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Review Article

Urologic oncology practice during COVID-19 pandemic: A systematic review on what can be deferrable vs. nondeferrable

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Abstract

Purpose: To provide a review of high-risk urologic cancers and the feasibility of delaying surgery without impacting oncologic or mortality outcomes.

Materials and methods: A thorough literature review was performed using PubMed and Google Scholar to identify articles pertaining to surgical delay and genitourinary oncology. We reviewed all relevant articles pertaining to kidney, upper tract urothelial cell, bladder, prostate, penile, and testicular cancer in regard to diagnostic, surgical, or treatment delay.

Results: The majority of urologic cancers rely on surgery as primary treatment. Treatment of unfavorable intermediate or high-risk prostate cancer, can likely be delayed for 3 to 6 months without affecting oncologic outcomes. Muscle-invasive bladder cancer and testicular cancer can be treated initially with chemotherapy. Surgical management of T3 renal masses, high-grade upper tract urothelial carcinoma, and penile cancer should not be delayed.

Conclusion: The majority of urologic oncologic surgeries can be safely deferred without impacting long-term cancer specific or overall survival. Notable exceptions are muscle-invasive bladder cancer, high-grade upper tract urothelial cell, large renal masses, testicular and penile cancer. Joint decision making among providers and patients should be encouraged. Clinicians must manage emotional anxiety and stress when decisions around treatment delays are necessary as a result of a pandemic. © 2020 Elsevier Inc. All rights reserved.

Keywords: Urologic oncology; Delayed treatment; COVID-19; Cancer; Urology

1. Introduction

The coronavirus-19 (COVID-19) pandemic has caused a major national shift in all aspects of healthcare, including urology. While many urologic surgical procedures can safely be delayed, urologic oncology presents a particularly challenging dilemma. Although the entire population is at risk, cancer patients and those over the age of 60 are at increased risk of significant morbidity and mortality if infected by this virus. Though many single institutions have released priority surgical items, a group from the United States and Europe released preliminary recommendations on triage of urologic surgery [1]. Further recommendations have been released by the American College of Surgeons (ACS) and European Association of Urology (EAU) to guide appropriate treatment delays [2,3].

First-hand experience from high-volume Italian academic centers suggested a 67.8% reduction in urologic oncology cases, with a significant proportion of the remaining 32.2% of patients being eligible for a temporizing alternative therapy [4]. While chemotherapy or radiation remains an option for some patients, a group of medical oncologists recommended initiating treatment for metastatic or patients with curative intent, but not necessarily for localized disease [5].

While proceeding with selected "high-priority" major urologic oncology surgeries, such as high-risk, nonmetastatic upper tract urothelial carcinoma (UTUC), testicular cancer, penile cancer, or cT2 or larger renal masses is recommended [3], it is shown that among patients undergoing

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surgery during the COVID-19 pandemic, 44% had developed COVID-19 postoperatively requiring intensive care unit admission with a mortality rate of 20.5% [6]. Surgery and cancer are suppressive to the immune system, and synergistically can be the mechanism of more severe COVID-19 infection leading to higher mortality rate. Recognizing these data is important and proper triage is necessary to justify which cancer patients should undergo immediate surgical treatment vs. further delay during the acute and recovery phases of the pandemic. The aim of our study is to provide a review of high-risk urologic cancers and the feasibility of delaying surgery without impacting oncologic or mortality outcomes.

2. Methods

We performed a search of the PubMed and Google Scholar databases during April 2020 to identify all relevant studies using the following keywords: "treatment delay" + "bladder cancer" or "upper tract urothelial carcinoma" or "kidney cancer" or "prostate cancer" or "penile cancer" or "testicular cancer." Emphasis was placed on identifying prospective studies, including randomized controlled trials (RCT), and meta-analyses that reported on oncological outcomes. Cited references from the relevant studies were also assessed for potential inclusion. Our inclusion criteria consisted of studies which had a primary endpoint of outcomes on delayed surgery. Studies with a secondary endpoint of outcomes after delayed surgery were also included if sufficiently powered. Articles which utilized alternative therapies for definitive treatment, such as chemotherapy or radiation were excluded. Full manuscripts were reviewed when available. Four authors (ABK, SR, BME, and RM) independently screened the search results to select those studies most relevant to this review.

3. Results

The majority of studies identified were retrospective in nature. A summary of the studies reviewed can be found in Table 1. Level of evidence is based on AUA guidelines. Recommendations for treatment is based on the authors' interpretation of the studies presented. A summary of recommendations is presented in Table 2.

3.1. Kidney cancer

Historically, patients with T1a renal masses (<4 cm) are treated with surgical excision. Yet, with a large increase in the number of small renal masses (SRM) seen over the past 20 years due to an increase in abdominal cross sectional imaging, active surveillance (AS) become more commonplace in the right patient population with favorable tumor kinetics. A systematic review published in 2009 analyzed 114 peer reviewed articles and created the clinical stage T1a guidelines. These recommendations state that for patients with increased surgical risk and/or other significant comorbidities, that although the standard of care should be to still discuss surgical excision of the SRM, that AS may be offered as an appropriate approach which can either prevent or delay more invasive treatment for this index patient with T1a disease [7]. Further, a retrospective study of 6,237 patients from the SEER database who underwent radical or partial nephrectomy had no difference in cancer specific mortality based on time to surgery (<3 months vs. >3 months) [8].

