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Review – Bladder Cancer – Editor's Choice

## Risks from Deferring Treatment for Genitourinary Cancers: A Collaborative Review to Aid Triage and Management During the COVID-19 Pandemic

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### Article info

#### Article history:

Accepted April 24, 2020

#### Associate Editor:

J.-N. Cornu

#### Keywords:

Coronavirus disease 2019  
Coronavirus  
Bladder cancer  
Prostate cancer  
Kidney cancer  
Upper tract urothelial carcinoma  
Testicular cancer  
Penile cancer  
Delayed treatment  
Surgery  
Stem cell therapy

### Abstract

**Context:** The coronavirus disease 2019 (COVID-19) pandemic is leading to delays in the treatment of many urologic cancers.

**Objective:** To provide a contemporary picture of the risks from delayed treatment for urologic cancers to assist with triage.

**Evidence acquisition:** A collaborative review using literature published as of April 2, 2020.

**Evidence synthesis:** Patients with low-grade non-muscle-invasive bladder cancer are unlikely to suffer from a 3–6-month delay. Patients with muscle-invasive bladder cancer are at risk of disease progression, with radical cystectomy delays beyond 12 wk from diagnosis or completion of neoadjuvant chemotherapy. Prioritization of these patients for surgery or management with radiochemotherapy is encouraged. Active surveillance should be used for low-risk prostate cancer (PCa). Treatment of most patients with intermediate- and high-risk PCa can be deferred 3–6 mo without change in outcomes. The same may be true for cancers with the highest risk of progression. With radiotherapy, neoadjuvant androgen deprivation therapy (ADT) is the standard of care. For surgery, although the added value of neoadjuvant ADT is questionable, it may be considered if a patient is interested in such an approach. Intervention may be safely deferred for T1/T2 renal masses, while locally advanced renal tumors ( $\geq$ T3) should be treated expeditiously. Patients with metastatic renal cancer may consider vascular endothelial growth factor targeted therapy over immunotherapy. Risks for delay in the treatment of upper tract urothelial cancer depend on grade and stage. For patients with high-grade disease, delays of 12 wk in nephroureterectomy are not associated with adverse survival outcomes. Expert guidance recommends expedient local treatment of testis cancer. In penile

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cancer, adverse outcomes have been observed with delays of  $\geq 3$  mo before inguinal lymphadenectomy. Limitations include a paucity of data and methodologic variations for many cancers.

**Conclusions:** Patients and clinicians should consider the oncologic risk of delayed cancer intervention versus the risks of COVID-19 to the patient, treating health care professionals, and the health care system.

**Patient summary:** The coronavirus disease 2019 pandemic has led to delays in the treatment of patients with urologic malignancies. Based on a review of the literature, patients with high-grade

## 1. Introduction

The rapid spread of coronavirus disease 2019 (COVID-19), caused by the a novel betacoronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), throughout the world has had dramatic effects on individuals and health care systems far beyond those infected with SARS-CoV-2 [1]. The heavy demand for resources, exacerbated by limited excess health system capacity, means that health care systems have become quickly overwhelmed and hospitals have become sources for virus transmission. In response, professional bodies have recommended reprioritizing surgical cases [2] depending on the risks of COVID-19 to individual patients and health care workers caring for patients potentially infected with SARS-CoV-2, and the need to conserve health care resources along with the risk from delaying cancer care.

A severe SARS-CoV-2 phenotype is seen more commonly in men and older, more comorbid patients [3]. These characteristics are common in many patients with urologic malignancies. Baseline characteristics among 1591 patients admitted to the intensive care unit (ICU) in the Lombardy region, Italy, showed that the median age was 63 yr (interquartile range [IQR] 56–70), 82% were male, 68% had more than one comorbidity, 88% required ventilator support, and the mortality rate was 26%, with a large proportion requiring ongoing ICU-level care at the time of data cut-off [4]. Work from China further demonstrated that patients with cancer had a higher incidence of COVID-19 than expected in the general population and had more severe manifestation of the disease, with a significantly higher proportion requiring invasive ventilation in the ICU or dying [5].

Recent data suggest that approximately 20% of asymptomatic COVID-19-positive patients may die after an elective operation [6]. To better inform decision making regarding deferring treatment of urologic cancers at this time, we undertook a collaborative review of the available data on the association between treatment delays and important oncologic outcomes including survival in patients with urologic cancers.

## 2. Evidence acquisition

To rapidly provide information, a formal systematic review was not undertaken. Instead, a scoping narrative review was performed. Following agreement on manuscript structure, a literature review was performed by teams based on clinical specialty (urologic oncology, radiation oncology, and medical oncology). To this end, PubMed was searched from

inception until April 2, 2020 to identify studies examining the association between delays in treatment and clinical outcomes, including upstaging, recurrence, and mortality for patients with bladder cancer (BC; both muscle-invasive and non-muscle-invasive disease), prostate cancer (PCa), kidney cancer, upper tract urothelial cancer, germ cell tumors, and penile cancer.

Where available, we relied on previously published systematic reviews and meta-analyses, supplemented by a narrative review of key studies and those published since the systematic review. The available data were qualitatively synthesized and presented, stratified by tumor site and urologic versus medical oncology intervention. In the absence of high-quality literature evidence, an expert opinion was given by the authors for this review.

Following agreement on manuscript structure, the authors drafted relevant sections of this narrative review according to their expertise. The resulting manuscript was critically revised by all authors. The final manuscript represents the consensus of the authors.

## 3. Evidence synthesis

### 3.1. Bladder cancer

According to estimates, there were 549 000 new cases of BC and 199 000 deaths worldwide in 2018 [7]. Among these cases, about 47% are estimated to be Ta/Tis at initial presentation, 21% stage I, 11% stage II, 4% stage III, and 6% stage IV disease in the USA [8]. Most cases are in men, and the average age of onset is over 70 yr. With regard to mortality risk from COVID-19, 63% of patients with BC have one comorbidity (such as hypertension, cardiovascular, or pulmonary), 32% have two or more comorbidities, and the risks of dying from BC or from a competing diseases are similar at 5 yr after diagnosis [9,10].

#### 3.1.1. Low-grade non-muscle-invasive bladder cancer

Low-grade non-muscle-invasive bladder cancer (NMIBC) is relatively an indolent disease. Long-term BC-specific mortality rates are around 1–2% [11], and active surveillance (AS) for recurrent low- and intermediate-risk NMIBCs is an important management option [12]. Guidelines suggest discharge after 12 or 60 mo if the patient is recurrence free [13,14].

