified in the Surveillance, Epidemiology, and End Results (SEER) Medicare linked database, treated with either RT or observation between 1991 and 2009 [13]. Thomsen et al. enrolled patients to AS vs RP and no significant difference in terms of CSS was demonstrated [14]. Moreover, AS did not negatively influence patients' Quality of Life (QoL) and did not increase the anxiety and stress levels [15,16].

Considering this, we strongly recommend that patients subjected to active treatment should be encouraged to have treatment deferred for 6–12 months.

### Intermediate risk

Intermediate risk prostate cancer patients can be divided into two prognostic groups, favorable and unfavorable, depending on specific intermediate risk factors (cT2b-T2c; PSA 10–20 ng/ml; Grade group 2–3) [17].

To choose the best clinical approach in these patients during the COVID-19 pandemic, it can be used a RADS framework as mentioned above. In the favorable intermediate risk group several clinical trials with a follow-up  $\geq 10$  years demonstrated that active surveillance is considered feasible and safe [3,18].

Unfavorable risk intermediate prostate cancer has survival rates similar to the high risk, so patients in both of these groups need an active treatment [19]. Regarding radiotherapy as an active treatment for localized PCa, several trials demonstrated the non-inferiority of moderate hypofractionation (60 Gy in 20 daily fractions) compared with conventional fractionation (74–78 Gy in 37–39 daily fractions) [20,21]. In the COVID-19 era, it is necessary to reduce hospital admissions in order to limit virus transmission. Short-course (6 months) neoadjuvant androgen deprivation therapy (ADT), which is part of the treatment strategy in unfavorable intermediate risk [22], allows for the start of radiotherapy to be delayed. The excessive prolongation of ADT use in this setting may increase the risk of morbidity (e.g. cardiovascular events), without influencing oncological outcome [23].

However, considering that ADT is protecting men to a certain extent to get serious complications from COVID19, this should be recommended for all unfavorable intermediate risk prostate cancer patients, such as those patients with a rapid PSA doubling time ( $\leq 3$  months). When ADT cannot be prescribed, as in case of high cardiovascular risk, a neoadjuvant hormonal regimen with bicalutamide should be considered. As shown by the CHHiP trial, 6 months bicalutamide is equivalent to LHRH therapy with less cardiac side effects [20]. Our conclusion is that the benefits of neoadjuvant ADT outweigh side effects. For what concern

radiotherapy regimen, ultra-hypofractionated (UHF) scheme should be considered.

In 2020, the National Comprehensive Cancer Network (NCCN) guidelines included UHF as a treatment option in intermediate risk patients, based on several recent randomized trials [24,25]. In agreement with the American Society of Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA), the UHF schedule contemplates 5- to 7-fractions with a single dose  $\geq 5$  Gy [26].

Two randomized phase 3 non-inferiority clinical trials compared UHF to conventional fractionation or moderate hypofractionation. The HYPO-RT-PC trial demonstrated that UHF (42.7 Gy in 7 fractions, 3 days per week) is non-inferior to conventionally fractionated radiotherapy, for intermediate-to-high risk prostate cancer, in terms of failure-free survival, reporting however early outcomes at 5 years. Early toxicity resulted increased in UHF arm but 5-year late side effects were similar in both treatment groups [25].

Instead PACE-B trial shows that UHF (36.25 Gy in 5 fractions over 1–2 weeks) has the same acute toxicity profile of conventional fractionation (78 Gy;  $39 \times 2$  Gy) or moderate hypofractionation (60 Gy;  $20 \times 3$  Gy), although results about late toxicity and clinical/biochemical recurrence are not yet available [24].

In conclusion, during the Covid pandemic, we should practice telehealth whenever possible. AS should be offered in favorable risk patients. Short-course neoadjuvant ADT combined with UHF should be considered in unfavorable risk patients informing them about the risks and data available in literature. In fact, neoadjuvant ADT allows to reduce outpatient care, furthermore a recent study evidenced that ADT might have a protective effect against COVID-19 infection regulating TMPRSS2 protein expression [27].

#### High risk and locally advanced

Locally advanced PCa (including cN1), as lately stated in EAU guidelines recommendations for COVID-19 [11], has to be considered as a high priority class of disease, for both clinical harm (very high risk of progression and metastases) and cancer related death (very likely if treatment is postponed longer than 6 weeks).