Mano et al. retrospectively analyzed 1,278 patients with localized renal masses >4 cm who underwent surgical treatment, 267 (21%) of whom had a delay to surgery >3 months and 82 (6%) who had delay to surgery of at least 6 months. There was no significant difference in disease upstaging at time of surgery, recurrence of malignancy, or cancer specific survival for patients having increased surgical wait time (>3 months) at a median follow up of 4 years, but there was a decrease in overall survival seen associated in the cohort with longer delays until surgery. A subgroup analysis including patients with Stage III and Stage IV cancer found that surgical wait time was not significant for recurrence at 2 or 5 years [9]. As such, patient co-morbidities, rather than the cancer itself, caused the patient's mortality. Another retrospective study analyzed 319 patients with stage 2 disease that underwent radical nephrectomy. Patients were separated based on time from diagnosis to surgery as <1 month ($n = 234$), or between 1 and 3 months ($n = 309$). They found no significant difference in pathological upstaging, cancer specific survival or recurrence free survival at 5 years between the 2 groups [10].

Mehrazin et al. evaluated the tumor growth kinetics of 68 patients with cT1b/T2 renal masses who were followed with repeat imaging every 3 to 6 months. Approximately 67% of the patients in this study were able to delay more invasive treatment options, with a median follow up of 34 months. They reported 33% of the patients showed tumor progression, defined as interval tumor growth or development of tumor related symptoms leading to surgery, with a mean delay in treatment of 31 months. Average tumor growth rate was .44 cm/year, with 15% of patients demonstrating a zero growth rate and 0% of patients showing progression to radiographic metastatic disease with median follow up of 32 months [11]. Similarly, a retrospective study of patients on AS for cT1b or cT2 RCC had a failure rate of 20% due to rapid growth kinetics or progression to metastatic disease [12]. Further, one study reported rapid growth of T3 kidney cancer with surgical delay of 30 days. This patient was initially diagnosed with a level I-II vena cava thrombus which progressed to a level III thrombus due to this short, one month delay [13].

While SRMs (<4 cm) can safely undergo AS, there is a paucity of data on oncological outcome of those with larger renal tumors. For larger localized masses, cT1b/cT2a/cT2b,

Table 1
Summary of studies for delayed oncologic surgery

Kidney

Authors	Study design	Sample size	Treatment	Outcome	Level of evidence
Becker et al. (2014)	Retrospective	6,237	Partial or radical nephrectomy for T1a RCC less than or greater than 3 months after diagnosis	No difference in cancer specific mortality based on time to surgery, less than or greater than 3 months	B
Mano et al. (2016)	Retrospective	1,278	Partial nephrectomy for >4 cm renal masses, >3 months or >6 months after diagnosis	No difference in cancer specific mortality or disease recurrence. Decreased overall survival in group with delayed surgery	B
Kim et al. (2012)	Retrospective	319	Radical nephrectomy with stage 2 disease < 1 month or between 1-3 months	No difference in pathological upstaging, cancer specific survival or recurrence free survival	B
Mehrazin et al. (2014)	Retrospective	68	Tumor growth kinetics of cT1b/cT2 disease	45 (66%) of patients on AS could avoid definitive treatment, (23) 34% had tumor progression leading to surgery	B
Mues et al. (2010)	Retrospective	42	Tumor growth kinetics of cT1b/cT2 disease while on AS	20% of patients on AS developed rapid tumor growth requiring intervention or development of metastatic disease	C
Froehner et al. (2016)	Case report	1	None	Progression of T3 with level 1-2 IVC thrombus to level 3 thrombus with 1 month delay in surgery	C

UTUC

Authors	Study design	Sample size	Treatment	Outcome	Level of evidence
Sundi et al. (2012)	Retrospective	240	RNU <3 vs. >3 months after diagnosis of UTUC. 50% patients in delayed group received NAC.	No significant difference in CSS or OS between groups	B
Gadzinski et al. (2012)	Retrospective	73	Immediate RNU after diagnosis of UTUC vs. after a trial of failed endoscopic management.	No significant difference in 5 year CSS, OS, or MFS	C
Kim et al. (2019)	Meta-analysis	568	Immediate RNU vs. NAC followed by surgery for localized UTUC	NAC improved OS, CSS, PFS by 57%, 59%, and 45% compared to immediate surgery.	B

MIBC

Authors	Study design	Sample size	Treatment	Outcome	Level of evidence
Sánchez-Ortiz et al. (2003)	Retrospective	247	Time from diagnosis of muscle invasion to RC was determined and outcomes measured.	Extravesical or node+ disease: 84% patients with RC > 12 weeks vs. 48.2% with RC < 12 weeks. 3-year OS: 34.9% RC > 12 weeks 62.1% RC < 12 weeks	B
Gore et al. (2009)	Retrospective	441	Time from diagnosis to RC was determined and outcomes measured.	Disease specific mortality: HR 2.0 with RC > 12 weeks vs. RC < 8 weeks Overall mortality HR1.6 with RC > 12 weeks vs. RC < 8 weeks	B
Kulkarni et al. (2009)	Retrospective	2,397	Time from TURBT to RC was determined and outcomes measured.	Wait time significant predictor of OS with risk of death increasing at 40 days	A
Bruins et al. (2016)	Retrospective	1,782		No significant difference in pathologic upstaging or node+	A