**3.1.1.1. Summary.** These data suggest that it is safe to defer cystoscopic surveillance and transurethral resection of bladder tumor (TURBT) for recurrence in patients with known low-grade (including low and intermediate

European Organisation for Research and Treatment of Cancer [EORTC] risk) NMIBC bladder tumors during the COVID-19 pandemic. Patients presenting with new symptoms, such as the onset of visible hematuria, should be re-evaluated (eg, with cytology and either radiologic imaging or clinic cystoscopy) to assess their disease status.

### 3.1.2. High-grade NMIBC

For high-grade NMIBC, progression to muscle invasion/metastases occurs in 15–40% and 10–20% of patients may die from BC [15,16]. Primary treatments include bacillus Calmette-Guérin (BCG) immunotherapy and radical cystectomy (RC) [17]. Early re-resection reveals muscle invasion in up to 8% of initial pTa and 32% of pT1 tumors [18]. The risks of progression in patients whose re-resection contains no tumor are lower (at around 10% every 5 yr [19,20]). Given limited surgical capacity during the COVID-19 pandemic and a lack of prospective data showing superiority of either approach, in our view, BCG is the preferred choice for most patients who have had their tumors visually resected. The use of re-resection should be individualized according to COVID-19 risk (local incidence and patient risk factors), BC risk, and initial TURBT features (eg, can be omitted if there are pTa and muscle in the first specimen). There are suggestions that BCG may enhance antibody response to SARS-CoV-2 [21,22]. RC should be considered in patients at low risk of COVID-19 mortality and with high-risk disease features, for example, presence of high-grade pT1 plus Tis, or tumors with lympho(vascular) invasion, variant histology (eg, micropapillary disease), residual grade 3/high-grade urothelial carcinoma on re-resection, or pT1 stage [23–25]. With respect to BCG therapy, while maintenance full-dose BCG is superior to alternatives, most benefit appears to come from the induction and first maintenance doses (so-called 6+3) [26]. As such, it appears reasonable in times of high SARS-CoV-2 prevalence to discontinue subsequent maintenance BCG instillations in persons at risk of COVID-19, who have responded to induction (6) and first maintenance (+3) BCG. If the COVID-19 pandemic subsides, we recommend continuation of to 12 mo of maintenance therapy. With regard to starting BCG, progression rate and re-resection data suggest that if BCG is deferred for 3–6 mo, restarting with a cystoscopy ± re-resection may be most suitable. In patients who undergo RC for BCG-unresponsive NMIBC, with or without further intravesical therapy, the delay caused by an additional (unsuccessful) course of intravesical therapy did not result in differences in 5-yr overall survival (OS) or cancer-specific survival (CSS) despite a median delay of 1.7 yr [27].

Finally, due to COVID-19 pandemic, especially in geographic areas where the infection is causing a health care emergency, physicians should be aware of the potential risk of stage migration due to simplification of diagnostic procedures such as TURBT. It is possible that urologists may opt for simpler minimally invasive procedures such as cystoscopy and biopsy, or even noninvasive procedures such as radiologic imaging prior to defining the therapeutic workup. We urge caution and highlight the importance of the TURBT specifically in these high-risk patients [28].

**3.1.2.1. Summary.** In patients with high-grade NMIBC, induction BCG and one course of maintenance therapy (6+3) should be offered as first-line therapy. Re-resection may be deferred in lower-risk cases (eg, pTa), but should not be abandoned in higher-stage (pT1) or higher-risk disease, especially if no muscle was present in the initial resection. The decision to start BCG immediately or defer it (following a repeat resection) depends on the risk of infection with SARS-CoV-2 and an unfavorable course of COVID-19, bladder tumor risk, and health care capacity. RC should be offered for higher-risk tumors, if hospital capacity allows and if patient comorbidities do not put them at a higher postoperative risk. Maintenance BCG after the first 3-mo booster series may be omitted until risks of COVID-19 become lower.

### 3.1.3. Muscle-invasive bladder cancer

The effect of delays in surgical intervention has been explored thoroughly in muscle-invasive bladder cancer (MIBC). A recent systematic review (19 studies) and a meta-analysis (10 studies) provide a contemporary picture of these data [29]. There was considerable variation in the nature of the delay investigated: from the diagnosis to RC (10 studies), from TURBT to RC (seven studies), from first clinic visit to RC (or radiotherapy; one study), from referral to first treatment (one study), and from neoadjuvant chemotherapy (NAC) to RC (four studies).

Assessing the delay between BC diagnosis and survival, four of nine studies assessing the question found a significant association between delay from diagnosis to RC and survival. Russell and colleagues [29] meta-analyzed the available studies assessing this question. In three studies with data that could be pooled, the authors found an increased risk of death for patients with significant delays between diagnosis and RC (hazard ratio [HR] 1.34, 95% confidence interval [CI] 1.18–1.53;  $I^2 = 0\%$ ).

Operationalizing delay as the interval between TURBT and RC, four of six studies assessing this question found an association with survival. Utilizing a cubic spline to model the nonlinear relationship, Kulkarni and colleagues [30] found that the risk of death began to rise, beginning at 40 d between TURBT and RC. In this case, Russell et al [29] meta-analyzed five studies and found a nonsignificant pooled effect estimate of 1.18 (95% CI 0.99–1.41) for OS, with significant between-study heterogeneity ( $I^2 = 73\%$ ).

Finally, five studies assessed the question of whether the time duration between completion of NAC and RC was associated with survival outcomes. Two studies demonstrated that prolonged time between NAC and RC was associated with adverse survival outcomes, and an additional study demonstrated that delays were associated with upstaging. Boeri et al [31] found that patients who had >10 wk between the last cycle of NAC and RC had significantly worse cancer-specific mortality (3 yr free rate: 70.3% at ≤10 wk vs 44.3% at >10 wk) and overall mortality (3 yr free rate: 63.5% at ≤10 wk vs 42.1% at >10 wk). Chu et al [32] found similar results, while three other analyses failed to support these results. Specifically, if we look at the data relevant to the context of the current COVID-19 pandemic, Audenet and

colleagues [33] found that delays of >8 wk in NAC were associated with an increased risk of upstaging, but no harm in delays up to 6 mo from diagnosis to RC, assuming that NAC was administered in the meantime. In this case, a meta-analysis of three studies with data suitable for pooling failed to demonstrate a significant association between delays from the termination of NAC to RC with survival (HR 1.04, 95% CI 0.93–1.16;  $I^2 = 82%$ ) [29].

Lin-Brandt et al [34] examined outcomes for patients with variant histology undergoing RC. The authors dichotomized surgical delays using thresholds of 4, 8, and 12 wk. On multivariable analysis, for patients with variant histology, no significant difference in OS was apparent when “early” versus “late” surgery was dichotomized at 4 wk (HR 0.92, 95% CI 0.32–2.59) or 8 wk (HR 1.50, 95% CI 0.68–3.29), but significant differences were apparent when delayed surgery was defined as surgery beyond 12 wk following diagnosis (HR 3.45, 95% CI 1.51–7.86).