Neoadjuvant ADT (with preference for longer formulation, 3 or 6 months), followed by delayed external beam radiotherapy (EBRT) (6–12 months after) is a valid alternative to surgery for this setting [28].

The shortest safe EBRT regimen (which can include ultra-hypofractionation in 5 to 7 fractions) should be offered according to the 2020 NCCN guidelines, for patients without clinical lymph nodes involvement [29].

The EAU recommendation also suggests avoiding invasive procedure such as fiducial markers and/or rectal spacers placement [11]. Based on recent published trials (HYPO-RT and PACE-B) that showed very good rates of toxicity without necessarily using these devices, especially rectal spacers [24, 25]. Twenty-seven percent of patients in the SBRT arm of the PACE-B trial were treated without fiducial markers, only 10% for UHF arm in the HYPO-RT, and for both trials rectal spacers were not applied. Nevertheless, for centers unable to perform IGRT, especially when fiducial markers are not implanted, moderate hypofractionation (60 in 20 fractions) should be preferred [20]. Results in terms of clinical outcomes of the PACE-B trials are eagerly awaited as well as longer follow-up data of the HYPO-RT (only 5 years follow-up has been published so far).

The benefit of pelvic nodal irradiation is really controversial and there are conflicting results in literature. RTOG 9413 demonstrated a progression-free survival (PFS) benefit with neoadjuvant/concurrent ADT and whole pelvis radiotherapy (WPRT) in patients with  $\geq 15\%$  risk of lymph node metastasis. A secondary analysis confirmed this result emphasizing the importance of a comprehensive nodal treatment in this subset of patients. On the other hand, GETUG-01 reported that the 5-year PFS and OS were not significantly different in the two treatment

arms analyzed (WPRT vs prostate-only RT). However this trial has been criticized for using low doses and also because one-half of patients had a risk of lymph node involvement  $\leq 15\%$ . Further information will be provided by RTOG 0924, a phase III trial in which high-risk or locally advanced prostate cancer patients are treated with ADT in association with either prostate-only RT or WPRT. Nevertheless, in the COVID-19 era prophylactic whole-pelvis radiotherapy should be carefully evaluated for each patient due to an augmented risk of developing lymphopenia.

*In conclusion, during the Covid pandemic, neoadjuvant ADT combined with moderate hypofractionation or UHF (for selected cases) should be used in high-risk patients. Whole-pelvis irradiation should be offered only to patients with positive lymph nodes.*

#### Prostatectomy

Many studies have shown advantage in survival, for men with unfavorable intermediate risk and high risk cancers, when receiving either radical prostatectomy or radiation therapy plus ADT, compared with watchful waiting.

The ProtecT trial is the only randomized trial which compared RP to RT for low and intermediate risk PCa patients and did not show a significant difference in terms of OS and CSS [3]. Most debated is the role of RP for high risk and locally advanced PCa because of the high rate of positive margins, PSA relapse and the consequent need for further treatments. Recently the Systematic Review and Meta-Analysis of Wang et al. shows that RP is associated with better OS and CSS compared to RT for high risk PCa patients, while RT shows better results in terms of Biochemical Relapse Free Survival (BRFS) and Metastases Free Survival (MFS) [30]. Despite this, on a subgroup analysis RT was associated with better OS and CSS in patients with high GS, high T Stage and treated with EBRT + Brachytherapy (BT).

Few studies found that time from diagnosis to treatment was not significantly associated with an increased risk of biochemical and clinical recurrence, or at least they had an increases recurrence rate, in high risk patients only, and at around 12 months after diagnosis [31,32].

During the Covid-19 pandemic we have to consider the dramatic reduction in operating room for urological procedures, so that all urology centers have been to prioritize surgical intervention for cancer patients. Very important as suggested by Campi et al., is the selection of patients, in order to refer to other options those patients with a high perioperative risk, that would require potentially longer hospitalization and a post-operative intensive care [33]. As Ficarra et al. stated, an implementation of non Covid-Hospital and the creation of hospital networks should be encouraged in order to ensure a safe surgery for non-deferrable or semi non-deferrable urological procedures such as RP [34].