(*continued*)

Table 1 (***Continued***)

MIBC

Authors	Study design	Sample size	Treatment	Outcome	Level of evidence
			Time from diagnosis of MIBC to RC was determined and outcomes measured.	disease between RC > 3 month and RC < 3 month groups. RC > 3 months not associated with decreased OS (HR 1.17, CI 0.92-1.49)	
Parker et al. (2014)	Restrospective	72	Time from diagnosis of MIBC to RC was determined and outcomes measured.	RC < 5 months had lower rates of progression (OR 0.14; $P = 0.038$) vs. RC > 5 months (OR 4.86; $P = 0.06$). No difference in RFS, CSS.	C
Park et al. (2016)	Retrospective	314	Three treatment intervals were analyzed for survival impact, from diagnosis of MIBC to initiation of NAC, from initiation of NAC to RC, and from diagnosis to RC.	RC performed <28 weeks from diagnosis of MIBC did not result in significant improvement in OS outcomes Neither timing of NAC initiation from diagnosis (median 6 weeks) nor timing of RC from NAC initiation (median 22 weeks) was associated with OS.	B
Chu et al. (2019)	Retrospective	1,509	1,238 patients underwent immediate RC after TURBT and 271 received NAC.	Delays in RC increased overall mortality, regardless of use of NAC (HR without NAC, 1.34; 95% CI 1.03−1.76; HR after NAC, 1.63; 95% CI, 1.06−2.52).	A
Audenet et al. (2019)	Retrospective	2,227	Times from diagnosis to NAC and RC were determined and outcomes measured.	Time to NAC and RC were not associated with OS. Delay to NAC ≥8 weeks predicted risk of upstaging (OR: 1.27; 95% CI: 1.02−1.59)	A

Prostate

Authors	Study design	Sample size	Treatment	Outcome	Level of evidence
Wilt et al. (2020)	RCT	659	RP vs. observation	All-cause mortality (22.1 years) 68% surgery vs. 73% observation [HR 0.84, CI 0.70-1.00]	A
Nam et al. (2003)	Retrospective	645	Time to recurrence after RP stratified by delays in surgery	Crude HR 1.47 for recurrence after treatment delay >3 months (not significant HR)	C
Singhal et al. (2015)	Retrospective	2,500	Surgical delay and time to metastasis in intermediate- and high-risk CaP	Treatment delay (avg 2.5 months) confers a higher risk of BCR and metastasis [HR 1.02, 1.06] respectively	B
Abern et al. (2013)	Retrospective	1,561	Interval between diagnosis and RP (<3, 3−6, 6−9, >9 months) in low- and intermediate-risk CaP	No increased risk for BCR, ECE, PSM, upstaging, in RP delay >9 months for low-risk. Intermediate-risk delay >9 months increases risk of BCR (OR 2.1) and PSM (4.8)	B
Graefen et al. (2005)	Retrospective	795	Time from diagnosis to RP as a prognostic factor for CaP recurrence in localized disease	No significant impact on treatment delay (mean 62 days) with recurrence rate, including high-risk disease	B
Kahn et al. (2004)	Retrospective	926	Comparison of RP delay after biopsy <60 days vs. >60 days	No significant difference in BCR between the 2 groups	B
Korets et al. (2012)	Retrospective	1,568	Comparison of RP after biopsy, <60, 61-90, >90 days on BCR	>60 day delay not associated with pathologic upstaging, BCR	B
Boorjian et al. (2005)	Retrospective	3,149			B

(*continued*)

Table 1 (***Continued***)

Prostate					
Authors	Study design	Sample size	Treatment	Outcome	Level of evidence
			Time from biopsy to RP as a predictor of BCR (<3 months vs. >3 months)	No difference in BCR between the 2 groups, including high-risk. All RP performed within 1 year of diagnosis	
Morini et al. (2018)	Retrospective	908	Analysis of upstaging, ECE, BCR after RP stratified by time to surgery (<6 months, 6-12 moths, >12 months)	No maximum cutoff time between biopsy and RP could be established to effect oncologic outcomes	B
Van Den Bergh et al. (2013)	Review	34,517	Review of treatment delays on CaP oncologic outcomes	Low risk: no difference in outcomes Intermediate/high risk: possible increase in BCR for delay 2.5-9 months	B