Taken together, these data suggest that prolonged delays (exceeding 90 d) between diagnosis/TURBT and RC are associated with worse survival, with the caveat that the data are mixed and pooled results demonstrate considerable heterogeneity. The European Association of Urology (EAU) guidelines advise to maintain the delay below the 12 wk threshold [35]. Further, when NAC is employed, impact of delays in RC no longer appear to be significant. An analysis of funnel plots indicates that there is a publication bias toward studies that demonstrate worse survival associated with delays, suggesting that this finding may be exaggerated in the literature [29].

Previous studies also reported shorter survival in patients who experienced a delay in definitive surgery, while they received NAC [32]. This potential risk for patients receiving preoperative chemotherapy may be exacerbated during the COVID-19 pandemic due to the predicted higher frequency of treatment-related side effects in patients developing an infection during treatment, as anticipated by Chinese authors [5,36]. There are no positive adjuvant studies for OS. This therapy should be avoided during the pandemic as the risks of chemotherapy increase the risk-benefit ratio further [37].

**3.1.3.1. Summary.** Delays in RC of up to 12 wk may be safe for MIBC. Oncologic principles and appropriate guidelines should be followed despite COVID-19. NAC should be considered where feasible, with due attention to the risk of immunosuppression weighed against the benefit. Clinicians should prioritize RC over other urologic oncology procedures during COVID-19 restrictions. Additionally, radiotherapy (trimodal therapy with radiosensitizing chemotherapy) could be considered an alternative based on individual hospital and patient factors [38]. Adjuvant therapy has no role.

#### 3.1.4. Advanced or metastatic BC

The use and choice of systemic therapies in patients with new BC metastases should be individualized according to symptoms, risk of infection with SARS-CoV-2, and unfavorable course of COVID-19, and likely prognosis. Cytotoxic

chemotherapy remains the treatment of choice for the majority of patients with advanced or metastatic BC. A regime comprising cisplatin and gemcitabine with granulocyte colony-stimulating factor, rather than methotrexate, vinblastine, doxorubicin/adriamycin, and cisplatin (MVAC), should be considered, given the higher likelihood of neutropenia in patients receiving MVAC [39], which may be dangerous during the COVID-19 pandemic. In patients with previously untreated programmed death ligand-1 (PD-L1)-positive locally advanced and metastatic urothelial carcinoma, immune-checkpoint inhibitors may be more attractive than cytotoxic chemotherapy due to a reduced likelihood of immunosuppression [40]. However, immune-checkpoint blockade is associated with potentially serious side effects, including those requiring ICU-level resources and need for high-dose glucocorticoids [41], which may be in short supply in the current environment.

Anecdotally, we have noted that both patients and health care professionals seem nervous about starting or pursuing immune therapy due to the belief that serious pulmonary complications from COVID-19 may be due to excessive inflammatory response caused by checkpoint inhibition. There are few data to support this view, and so an individualized approach is recommended.

**3.1.4.1. Summary.** Our consensus is that first-line treatment should be commenced when possible for metastatic urothelial carcinoma and should not be stopped without justification (Table 1) [42]. Immunotherapy rather than chemotherapy may be given preferentially to patients with PD-L1-positive tumors. During the COVID-19 pandemic, risks and benefits of systemic therapy should be considered on an individual level, taking into account disease characteristics (ie, PD-L1 positivity), tumor load and dynamics, patient performance status, geographical COVID-19 burden, and hospital resources. Palliative chemotherapy should be deferred at this time.

## 3.2. Prostate cancer

PCa is the commonest noncutaneous male malignancy in the Western world [43]. According to estimates, there were 1 276 000 new cases of PCa and 359 000 deaths worldwide in 2018 [7]. At diagnosis, 78% of the patients are estimated to present localized disease, 12% regional disease, and 5% metastatic disease in the USA [44]. With regard to the current pandemic, PCa is more common in men at risk of adverse outcomes from COVID-19. For example, the incidence of PCa increases with age and in black men [43], and >50% of affected men have one or more comorbidities [45]. For the vast majority of men, it will be more prudent to perform PCa investigations, including imaging or biopsy, when the risks from COVID-19 are lower.

#### 3.2.1. Localized PCa: low-risk disease

Urologists have recognized for many years that definitive intervention (radical prostatectomy [RP] or radiotherapy) may be delayed for long durations (years and potentially indefinitely) for patients with low-risk PCa, as AS is very

**Table 1 – Overview of suggestions regarding systemic therapy during the COVID-19 pandemic<sup>a</sup>.**

	Prostate cancer	Renal cancer	Germ cell tumors	Urothelial cancer
Treatment should be commenced where possible	Frontline treatment for metastatic disease	Treatment for frontline IMDC intermediate- and poor-risk metastatic disease <sup>b</sup>	Treatment with curative intent	First-line treatment for metastatic disease
Treatment should not be commenced without justification	CTx in patients at significant COVID-19-related risk <sup>c</sup>	Nephrectomy for metastatic disease	Adjuvant therapy after orchidectomy for stage I disease	CTx in platinum-refractory disease Perioperative CTx for operable disease <sup>d</sup>
Treatment should not be stopped without justification	AR-targeted therapy <sup>e</sup>	Treatment for frontline metastatic disease	First- and second-line treatment for metastatic disease	Treatment for frontline metastatic disease
Treatment that can potentially be stopped or delayed after careful consideration <sup>f</sup>	Minimizing the number of CTx cycles or prolonging cycle length may be justified Steroids as a cancer therapy	ICI or oral VEGF-targeted therapy after prolonged period (1–2 yr) <sup>e</sup>		CTx for platinum-refractory patients who are not responding to therapy More than 3 CTx cycles in the perioperative setting
Treatments that can be given preferentially compared with other options	Oral AR-targeted therapy rather than CTx <sup>g</sup>	Oral VEGF therapy rather than IV immune therapy	Conventional dose rather than high-dose therapy	ICIs rather than CTx in PD-L1-positive frontline metastatic disease

AR = androgen receptor; COVID-19 = coronavirus disease 2019; CTx = chemotherapy; ICI = immune checkpoint inhibitor; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IV = intravenous; PD-L1 = programmed death ligand-1; VEGF = vascular endothelial growth factor.

<sup>a</sup> Suggestions in the table were used with permission from Gillessen-Sommer and Powles [42].

<sup>b</sup> Oral VEGF-targeted therapy rather than IV ICIs may be attractive as it requires less health care interactions and resources.

<sup>c</sup> Younger cancer patients and those without comorbidities may be at lower risk, which should be considered.