#### Prostatectomy could be postpone until after the covid pandemic

##### PSA relapse after local treatment

Concerning the setting of PSA relapse, we suggest to defer diagnostic imaging until after the pandemic for low priority patients, while the previously performed treatment should be considered for those with higher priority.

As a general rule, early salvage radiotherapy is a preferable option over adjuvant radiotherapy after radical prostatectomy. Such therapeutic strategy, which has been recently significantly sustained by the evidence coming from RAVES and RADICALS [35,36], represents an even more valid approach in a pandemic scenario [37].

Salvage EBRT should be offered to patients with EAU high risk BCR (biochemical recurrence); alternatively, a combination of ADT and EBRT could constitute a reasonable therapeutic approach to be adopted after the pandemic in the same group of patients.

As it is for primary tumor, hypofractionated RT regimens should be preferred also in the post-prostatectomy setting (NCT00541947) [38], in

**Table 1**  
recommendations and current evidence.

Treatment of localized prostate cancer: Low risk			
	Low Priority	Intermediate Priority	High Priority
Definition	<ul style="list-style-type: none"> <li>• <math>\hat{A}</math> &gt; 75 years</li> <li>• life expectancy &lt;10 years</li> <li>• unfit for local treatment</li> </ul>	<ul style="list-style-type: none"> <li>• &lt; 75 years</li> <li>• life expectancy &lt;10 years</li> </ul>	<ul style="list-style-type: none"> <li>• &lt; 75 years</li> <li>• life expectancy &lt;10 years</li> <li>• Progression during AS</li> </ul>
COVID-recommendations	<ul style="list-style-type: none"> <li>• Watchful Waiting strategy (WW)</li> <li>• Defer visit until symptoms compare</li> </ul>	<ul style="list-style-type: none"> <li>• Active Surveillance strategy (AS)</li> <li>• Defer visit by 6 months</li> <li>• Consider mp-MRI instead of re-biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Defer treatment (RP or RT) by 6–12 months</li> </ul>
Treatment of localized prostate cancer: Intermediate risk			
	Low - Intermediate Priority	High Priority	
Definition	Favorable (cT2b-cT2c; PSA 10–20 ng/ml; Grade Group 2–3)	Unfavorable (similar to high risk PCa patients)	
COVID-recommendations	<ul style="list-style-type: none"> <li>• AS strategy</li> <li>• Defer visit by 6 months</li> <li>• Consider the use of mp-MRI</li> <li>• Use Telehealth and remote monitoring</li> </ul>	<ul style="list-style-type: none"> <li>• Use neoadjuvant ADT therapy up to 6 months before EBRT</li> <li>• In case of high risk cardiovascular adverse event consider bicalutamide instead of LHRH</li> <li>• For EBRT consider moderate and ultra-hypofractionated regimen</li> <li>• Not use neoadjuvant ADT before RP that should be deferred up to 6 months</li> </ul>	
Treatment of localized prostate cancer: High risk and Locally Advanced			
	High Priority		
Definition	Very high risk of progression, metastases and cancer death		
COVID-recommendations	<ul style="list-style-type: none"> <li>• Use neoadjuvant ADT for 3 or 6 months followed by EBRT</li> <li>• Consider moderate and ultra-hypofractionated regimen for cN0 patients</li> <li>• Avoid the use of fiducial markers and rectal spacers placement</li> <li>• Carefully evaluate whole pelvis RT only for cN+ patients</li> </ul>		
Treatment of PSA relapse after local treatment			
	Low Priority	High Priority	
Definition	PSA doubling time >12 months	PSA doubling time <12 months	
COVID-recommendations	<ul style="list-style-type: none"> <li>• Postpone imaging until after the pandemic is solved</li> </ul>	<ul style="list-style-type: none"> <li>• After RP offer salvage EBRT: consider moderate hypofractionated regimen; a combination of ADT and EBRT can be considered to delay radiotherapy treatment</li> <li>• After EBRT offer ADT</li> </ul>	
Treatment of metastatic hormone sensitive prostate cancer			
	Low Priority	High Priority	
Definition	Low Volume	High Volume	
COVID-recommendations	<ul style="list-style-type: none"> <li>• Start ADT</li> <li>• If local EBRT is indicated, offer hypofractionated regimen</li> </ul>	<ul style="list-style-type: none"> <li>• Start a systemic treatment</li> <li>• Consider single dose of EBRT (8 Gy) for bone metastases</li> </ul>	

Recommendation for the treatment of Prostate Cancer applicable during the Covid-19 pandemic.

order to minimize patient’s access to the hospital.