Penile					
Authors	Study design	Sample size	Treatment	Outcome	Level of evidence
Hardner et al. (1972)	Retrospective	100	Analysis of survival and surgical management	Nonsignificant difference in survival symptomatic >1 year vs. prompt treatment	C
Lucky et al. (2009)	Retrospective	100	Assessment of delay from patient reported symptom to diagnosis	47% of patients with delayed diagnosis of 6 months had locally advanced disease	C
Chipollini et al. (2017)	Retrospective	84	Early vs. delayed ILND (3 month cutoff) on recurrence-free and disease-specific survival	Early dissection demonstrated 5-year RFS 77% vs. 37.8 delayed. 5-year DSS 61.4% vs. 39.5% early vs. delayed	B
Testicular					
Authors	Study design	Sample size	Treatment	Outcome	Level of Evidence
Wishnow et al. (1990)	Retrospective	154	Prompt (<30 days) vs. delayed (>30 days) orchiectomy for NSGCT compared for morbidity and mortality	Prompt group had significantly more stage I Delayed group had significantly more stage III and mortality.	B
Moul et al. (1990)	Retrospective	148	Assessment of the impact on surgical delay and DSS	No effect for seminoma NSGCT delay >16 weeks associated with significantly reduced DSS in pre-cisplatin era Differences in DSS were not significant in cisplatin era	B
Moul et al. (2007)	Review		Review of the literature on the impact of timely testicular cancer diagnosis	There is no difference in DSS in the era of effective chemotherapy for NSGCT	C
Spermon et al. (2002)	Retrospective	191	Comparison of observation vs. RPLND for Stage I NSGCT	Disease-free survival at 7.7 years 98.5% vs. 98% observation vs. RPLND. Observation group underwent chemotherapy if evidence of recurrence	B

there is less substantial data on how long patients can safely delay treatment before disease progression. Therefore, it is unclear if cT1b/cT2 disease can be delayed without affecting oncologic outcomes. Patients with cT3 disease or above should not have surgical delay.

3.2. UTUC

There are fewer studies in the literature that have examined the effect of time to extirpative surgery on overall survival in patients with clinically localized UTUC. The

Table 2
Summary of recommendations

Kidney	UTUC	MIBC	Prostate	Penile	Testicular
• T1a—can safely defer on AS • T1b/T2—insufficient data • ≥T3—do not delay	• Consider NAC prior to surgery based on multidisciplinary discussion • [a]Nephroureterectomy within 12 weeks if chemo if NAC ineligible	• Consider NAC prior to surgery based on multidisciplinary discussion • [a]Cystectomy within 12 weeks if NAC ineligible	• Low-risk can be deferred possibly years • Intermediate- and high-risk may have increased BCR rates if delayed >3 months	• Do not delay primary treatment or ILND	• Do not delay orchiectomy • Consider chemotherapy prior to RPLND

[a] Multidisciplinary discussion is critical to determine optimized individual care plans.

difficulty in standardizing time to surgery lies in the inherent difficulty of staging UTUC. Biopsies obtained during ureteroscopy are usually unable to obtain adequate depth of invasion, and thus management decisions are based on tumor burden noted on preoperative imaging and tumor grade from biopsy. The treatment paradigm for UTUC is also influenced by location of tumor, and the combination of tumor size, location, and grade can lend itself to primary endoscopic management or radical surgery. Invasive UTUC has a poor prognosis with 5-year survival rates of 73% for T2 disease and 40% for T3 disease, and a median 6-month survival for T4 disease [14].

A retrospective review of 247 patients with UTUC who underwent radical nephroureterectomy (RNU) or distal ureterectomy was performed to determine effect of time to definitive surgery on recurrence-free (RFS), disease-specific (CSS), and overall survival (OS). Patients were analyzed based on whether they underwent surgery within 3 months of diagnosis ("early") or after 3 months ("delayed"). Of 54 patients who underwent delayed surgery, 50% were delayed due to receiving neoadjuvant chemotherapy (NAC), while an additional 17% were delayed due to decision to undergo endoscopic management with close surveillance. The 5-year CSS and OS was not significantly different between the 2 groups. A quarter of all patients experienced disease relapse at 5 years with 25.3% of the early group and 25.9% of the delayed surgery group. When specifically analyzing patients who did not receive NAC, similar findings were seen [15].

Another retrospective review of 73 patients who underwent immediate RNU or delayed RNU (median delay of 10 months) after trial of endoscopic surgery for UTUC also found no difference in time to recurrence, metastasis, or CSS and OS. Patients that underwent immediate RNU tended to have larger lesions. While the time interval that defined "immediate" was not explicitly elucidated in the study, results were on par with other studies that showed delayed RNU had no adverse effect on survival. However, there was evidence of significant pathologic progression (43%) when compared to initial endoscopic pathology in the delayed surgical group. Further, no patients in the delayed group had ureteral tumors at the time of diagnosis, but 64% of patients had evidence of disease in both the renal pelvis and ureter at the time of RNU [16]. It should be noted that patients in which endoscopic management can be attempted typically have a lower disease burden, and the true impact of a pure surgical delay may not be accurately represented by this study.

Several retrospective studies have evaluated the use of platinum-based NAC on UTUC in terms of overall, cancer specific, and recurrence free survival. A metanalysis reveled that patients with UTUC who received NAC had improved overall, cancer specific, and recurrence free survival compared to those who received surgery alone. Further, those receiving NAC had a significantly higher probability of downstaging to pT0 disease [17]. While these results are promising, no prospective trials have been conducted to confirm the efficacy of NAC. Patients with high grade UTUC should consider treatment with NAC prior to surgical therapy, or undergo RNU within 12 weeks of diagnosis.