<sup>d</sup> Neoadjuvant chemotherapy may be helpful in bridging the time to surgery in cases in which elective surgery is not possible.

<sup>e</sup> Regimens with a longer interval (4-weekly nivolumab or 6-weekly pembrolizumab) should be used where possible.

<sup>f</sup> Palliative CTx was tested with a specific number of cycles. The risk associated with stopping before this has not been assessed, nor the principles of delaying chemotherapy. There are subgroups of prostate and urothelial cancer patients for whom continuing CTx to the full number of cycles may be associated with more risk than benefit. Patients will need to participate in this discussion.

<sup>g</sup> Assuming similar efficacy between the regimens.

rarely associated with adverse clinical outcomes in this population [46–48]. However, metastasis-free survival (MFS) and PCa-specific survival are significantly worse for patients with Gleason 3+4 disease undergoing AS compared with those with Gleason 3+3 disease [49]. Thus, it appears that for men with intermediate-risk disease (and presumably also for those with high-risk disease), there is risk to a surveillance strategy.

In our literature review, two relevant review articles were identified: one was a narrative review [50] and the other a systematic review [51]. The narrative review of Bourgade and colleagues [50] concluded that the heterogeneous nature of PCa meant that generalizable conclusions could not be drawn, in routine care, on the basis of three cited studies.

Van den Bergh and colleagues [51] provided a more comprehensive systematic review including 17 studies, of which 13 assessed patients treated with RP, three studies assessed patients treated with radiotherapy, and one study assessed patients treated with either modality. Four of 17 studies published at that time demonstrated a significant effect of treatment delay on outcomes. While all included studies were retrospective and nonrandomized, the authors concluded that a treatment delay of several months or years is unlikely to affect treatment outcomes of men with low-risk PCa, while limited data suggested that there may be an effect in men with intermediate- or high-risk PCa [51].

**3.2.1.1. Summary.** AS should be the preferred management strategy for patients with low-risk PCa. Patients considering

focal therapy may safely defer treatment until the pandemic is over.

### 3.2.2. Localized PCa: intermediate- and high-risk disease

While Van den Bergh and colleagues [51] found limited data suggesting that there may be an effect in delaying treatment for intermediate- or high-risk PCa, the majority of the literature supports that delays up to 6 mo in radical treatment are safe in men with intermediate- and high risk PCa. For example, in men with localized intermediate-risk disease from Toronto, long-term deferral led to worsening in MFS (HR 3.14, 95% CI 1.51–6.53) and PCa-specific survival. However, the estimated 10- and 15-yr treatment-free survival for intermediate-risk patients was 61% and 48%, respectively [49].

Among 2303 patients with unfavorable intermediate-risk PCa, high-risk PCa, and very high-risk clinically localized PCa who were treated with RP at Johns Hopkins, Gupta and colleagues [52] found no significant differences in pathologic findings (positive surgical margins, extraprostatic extension, seminal vesicle invasion, or lymph node involvement) or use of adjuvant therapy between patients who received surgery within 3 mo and those who received surgery 3–6 mo following diagnosis, when stratified by biopsy Gleason grade group (GGG). Similarly, there were no differences in 2- or 5-yr biochemical recurrence-free survival (RFS) or 2-, 5-, or 10-yr MFS between patients receiving earlier surgery and those who had delayed treatment, when stratified by biopsy GGG.

Delays up to 6 mo from diagnosis were not associated with adverse pathologic findings (Gleason upgrading, extraprostatic extension, seminal vesicle invasion, positive surgical margins, or lymph node involvement) [53,54] or PCa-specific mortality [54], across risk strata and including patients with intermediate-risk localized disease, high-risk localized disease, and high-risk locally advanced disease [54].

Fossati and colleagues [55] examined even longer durations of delay between diagnosis and surgery. Among 2653 patients treated with RP at San Raffaele Hospital in Milan, the authors used nonparametric curve fitting models to assess the relationship between the time from diagnosis to surgery and oncologic outcomes, including biochemical recurrence and clinical recurrence. The median time from diagnosis to surgery was 2.8 mo. Among all patients, the authors identified a significant association between the time to surgery and risk of biochemical recurrence (HR 1.02,  $p = 0.0005$ ) and clinical recurrence (HR 1.03,  $p = 0.0002$ ), although this relationship was nonlinear. Utilizing nonparametric curve fitting, the authors identified that the risk of biochemical recurrence increased significantly with delays of >18 mo. In sensitivity analyses, this effect was seen only in patients with high-risk disease. Among patients with high-risk disease, an increased risk of biochemical recurrence was seen with presurgical delays exceeding 12 mo.

However, others have found that safe delays may be considerably shorter. Berg et al [56] found that among their cohort (which was much less contemporary), the risk of adverse pathologic findings increased beyond 60 d for patients with intermediate-risk disease and 30 d for patients with high-risk disease. Meunier and colleagues [57] found that there was an increased risk with delays of >90 and 60 d for patients with Gleason 3+4 disease and Gleason  $\geq 8$  disease, respectively. While Zanaty et al [58] found no significant association between the time to surgery and pathologic outcomes, regardless of preoperative risk stratification, they found a significant increase in the risk of biochemical recurrence for patients with high-risk disease who waited longer than 90 d. Finally, a recent analysis from the Mayo Clinic suggested that patients with high-risk disease who waited for >6 mo without neoadjuvant androgen deprivation therapy (ADT) had an increased risk of biochemical recurrence, although they did not assess shorter time intervals [59].

The analyses presented thus far have examined patients who received no therapy during the delay to definitive local treatment. However, neoadjuvant ADT may offer an option to temporize patients at particularly high risk of progression during forecasted delays. In a Cochrane systematic review and meta-analysis of randomized or quasirandomized clinical trials, Kumar and colleagues [60] found that, while there was a marginal benefit in terms of disease recurrence (OR 0.74, 95% CI 0.55–1.00), there was no benefit or harm to neoadjuvant ADT compared with immediate RP in terms of PCa-specific survival (OR 0.99, 95% CI 0.75–1.32) or OS (OR 1.11, 95% CI 0.67–1.85) for patients with localized and locally advanced PCa. While neoadjuvant ADT has not been adopted routinely on the basis of a failure to improve survival outcomes compared with early definitive treat-

ment, in the current environment, these data may be viewed in another manner: namely, that neoadjuvant ADT may offer the ability to defer definitive intervention safely without compromising long-term outcomes.

In the post-RP setting, based on recently presented, but unpublished, evidence from Radiotherapy – Adjuvant Versus Early Salvage (RAVES) [61] and Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS) [62] trials, early salvage is a preferable option as compared with immediate, adjuvant irradiation when needed.