In case of radio-recurrent prostate cancer, systemic therapy with ADT should be initiated if PSA doubling time (PSADT) is < 12 months.

**Metastatic hormone sensitive prostate cancer (MHSPC)**

In the setting of low priority/low volume - Metastatic Hormone Sensitive Prostate Cancer (mHSPC) in COVID-19 era, local treatment should be withheld and delayed, while Androgen Deprivation Therapy (ADT) remains key in the therapeutic management of these patients [39]. However, when RT is considered, hypofractionated regimens should be offered [40].

For high priority class M1 patients, immediate systemic treatment other than chemo is strongly suggested (in alphabetical order: Abiraterone Acetate plus Prednisone or Apalutamide or Enzalutamide – ARTA (androgen receptor-targeted agents). More specifically, in men with newly diagnosed mHSPC, we recommend treatment with one of the novel drugs targeting the androgen receptor axis rather than docetaxel chemotherapy (in addition to ADT). Chemotherapy administration by itself is associated with higher exposure to infection and frequent hospital visits, while for patients receiving ARTA, the home-monitoring program should be instituted, to avoid unnecessary access to the hospital [41].

Palliative radiotherapy for painful bone metastasis, remains an important option for patients experiencing significant pain [42], especially if the symptoms can’t be controlled with opioids or other analgesic drugs.

We recommend the adoption of single fraction radiotherapy of 8 Gy delivered with common conformal techniques.

All together these recommendations should lead towards a limited

access to the hospital, when feasible, shortening the overall treatment time, and/or in some cases postponing the therapeutic intervention, in order to reduce patients’ exposure. In such a scenario, the traditional seven weeks-long prostate radiotherapy course should not represent the standard approach, to be adopted during the outbreak. While for the low risk patients, the “watchful waiting” approach needs to be taken in greater consideration, neoadjuvant strategies involving ADT can allow a safe delay of local treatment, without compromising the oncologic outcomes.

Given the current epidemic crisis, delaying radiation therapy treatment for patients with prostate cancer may potentially reduce the risk of iatrogenic exposure to COVID-19. Delays in consultations and return visits of between 1 and 6 months were deemed safe based on stage of disease. Treatment can be avoided or delayed until safe for very low, low, and favorable intermediate-risk disease. Androgen deprivation therapy (ADT), as mentioned above, can allow for further deferral of radiation therapy with 6–12 months. Nevertheless excessive delay of radiation therapy in patients with aggressive prostate cancer should be avoided and the possible consequences arising from prolonged or life-long ADT must be kept in mind.25 If ADT cannot be delivered, for patients with rapid PSA doubling times ( $\leq 3$  months) the benefits of immediate treatment during a window of potential cure must be weighed against the risk of COVID-19 exposure considering however that, unlike the majority of chemotherapies, most radiotherapy regimens are only moderately immunosuppressive, and this applies particularly to hypofractionated radiotherapy schedules [43].

**Clinical practice points**

The COVID-19 pandemic is unlike anything seen before by modern

science-based medicine. In order to treat patients safely, while protecting medical teams, the entire health care system must optimize the way it approaches prevention and treatment at a time, when social distancing is the key player to fight against COVID-19 pandemic.

EAU recently published recommendations on possible modification to latest Guidelines 2020: we utilize same levels of priority to adapt our treatment flowchart; this classification is resumed in a color-coded risk stratification tool, presented in a figure. As PCa is a heterogeneous disease and most hospitals worldwide are affected by COVID-19, prioritization of cases could take advantage of stratification into risk classes (Low risk, Intermediate risk, High risk, locally advanced, Psa relapse after primary treatment, Metastatic prostate cancer. Our goal is to minimize the impact and risks for both patients and health professionals delivering urological care, whenever possible although it is clear, it is not always possible to mitigate them entirely. It should be understood there may not be high quality evidence, for the compromises proposed, but we hope this document will function as an important additional guide to the management of urological conditions, during the current COVID-19 pandemic.

In Table 1 recommendations and current evidence.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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