3.3. Muscle invasive bladder cancer (MIBC)

Radical cystectomy (RC) in conjunction with neoadjuvant or adjuvant systemic therapy, is considered the standard for treatment of muscle invasive bladder cancer (MIBC), with 5-year survival rate of 62% to 80% [18]. Typically, RC is recommended to be performed within 3 months of MIBC diagnosis. A retrospective study of 290 patients by Sánchez-Ortiz and colleagues showed locoregional extension and nodal metastasis were higher in the groups that had RC delayed for more than 12 weeks. OS rates at 3 years were also lower in patients who had delayed RC by more than 12 weeks. This difference persisted even when adjusting for clinicopathologic stage at cystectomy [19]. These findings were further corroborated by a retrospective study that utilized the Surveillance, Epidemiology, and End Results (SEER) and Medicare claims database between the years 1992 and 2001 of patients with T2 urothelial carcinoma (UC) of the bladder. Differences in time between tumor resection (TURBT) and radical extirpation of bladder were examined and it was determined that a delay of over 12 weeks significantly worsened disease specific and overall survival [20].

Other studies have proposed a more aggressive treatment timeline, suggesting RC within 30 days of diagnosis and have mixed results. Kulkarni et al. analyzed 2,535 patients retrospectively and found treatment delay >40 days from the time of TURBT was a significant predictor of worse overall survival. For all stage pathologic lesions, an increase in wait time of 30 days increased the hazard ratio for death 4 years after surgery by 27% (pT0, pTa, and pTIS), 12% (pT1), 11% (pT2), 2% (pT3), and 4% (pT4) [21]. However, utilizing the Netherlands Cancer Registry, 1,782 patients with MIBC underwent RC and were stratified into early (<30 days) or delayed (>30 days). Although 93% of patients underwent RC <30 days after diagnosis, there was no change in rate of pathologic upstaging (43.9% vs. 42.1%), node-positive disease (20.2% vs. 21.7%), or decreased OS (hazard ratio = 1.16; 95% CI: 0.91−1.48; $P = 0.25$) when compared to patients who had delayed RC. This was seen both in patients who received NAC and those who did not (hazard ratio = 0.90; 95% CI: 0.45−1.82) [22].

With the advent of NAC and immunotherapy, the debate regarding time to RC has gained new vigor. In 2014, a retrospective review of 72 patients who underwent RC after NAC between the years 2006 and 2012 was performed specifically examining time intervals between time of diagnosis and ultimate RC and their effect on overall and recurrence free survival. The majority (75%) of patients received gemcitabine/cisplatin chemotherapy. When stratifying by time to RC (1−4 months, 5 months, 6 months) there was no statistical difference in recurrence free or cancer specific survival. However, on multivariate analysis patients who had RC less than 5 months from diagnosis had lower rates of progression (OR 0.14; 95% CI 0.02−0.08, $P = 0.038$) compared to those with RC after 5 months (OR 4.86 95% CI 0.9−26, $P = 0.06$) [23].

A larger retrospective analysis identified 314 patients who received NAC followed by RC for MIBC between 1996 and 2014, of whom 201 were included in the final analysis. Patients received either gemcitabine/cisplatin (83.5%), dose dense methotrexate, vinblastine, adriamycin, and cisplatin (5%), or non-cisplatin based chemotherapeutic agents (9%). Median survival for patients with cystectomy performed less than 28 weeks from TURBT diagnosis was not significantly different compared to a survival for patients with cystectomy performed beyond 28 weeks from TURBT diagnosis date (HR 0.68, 95% CI 0.28−1.63, $P = 0.388$). Similarly, the difference in median survival between patients who received NAC within 6 weeks from TURBT diagnosis date and those whose NAC was delayed beyond 6 weeks was not significant (HR 1.28, 95% CI 0.75−2.20, $P = 0.360$). The timing of cystectomy from initiation of NAC before and after 22 weeks did not have a significant impact on median survival (HR 1.12, 95% CI 0.47−2.60, $P = 0.801$) [24]. In contrary, a repeat analysis of the SEER and Medicare claims database compared patients who received NAC to those who did not. In comparison with timely surgery (defined as surgery within 12 weeks from diagnosis), delays in RC increased overall mortality, regardless of the use of NAC (hazard ratio [HR] without NAC, 1.34; 95% confidence interval [CI], 1.03−1.76; HR after NAC, 1.63; 95% CI, 1.06−2.52) [25].

A review of the National Cancer Database found 2,227 patients who underwent NAC and RC for cT2-T4a UC between 2004 and 2014. Times from diagnosis to treatments were tested for association with overall survival and pathologic outcomes. On Cox regression, time to NAC and time to RC were not associated with differences in overall survival, and this was seen in subgroups of responders and nonresponders to NAC. In fact, time from diagnosis to surgery up to 7 months did not affect OS in patients treated with NAC. However, a delay of ≥8 weeks to start NAC was significantly associated with a higher risk of upstaging and lymph node positivity on final pathology (OR: 1.27; 95% CI: 1.02−1.59; $P = 0.031$) [26].