**3.2.2.1. Summary.** For patients with intermediate- and high-risk disease, delays of 3–6 mo appear not to be associated with adverse pathologic outcomes, biochemical recurrence, or survival outcomes. Some data suggest that these intervals may be longer (up to 12 mo in patients with high-risk disease [55]). Neoadjuvant ADT prior to radiotherapy is the standard of care usually for 2–3 mo. It might be prolonged much longer for those at particularly high risk of progression or recurrence if radiotherapy has to be delayed until after peak health care resource utilization associated with COVID-19. For surgery, although added value of neoadjuvant ADT is questionable, it might also be considered if a patient is interested in such an approach.

### 3.2.3. Considerations for radiotherapy in PCa

While the majority of the literature assessing delays in the treatment of PCa has assessed patients undergoing RP, Van den Bergh et al [51] identified four studies assessing patients treated with radiotherapy. Notably, none of these included patients receiving brachytherapy. While three of these studies reported no significant difference in biochemical RFS, MFS, CSS, or OS, Nguyen et al [63] found that treatment delays, particularly those exceeding 2.5 mo, were associated with worse biochemical control in patients with high-risk disease. There is no biologic rationale to suggest that treatment delays should differentially affect patients opting for radiotherapy, rather than RP, in the treatment of localized PCa. Thus, it is likely safe to delay treatment for 3–6 mo for these patients.

In circumstances where treatment is offered, COVID-19-related risks differ somewhat for patients receiving surgery and radiotherapy. Whereas surgery entails short hospitalization with the use of operating room resources, radiotherapy requires multiple outpatient visits. It is unclear which will contribute a greater patient- and system-level COVID-19-related risk.

Where radiotherapy is planned to be administered, a recent Cochrane Database systematic review and meta-analysis of 10 studies including 8278 patients demonstrated that for those with intermediate- and high-risk PCa, hypofractionation is associated with equivalent oncologic outcomes (MFS, disease-specific survival, and OS), as well as functional outcomes [64]. Use of an ultrahypofractionated schedule (five to seven fractions) is both in line with clinical guidelines [65] and a way to reduce resource utilization and individual patient exposure [66].

Based on level 1 evidence, patients with intermediate- or high-risk PCa who are undergoing primary radiotherapy

are recommended to receive neoadjuvant, concurrent, and adjuvant ADT. While the RTOG 9910 trial demonstrated that 28 wk of neoadjuvant ADT was comparable with 8 wk of therapy, when administered with a further 8 wk of concurrent ADT [67], the TROG 96.01 trial demonstrated that 6 mo, compared with 3 mo, of neoadjuvant ADT provided additional benefit in terms of distant progression, cause-specific survival, and OS [68]. Utilization of a longer period of neoadjuvant ADT may allow for resolution of the current limitations in health care resources before the planned initiation of radiotherapy. A recent paper by Zaorsky et al [66] introduced the concept of a remote visits, avoidance, deferment, and shortening of radiotherapy (RADS) framework to determine the appropriate management for patients with PCa in the COVID-19 pandemic.

**3.2.3.1. Summary.** Men starting radiotherapy can safely defer treatment for 3–6 mo. Hypofractionation (either moderate, 19–20 fractions over 3.8–4 wk [69], or extreme, five to seven fractions—an stereotactic body radiotherapy approach) may decrease health care burden and patient SARS-CoV-2 exposure. Neoadjuvant ADT allows safe deferral of radiotherapy until resolution of the current COVID-19-related health care resource pressures.

#### 3.2.4. Metastatic PCa

The treatment of both metastatic hormone-sensitive PCa (mHSPC) and castration-resistant PCa (mCRPC) over the past decade has evolved to provide several treatment options for these patients. Debate continues as to the proper sequencing of these agents, specifically regarding chemotherapy and androgen-receptor (AR) targeted therapies. In the current landscape of the COVID-19 pandemic, there is a paucity of data with regard to treatment delays in the metastatic setting; thus, the following recommendations are based on expert opinion. First, frontline treatment should be commenced where possible and oral AR targeted therapies should be prioritized over chemotherapy (Table 1) [42]. Although there is a proven survival benefit for docetaxel in the mHSPC [70–72] and mCRPC [73] setting, the associated side effects (ie, neutropenia) that may require hospitalization should be avoided at this time. Second, in patients requiring second- and third-line therapy, AR targeted therapies that have not been used previously should be prioritized. Third, for patients currently on chemotherapy, it may be prudent to minimize the number of chemotherapy cycles and/or prolonging the cycle length. Fourth, where possible, consideration for 3–6-mo ADT injections should be preferred over 1-mo injections. Finally, glucocorticoids as part of treatment regimens should be minimized as feasibly possible, given the increased infectious risk.

**3.2.4.1. Summary.** Patients with metastatic PCa should commence treatment, prioritizing AR targeted therapies over chemotherapy. Glucocorticoid use should be minimized and patients should be considered for longer-duration ADT injections.

### 3.3. Kidney cancer

On a global scale, renal cell carcinoma (RCC) represents the sixth and 10th most diagnosed cancer in men and women, and accounts for 5% and 3% of all cancers in males and females, respectively. For both sexes, incidence rates increased in the UK by 1.8–2.2% annually, while they decreased or stabilized in other Northern European countries [74]. At presentation, 65% of patients are estimated to have localized disease, 16% regional disease, and 16% metastatic disease in the USA [44]. Although declining, primary metastatic RCC still represents a significant fraction of the cases at the time of diagnosis and mortality rates remain stable despite the introduction of new systemic therapies [43]. Patients at an increased risk of COVID-19 are comparable with the kidney cancer population, more likely males, hypertensive patients, and patients with more than one comorbidity [4].

We identified a single narrative review [50] but no systematic reviews assessing delays in treatment of kidney cancer. The following is a narrative summation of the primary literature identified.

#### 3.3.1. Localized kidney cancer (T1/2)

As with low-risk PCa, numerous studies have demonstrated that small renal masses (SRMs) may be observed safely on an AS protocol [75,76]. Among 457 patients treated at Fox Chase Cancer Center, McIntosh et al [75] found a median initial linear growth rate of 1.9 mm/yr (IQR 0–7), which was not associated with OS. The cumulative incidence of delayed intervention was 9% at 1 yr, 22% at 2 yr, 29% at 3 yr, 35% at 4 yr, and 42% at 5 yr. Importantly, delayed intervention was also not associated with OS (HR 1.34, 95% CI 0.79–2.29), and of the 99 patients on AS without delayed intervention for >5 yr, only one patient metastasized. Among 497 patients in the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry followed for a median of 2.1 yr (IQR 0.9–3.8), 223 (43%) chose AS and 274 (57%) chose primary intervention, with 21 (9%) eventually undergoing delayed intervention after a period of AS [76]. There was no difference in CSS at 5 yr between the groups (primary intervention: 99%; AS 100%,  $p = 0.3$ ), although patients choosing surveillance had lower 5-yr OS (75% vs 92%), likely attributable to comorbidity that drove their initial selection of surveillance.