In sum, MIBC is undoubtedly an aggressive disease and associated with rapid and high cancer specific mortality. In patients who are ineligible for up front NAC, a delay of at most 12 weeks prior to RC is within appropriate clinical practice. Patients who are eligible for cisplatin-based NAC should receive chemotherapy within a few weeks of diagnosis, and subsequent RC can possibly be delayed up to 5 to 7 months after diagnosis, although earlier cystectomy would be more prudent to avoid upstaging on final pathology. While it heavily depends on institutional resources at the time of pandemic, multidisciplinary approach is needed to decide whether to proceed with upfront surgery vs. subjecting patients to an immunocompromised state with neoadjuvant systemic therapy. Further studies needed to address the potential risk of exposure to COVID-19 by frequent visits to the infusion centers. Radiotherapy after induction of chemo-sensitizing agents can be considered in select patients.

3.4. Prostate cancer (CaP)

The paradigm for treatment of localized prostate cancer, particularly very low risk and low risk disease, has shifted to that of AS. The prostate cancer intervention vs. observation trial (PIVOT) is one of the largest studies randomizing patients with prostate cancer to radical prostatectomy (RP) vs. observation. Long term results showed an overall survival benefit of 1 year for the surgical group compared to the observation group. Though not sufficiently powered, there appeared to be a larger benefit for patients with intermediate risk disease undergoing RP compared to observation, but the increased survival was not found in low risk or high risk patients [27]. However, the true effect of delaying definitive treatment, particularly in the intermediate and high risk groups has been less clear.

One of the first studies to evaluate delay of surgery as a prognostic factor concluded that there is a 1.5x risk of developing recurrence if cancer treatment is delayed greater than 3 months. This study retrospectively evaluated 645

patients that underwent radical prostatectomy. On multivariate analysis, Gleason grade ≥7, PSA ≥20, and extracapsular extension or seminal vesicle invasion were all predictors of biochemical recurrence (BCR). Treatment delay >3 months from the time of biopsy, while revealing a significant crude HR of 1.47 (CI 1.0−2.2, $P = 0.05$) was not significant when adjusted for confounding variables [28].

Few subsequent studies have shown negative oncologic outcomes for delayed treatment. A group from the University of Michigan analyzed 2,500 men with D'Amico intermediate or high risk CaP and found a small, but statistically significant increased risk for BCR and metastasis for each month of delay (BCR HR 1.02 [CI 1.01−1.04] $P = 0.002$; metastasis HR 1.06 [CI 1.02−1.09] $P = 0.001$). There was no difference in overall survival [29]. These findings were corroborated by Abern et al. who found that for D'Amico intermediate risk, surgical delay of >9 months led to a 2-fold increase in BCR (HR 2.19 [CI 1.24−3.87] $P = 0.007$) and also increased rates of positive surgical margin (OR 4.08 [CI 1.52−10.91] $P = 0.005$) [30].

A retrospective study of 795 men evaluated those with CaP who underwent early treatment (<31 days) vs. surgical delay (>70 days). In this study, there was no effect on surgical delay in terms of progression free survival. This remained true for patients with high-grade disease. There was no significant prognostic effect of time to treatment when taking into consideration Gleason grade, pretreatment PSA, or clinical stage [31]. In line with these findings, Khan also found that a delay in surgery, up to 150 days after biopsy had no effect on biochemical recurrence rate. This remained true for patients with Gleason sum ≥7, PSA ≥10, or clinical stage ≥T2a, though the cohort of 55 patients was relatively small [32].

Several studies have had no significant results upon studying time to surgery (TTS) as an independent prognosticator. Korets et al. conducted a retrospective review of 1,568 men with CaP to assess TTS as a risk factor for BCR. In this study, high PSA, Gleason sum, clinical stage, and patients who were African-American all were at increased risk of BCR. Regardless of the risk stratification at the time of biopsy (low, intermediate, or high), a delay of surgery >60 days did not increase BCR or have worse pathological outcomes [33]. Boorjian et al. also found similar results in regard to predicting risk factors for BCR after RP in a group of 3,149 men. Gleason score, high PSA prior to biopsy, and clinical stage were all risk factors for BCR. However, time from biopsy to surgery failed to predict BCR for any risk group, including those with TTS > 90 days [34]. Further, a study of 908 patients with CaP in Brazil were retrospectively analyzed and, regardless of interval from biopsy to surgery, had no correlation with poor surgical outcomes. This remained true for those at intermediate and high risk [35].

In general, there is limited, retrospective data on delaying treatment for intermediate and high risk nonmetastatic CaP patients. Treatment delay for very low and low risk disease does not seem to impact oncologic outcomes, even if treatment is deferred for years. There may be an increased risk of BCR in intermediate and high risk patient groups when delaying surgery 2.5 to 9 months [36]. BCR is more readily predicted by a high prebiopsy PSA, clinical stage, and Gleason score rather than time to surgery. Clinicians should also consider nonsurgical curative treatment modalities, such as radiation therapy with androgen deprivation, for intermediate or high-risk disease.