Authors from the University of Michigan have also assessed the effect of delayed resection (at least 6 mo from presentation) after initial AS for SRMs [77]. In this study, 401 patients underwent early resection and 94 (19%) underwent delayed resection. The median time to resection was 84 d (IQR 59–121) in the early intervention group and 386 d (IQR 272–702) in the delayed intervention group. Importantly, there was no difference in adverse final pathology (grade 3–4, papillary type 2, sarcomatoid histology, angiomyolipoma with epithelioid features, or stage  $\geq$  pT3) comparing those who underwent early versus late intervention.

Taken together, there are robust data supporting AS for masses <4 cm, even up to 5 yr after initial diagnosis,



without age restriction [76,78]. While biopsy is often useful in the management of patients with SRMs, risk of harm from delays in SRM management are minimal and, like intervention, a biopsy may safely be deferred.

Although the data are less robust, several studies have assessed the impact of a surgical delay for localized  $\geq$  pT1b kidney tumors. The group at Memorial Sloan Kettering Cancer Center identified 1278 patients between 1995 and 2013 who underwent radical or partial nephrectomy with renal masses  $>4$  cm, testing the association between surgical wait time and disease upstaging at the time of surgery, as well as 2- and 5-yr recurrence rates [79]. Among these patients, 267 (21%) had a surgical wait time of  $>3$  mo, including 82 patients (6%) with a wait time of  $>6$  mo. On multivariable analysis, surgical wait time was not associated with disease upstaging, recurrence, or CSS, but longer wait time was associated with worse OS (HR 1.17, 95% CI 1.08–1.27), potentially reflecting comorbidity that necessitated the initial delays. The Fox Chase Cancer Center group identified 61 patients with cT1b renal masses and seven with cT2 masses initially treated with AS, with 23 (34%) undergoing delayed intervention [80]. Over a median follow-up of 32 mo (range 6–119 mo), no patients progressed to metastatic disease or died of kidney cancer. The median linear growth rate was 0.34 cm/yr (range 0–1.48 cm/yr), suggesting that delays of months to years are unlikely to affect the resectability of these tumors. Unfortunately, the small number of patients with cT2 disease precludes meaningful conclusions regarding these patients.

In a retrospective review of 722 patients undergoing partial or radical nephrectomy for relatively large kidney tumors (mean tumor size of  $6.4 \pm 4.4$  cm; 64.7%  $\geq$  pT1b and 49.0%  $\geq$  pT2), Stec et al [81] found that the mean time from initial visit to surgery was 1.2 mo (range 0–30 mo); 64.1% of patients underwent surgery within 30 d of initial visit and 94.3% within 3 mo. The authors found no difference in OS for patients receiving early versus late surgery, irrespective of whether using a threshold of 1 mo ( $p = 0.87$ ), 2 mo ( $p = 0.46$ ), 3 mo ( $p = 0.71$ ), or 6 mo ( $p = 0.75$ ). However, T stage was a significant predictor of RFS, independent of time to surgery.

**3.3.1.1. Summary.** Surveillance of SRMs is safe. When treatment is necessary (ie, SRM growth over time), it should be delayed under the current circumstances. Although there are fewer data regarding T1b and T2 disease, delays of 3–6 mo do not appear to affect outcomes adversely.

### 3.3.2. Locally advanced kidney cancer (T3)

We were unable to identify any study assessing the impact of delayed surgical intervention among patients with locally advanced kidney cancer; thus, the impact of delayed intervention is essentially unknown. However, several large institutional studies have described timing of preoperative imaging for assessing renal vein/inferior vena cava (IVC) thrombus, which may guide urgency of surgical timing. While Woodruff et al [82] recommended the longest interval between imaging (computed tomography [CT]/

magnetic resonance imaging) and surgery being no longer than 30 d, studies from the Mayo Clinic and Berlin, Germany, report a median interval from imaging to resection of 4 and 16 d, respectively [83,84].

**3.3.2.1. Summary.** The data are scant regarding the safety of delaying surgery in patients with  $\geq$  cT3 renal masses, in particular those with renal vein or IVC tumor thrombus involvement. These patients should be prioritized for surgical intervention, given the locally advanced nature of their disease, unknown risk of delayed resection, and potential for significant symptomatic complications including bleeding and IVC occlusion.

### 3.3.3. Cytoreductive nephrectomy in metastatic kidney cancer

The Immediate Surgery or Surgery after Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer (SURTIME [NCT01099423]) trial randomized 99 patients to immediate cytoreductive nephrectomy (CN) followed by sunitinib or sunitinib followed by CN followed by two courses of adjuvant sunitinib. While significantly underpowered due to poor accrual, the trial reported a 28-wk progression-free rate of 42% in the immediate CN arm and 43% in the deferred CN arm ( $p = 0.6$ ) [85]. Intention-to-treat analysis of the secondary outcome of OS demonstrated significantly longer survival among patients in the delayed CN arm (median 32.4 mo) than in the immediate CN arm (median 15.1 mo; HR 0.57, 95% CI 0.34–0.95). Further, the CARMENA trial, which enrolled mostly poor-risk patients, was a noninferiority trial and used sunitinib, demonstrated no survival benefit from the addition of CN to systemic therapy in 450 asymptomatic patients with metastatic kidney cancer [86]. Thus, CN should be avoided during the pandemic with delayed surgery, in keeping with the SURTIME approach, considered as an alternative to immediate nephrectomy in those who need surgery.

**3.3.3.1. Summary.** In the current landscape, upfront systemic therapy should be prioritized over CN in asymptomatic patients with metastatic kidney cancer. Nephrectomy should be reserved for symptomatic patients.

### 3.3.4. Metastatic RCC

In patients with locally advanced or metastatic RCC, the decision to start systemic therapy and the selection of agents depend on symptoms, patient comorbidities, and tumor risk stratification.

Apart from imperative indications due to the COVID-19 pandemic, the notion of deliberate treatment delays in selected patients with metastatic RCC, particularly those with International Metastatic RCC Database Consortium (IMDC) good-risk disease, has previously been assessed in a number of studies, including two narrative reviews [87,88], two prospective studies [89,90], six retrospective studies [91–96], and a further three abstracts of retrospective studies. In each, the majority of patients initiated treatment at disease progression.

In the largest prospective study of this approach to date, Rini et al [90] enrolled 52 asymptomatic patients in a phase

2 trial. All but one patient had favorable (23%) or intermediate (75%) risk disease according to the IMDC criteria, and >80% of patients had one or two organ sites with metastases. The median time on surveillance was 14.9 mo, and 37 of 43 patients experiencing response evaluation criteria in solid tumors–defined disease progression started systemic treatment. The median progression-free survival and OS from the start of surveillance were 9.4 and 44.5 mo, respectively. In a smaller study of 15 patients who received CN followed by observation until progression, Wong et al [89] found a median time to progression of 8 wk and median OS of 25 mo.

A contemporary retrospective study of observation in 40 patients after CN who had low-volume multiple metastasis considered not completely resectable (19 single site and 21 with two or more sites) showed a median time to systemic therapy of 16 mo (2–43 mo) [94]. Local therapy to control the most rapidly progressing lesion or observation beyond progression was an additional means to defer systemic therapy. In a large, retrospective European cohort of patients ineligible for AS, Iacovelli and colleagues [96] found that a delay of >6 wk in the initiation of systemic therapy did not significantly affect the cancer-specific outcomes. Finally, the survival implications of delayed initiation of targeted therapy have also been investigated at the population level using the National Cancer Database (NCDB) data [95]. Time to initiation of targeted therapy was defined as “early” (within 2 mo), “moderately delayed” (2–4 mo), “delayed” (4–6 mo), and “late” (>6 mo). On multivariable logistic regression analyses, delayed treatment initiation was not independently associated with worse OS.

There is no consensus as to the optimal therapeutic agent (s) to use during the COVID-19 pandemic; thus, it is advisable to follow the EAU guidelines, which provide first-, second-, and third-line options based on IMDC favorable-versus intermediate/poor-risk disease [97]. Depending on the outcome prioritized (PFS, OS, or toxicity), different agents may appear preferable [98,99]. While checkpoint inhibitor–based regimes have demonstrated OS advantages compared with sunitinib, in the context of the current pandemic, it is worth considering that these came at the cost of more severe treatment-related adverse events (TRAEs) [100], including those that may require hospitalization. Among the 436 N+I patients in CheckMate 214 who had immune-mediated TRAEs, 35% received high-dose glucocorticoids [100]. Thus, although vascular endothelial growth factor (VEGF) targeted therapy is associated with inferior OS compared with immunotherapy, in the context of the COVID-19 pandemic, these agents may be considered given their decreased risk of severe toxicity.

**3.3.4.1. Summary.** Patients with treatment-naïve favorable- and intermediate-risk disease who are asymptomatic or minimally symptomatic with limited disease burden may be considered for AS until disease progression during the COVID-19 pandemic. For poor-risk patients and those requiring treatment, there is no consensus regarding the optimal first-line therapy; however, VEGF targeted therapy

is less likely to require toxicity-related hospitalization and/or glucocorticoids than immunotherapy regimens.

### 3.4. Upper tract urothelial cancer

As with kidney cancer, we identified only a single narrative review [50] and thus based our conclusions on the available primary literature. The management of upper tract urothelial carcinoma (UTUC) is typically directed by a combination of disease grade (low vs high) and patient comorbidity. Numerous studies have demonstrated that a period of endoscopic management of low-grade UTUC is safe [101]. The impact of delayed radical nephroureterectomy (RNU) for those requiring a more aggressive intervention is less clear.

Four studies were identified that assessed the impact of delaying RNU for diagnostic ureteroscopy ± biopsy. In patients eventually undergoing RNU, single-center studies have shown that delays in surgery due to ureteroscopy beforehand did not affect survival in cohorts of patients with predominately low-grade disease (high grade comprising approximately one-third of cohort) or mixed disease characteristics (high grade comprising approximately 50% of cohort), although undergoing two ureteroscopic treatments prior to RNU was associated with an increased risk of intravesical recurrence in patients with predominately high-grade disease (high grade comprising approximately 70% of cohort) [102]. Subsequently, a study from the French Collaborative National Database on upper urinary tract urothelial carcinoma evaluated the influence of ureteroscopy prior to RNU on CSS, RFS, and MFS [103]. As expected, time from diagnosis to RNU was longer among patients undergoing ureteroscopy (79.5 vs 44.5 d,  $p = 0.04$ ). However, there were no differences in 5-yr CSS, RFS, or MFS, even in a subset of patients with confirmed muscle-invasive disease.

Not specifically assessing delays due to ureteroscopy, two institutional studies have assessed the impact of delayed RNU on pathologic and survival outcomes, both using a 3-mo threshold. RNU ≥ 3 mo after diagnosis ( $n = 41$ ; median time to RNU 110 d, range 93–137 d) was associated with a worse pathologic stage ( $p = 0.044$ ), lymph node involvement ( $n = 0.002$ ), lymphovascular invasion ( $p = 0.010$ ), tumor necrosis ( $p = 0.026$ ), and infiltrative tumor architectures ( $p = 0.039$ ), compared with those <3 mo ( $n = 146$ ; median time to RNU 33 d, range 3–89 d); there was no difference in the risk of disease recurrence ( $p = 0.066$ ) and cancer-specific mortality ( $p = 0.153$ ) [104]. Similar findings were noted in a subgroup analysis of patients with muscle-invasive disease. A second analysis from the M.D. Anderson Cancer Center similarly found no difference in 5-yr CSS (71% vs 72%,  $p = 0.39$ ) or OS (69% vs 60%,  $p = 0.69$ ) rates for patients treated at ≥3 or <3 mo from diagnosis, respectively [105].

Utilizing a multivariable analysis of the NCDB [121], Xia et al found no difference in OS for those undergoing RNU at 31–60, 61–90, and 91–120 d, compared with 8–30 d, after diagnosis among a cohort of predominately high-risk disease (66.9% of patients had high-risk disease [high grade or ≥ pT2]). However, those with a delay of 121–180 d had

worse OS in the overall cohort (vs 8–30 d; HR 1.61, 95% CI 1.19–2.19) as well as in the high-risk cohort (HR 1.56, 95% CI 1.11–2.20).

Two notable factors should be considered in the management of patients with UTUC. First, where UTUC exists in a solitary renal unit, intervention should be considered expeditiously, even in the case of low-grade disease, to protect long-term renal function. Second, accurate grading and staging are much more difficult in UTUC than in urothelial carcinoma of the bladder [106,107].

#### 3.4.1. Summary

Patients with suspected UTUC may be initially investigated with urine cytology and CT urogram, forgoing diagnostic ureteroscopy unless there is considerable diagnostic uncertainty. Patients with low-grade UTUC are often managed with nephron-sparing approaches and thus are likely to have minimal to no risk with a surgical delay. In patients with high-grade disease, delays of up to 12 wk may not be associated with changes in survival, despite worse pathologic outcomes.