3.5. Penile

Penile cancer is a rare malignancy, accounting for 0.4% to 0.6% of all malignancies in men. It is an extremely aggressive malignancy and will be the cause of death for nearly all patients within 2 years if left untreated [37,38]. Further, given this malignancy's relative radio- and chemoresistance, the cornerstone of therapy remains surgical. Because of the aggressive course, few studies have been able to analyze surgical delay on patient outcomes.

In the 1970s, one study found that patients who were symptomatic for >1 year prior to diagnosis had slightly worse survival compared to those treated promptly, but this difference was not statistically significant [39]. Another study found that among patients who had referral delays >6 months, 47% had locally advanced disease [40]. With that, there have been no studies comparing outcomes of patients who underwent prompt vs. delayed treatment.

There has been more controversy on the role of early vs. delayed inguinal lymph node dissection (ILND). Historically, there was an arbitrary wait period of 6 weeks after treatment of the primary lesion to allow for possible treatment with antibiotics [41]. There is also evidence to suggest that prophylactic ILND provides a significant survival benefit compared to delayed or therapeutic ILND. Patients with cN0 disease who underwent a "wait-and-see" policy had a 9.1% chance of developing regional recurrence. It is noteworthy that only 1/3 of patients with regional recurrence are alive after 5 years [42].

Early ILND has been shown to have improved disease specific survival (DSS) at 5 years for a cohort of patients who underwent ILND prior to 3 months from primary tumor excision. The early ILND group had a 64.1% 5-year DSS compared to 39.5 in the late dissection group specifically in patients with cN0 disease. This survival benefit was not seen for patients with palpable nodal disease [43].

Though there is limited data, primary treatment of penile cancer should not be delayed. Further, deferring ILND will likely cause a decrease in disease-specific survival.

3.6. Testicular

Early orchiectomy has been traditionally associated with improved survival in testicular cancer. Particularly true for nonseminomatous germ cell tumors (NSGCT), prompt orchiectomy (within 30 days) diagnosed more patients with

stage 1 disease and fewer patients with stage 3 disease compared to delayed orchiectomy [44]. However, most studies published do not take into account overcoming surgical delays with chemotherapy. Indeed, in the pre-cisplatin era, patients had significantly worse survival with delayed surgery. However, with effective chemotherapy, there was no difference in survival between early vs. delayed surgery. This finding was not true for patients with seminomatous tumors, which are typically slow growing and can have long surgical delays without affecting outcome [45]. There should be consideration that patients in which surgical delay must be overcome often require more extensive chemotherapy and/or surgery [46].

There is a paucity of data on delayed retroperitoneal lymph node dissection (RPLND). In a comparison of patients with Stage 1 NSGCT either undergoing surveillance or primary RPLND, there was no difference in disease specific survival in the setting of cisplatin. For example. If a patient developed disease in the surveillance group, treatment with cisplatin based chemotherapy was initiated. Further, if a patient had a tumor identified on RPLND, they also underwent subsequent chemotherapy [47]. Cisplatin-based chemotherapy appears to abate the need for immediate surgical intervention, primarily for localized testicular malignancy.

Primary treatment for testicular cancer should not be delayed, as the benefits of a quick, ambulatory surgery outweigh the risks of prolonged chemotherapy. Retroperitoneal lymph nodes can be managed initially with a trial of chemotherapy, but this decision should be undertaken with a multidisciplinary approach. Further, it is the opinion of the authors that RPLND should not be delayed in those after an initial trial of chemotherapy with NSGCT and a residual mass given the possibility of a teratoma.

4. Conclusion

Many urologic oncologic surgeries can be safely deferred without impacting long-term cancer specific or overall survival. Notable exceptions are MIBC, high-grade UTUC (especially ureteral cancer), testicular, and penile cancer, often presenting with an aggressive and relentless course. While NAC may allow for a delay in MIBC and UTUC, clinicians must also consider the morbidity associated with immune suppression, particularly during a viral pandemic. Further, those with high stage tumors, such as T3 kidney cancer, likely cannot afford a surgical delay. High risk cancer patients should be counseled on available data in regard to delay in treatment, as well as risks associated with contracting COVID-19 during postoperative recovery prior to treatment decisions. Joint decision making among providers and patients should be encouraged. Clinicians must manage emotional anxiety and stress when decisions around treatment delays are necessary as a result of a pandemic.

References

[1] Stensland KD, Morgan TM, Moinzadeh A, et al. Considerations in the Triage of Urologic Surgeries During the COVID-19 Pandemic. Eur Urol 2020:Epub ahead.

[2] American College of Surgeons. COVID-19 Guidelines for Triage of Urology Patients. ACS: COVID-19 and Surgery.

[3] Combined Oncology Recommendations. EAU Rapid Response Group: An organisation-wide collaborative effort to adapt the EAU guidelines recommendations to the COVID era. https://uroweb.org/wp-content/uploads/Combined-oncology-COVID-19-recommendations.pdf. Published 2020.

[4] Campi R, Amparore D, Capitanio U, et al. Assessing the Burden of Nondeferrable Major Uro-oncologic Surgery to Guide Prioritisation Strategies During the COVID-19 Pandemic: Insights from Three Itialian High-volume Referral Centres. Eur Urol 2020:Epub ahead.