### 3.5. Testicular cancer

According to estimates, there were 71 100 new cases of testicular cancer and 9500 deaths worldwide in 2018 [7]. Among those cases, 63% are estimated to have localized disease, 12% regional disease, and 12% metastatic disease in the USA [8].

Limited data, and no systematic reviews, were identified with respect to delays in treatment, including both orchiectomy and retroperitoneal lymph node dissection (RPLND), for testis cancer.

Urologic oncology dogma has been that testis masses should be treated with radical orchiectomy as soon as possible. In the NCDB, Macleod et al [108] found that most patients underwent orchiectomy within several days of diagnosis, with the highest quartile of delay corresponding to a 2-d delay. Thus, they defined a delayed orchiectomy as the 90th percentile (11 d from presentation). However, the authors did not assess whether delays in orchiectomy were associated with pathologic or survival outcomes.

In patients with clinical stage I germ cell tumors (GCTs), AS, rather than adjuvant therapy, is a standard of care [109–111]. Although there are no randomized trials comparing these approaches, the available data suggest no difference in survival [112].

We were unable to identify any studies that assessed the effect of delayed RPLND for metastatic GCTs. Surgery is rarely indicated for patients with metastatic seminoma, and in the current environment, only imperative indications should be considered. For patients with nonseminomatous germ cell tumors (NSGCTs), chemotherapy is typically the preferred initial approach. Historically, NSGCT patients with postchemotherapy masses <1 cm are observed; however, the impact of delaying postchemotherapy RPLND for masses larger than 1 cm is unknown.

For patients with advanced GCTs, data are limited. However, the association between timely delivery of

standard chemotherapy and the probability of cure is well recognized [113]. This is particularly important in patients with International Germ Cell Cancer Collaborative Group (IGCCCG) intermediate and poor prognosis disease due to the aggressive and rapidly evolving nature of this disease, as well as for patients undergoing salvage treatment. Despite limited evidence, it is likely that stage II seminoma patients and some good prognosis NSGCT patients (ie, stage IIA tumor marker negative) may delay systemic treatment at the peak of the pandemic when health care resources are limited.

#### 3.5.1. Summary

Guidelines and expert opinion recommend avoiding surgical delays for radical orchiectomy. The burden on the health care system is likely minimal, as these operations are short and routinely performed in a same-day surgical setting. Surveillance should be the preferred option for most patients with clinical stage I disease. There are insufficient data to provide guidance on the effects of delaying postchemotherapy RPLND. Patients with intermediate and poor prognosis metastatic GCTs should receive chemotherapy without a delay.

### 3.6. Penile cancer

According to estimates, there were 35 000 new cases of penile cancer and 15 100 deaths worldwide in 2018 [7].

No systematic or narrative reviews, and little primary literature, assessing the effect of delays in management of penile cancer were identified, likely due to its rarity. No studies assessing delays between initial presentation/diagnosis and primary penectomy (partial, total, or radical) were identified. However, delays between initial appearance of a penile lesion and first medical consultation are common due, in part, to social stigma. De Rose et al [114] found that this interval averaged 53 d among 113 patients with penile cancer.

The EAU guidelines recommend modified inguinal lymphadenectomy or dynamic sentinel-node biopsy for all patients with intermediate- or high-risk tumors and nonpalpable nodes [115], given the risk for micrometastatic disease [116]. Among 23 patients, those who received early inguinal lymphadenectomy (median time to surgery 1.7 mo, range 0–6 mo) had significantly lower 5-yr cancer-specific mortality than those who underwent delayed intervention (median time to surgery 14 mo, range 7–24 mo; 5-yr CSS 91% vs 13%;  $p = 0.007$ ) [117].

In the largest study to date, the group at the Moffitt Cancer Center assessed the impact of early (<3 mo,  $n = 51$ ) and delayed ( $\geq 3$  mo,  $n = 33$ ) lymphadenectomy on regional recurrence and disease-free survival (DFS) [118]. Over a median follow-up of 21 mo, early lymphadenectomy resulted in improved 5-yr RFS (77.0% vs 37.8%; HR 0.48, 95% CI 0.21–0.98) and 5-yr DFS (64.1% vs 39.5%), compared with those in men undergoing delayed lymphadenectomy.

For these reasons, and considering the ineffectiveness of chemotherapy in this tumor type, the use of perioperative

systemic therapy in lymphadenectomy candidates should be carefully considered case by case after multidisciplinary discussion.

### 3.6.1. Summary

We were unable to identify studies assessing the risk of delayed intervention of the primary penile carcinoma; however, given the rarity of this malignancy, symptomatology, and high risk for metastatic progression, it seems reasonable to avoid delays in primary surgical treatment. Additionally, inguinal lymphadenectomy for men with clinicopathologic indications should occur within 3 mo of treating the primary lesion.

### 3.7. Role of clinical trials during the COVID-19 pandemic

Clinical trials represent a key platform of comprehensive cancer centers and may provide unique therapeutic options in patients with aggressive malignancies with limited standard therapies. These opportunities may still be provided to patients during the COVID-19 outbreak, but likely require thorough evaluation on a case-by-case basis [119].

Considerations should be made as to whether clinical investigators and supporting staff are able to comply safely with the trial requirements and guarantee patients' compliance. Furthermore, a patient's ability and risk to travel for therapy during a time of rigorous social distancing and household quarantine must be considered. In an attempt to offer optimal therapeutic options with inclusion in clinical trials, investigators should carefully evaluate the risks of adding extra delays in treatment initiation due to administrative issues or bureaucratic constraint related to COVID-19 pandemic and extra visits requiring travel associated with a higher risk of infection in this mostly vulnerable population. Early evidence from China has suggested that investigators who continue to enroll to clinical trials during the COVID-19 pandemic should expect frequent protocol violations, with an average deviation of  $27 \pm 13$  d [120].

## 4. Conclusions

While acknowledging the significant psychologic burden associated with a cancer diagnosis, likely magnified by delays in treatment, physicians who treat cancer patients must be good stewards of limited health care resources, particularly in the time of a pandemic. As a result, it is important to prioritize the timely care of patients for whom delays are most likely to result in adverse outcomes, also taking into account the patient's age, comorbidities, symptoms, and life expectancy. This review aims to assist with case triage and patient counseling by summarizing the available data on outcomes of delays in treatment for patients with urologic cancers.

**Author contributions:** Zachary Klaassen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Wallis, Novara, Marandino, Necchi, Catto, Klaassen.

**Acquisition of data:** Wallis, Novara, Marandino, Necchi, Catto, Klaassen.

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**Statistical analysis:** None.

**Obtaining funding:** None.

**Administrative, technical, or material support:** Catto.

**Supervision:** Wallis, Catto, Novara, Klaassen.

**Other:** None.

**Financial disclosures:** Zachary Klaassen certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** None.

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