[5] Gillessen S, Powles T. Advice Regarding Systemic Therapy in Patients with Urological Cancers during the COVID-19 Pandemic. Eur Urol 2020:Epub ahead.

[6] Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine 2020:100331.

[7] Campbell S, Uzzo RG, Allaf ME, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol 2017;182(4):1271–9.

[8] Becker A, Roghmann F, Ravi P, et al. Delay in nephrectomy and cancer control outcomes in elderly patients with small renal masses. Urol Int 2014;92(4):455–61.

[9] Mano R, Vertosick EA, Hakimi AA, et al. The effect of delaying nephrectomy on oncologic outcomes in patients with renal tumors greater than 4 cm. Urol Oncol Semin Orig Investig 2016;34(5):239–e1.

[10] Kim KH, You D, Jeong IG, et al. The impact of delaying radical nephrectomy for stage II or higher renal cell carcinoma. J Cancer Res Clin Oncol 2012;138(9):1561–7.

[11] Mehrazin R, Smaldone MC, Kutikov A, et al. Growth kinetics and short-term outcomes of cT1b and cT2 renal masses under active surveillance. J Urol 2014;192(3):659–64.

[12] Mues AC, Haramis G, Badani K, et al. Active surveillance for larger (cT1bN0M0 and cT2N0M0) renal cortical neoplasms. Urology 2010;76(3):620–3.

[13] Froehner M, Heberling U, Zastrow S, Toma M, Wirth MP. Growth of a Level III Vena Cava Tumor Thrombus Within 1 Month. Urology 2016;90:e1–2.

[14] Audenet F, Yates DR, Cussenot O, Rouprêt M. The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UCC). Urol Oncol Semin Orig Investig 2013;31(4):407–13.

[15] Sundi D, Svatek RS, Margulis V, et al. Upper tract urothelial carcinoma: Impact of time to surgery. Urol Oncol Semin Orig Investig 2012;30(3):266–72.

[16] Gadzinski AJ, Roberts WW, Faerber GJ, Wolf JS. Long-term outcomes of immediate versus delayed nephroureterectomy for upper tract urothelial carcinoma. J Endourol 2012;26(5):566–73.

[17] Kim DK, Lee JY, Kim JW, Hah YS, Cho KS. Effect of neoadjuvant chemotherapy on locally advanced upper tract urothelial carcinoma: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2019;135:59–65.

[18] Gore JL, Litwin MS, Lai J, et al. Use of radical cystectomy for patients with invasive bladder cancer. J Natl Cancer Inst 2010;102(11):802–11.

[19] Sánchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J Urol 2003;169(1):110–5.

[20] Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS. Mortality increases when radical cystectomy is delayed more than 12 weeks:

Results from a surveillance, epidemiology, and end results-medicare analysis. Cancer 2009;115(5):988–96.
[21] Kulkarni GS, Urbach DR, Austin PC, Fleshner NE, Laupacis A. Longer Wait Times Increase Overall Mortality in Patients With Bladder Cancer. J Urol 2009;182(4):1318–24.
[22] Bruins HM, Aben KKH, Arends TJ, van der Heijden AG, Witjes AJ. The effect of the time interval between diagnosis of muscle-invasive bladder cancer and radical cystectomy on staging and survival: A Netherlands Cancer Registry analysis. Urol Oncol Semin Orig Investig 2016;34(4):166–e1.
[23] Parker WP, Nehra A, Griffin J, Lopez-Corona E, Holzbeierlein JM. Association of time delays to radical cystectomy by use of neoadjuvant chemotherapy with higher rates of progression. J Clin Oncol 2014;32(4_suppl):345.
[24] Park JC, Gandhi NM, Carducci MA, et al. A Retrospective Analysis of the Effect on Survival of Time from Diagnosis to Neoadjuvant Chemotherapy to Cystectomy for Muscle Invasive Bladder Cancer. J Urol 2016;195(4):880–5.
[25] Chu AT, Holt SK, Wright JL, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. Cancer 2019;125(12):2011–7.
[26] Audenet F, Sfakianos JP, Waingankar N, et al. A delay 8 weeks to neoadjuvant chemotherapy before radical cystectomy increases the risk of upstaging. Urol Oncol Semin Orig Investig 2019;37(2):116–22.
[27] Wilt TJ, Vo TN, Langsetmo L, et al. Radical Prostatectomy or Observation for Clinically Localized Prostate Cancer: Extended Follow-up of the Prostate Cancer Intervention Versus Observation Trial (PIVOT). Eur Urol 2020.
[28] Nam RK, Jewett MAS, Krahn MD, et al. Delay in surgical therapy for clinically localized prostate cancer and biochemical recurrence after radical prostatectomy. Can J Urol 2003;10(3):1891.
[29] Singhal U, Lu L, Skolarus T, et al. PD43-12 EFFECT OF TREATMENT DELAY ON LONG-TERM OUTCOMES IN MEN UNDERGOING RADICAL PROSTATECTOMY FOR PROSTATE CANCER. J Urol 2015;193(4S).
[30] Abern MR, Aronson WJ, Terris MK, et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: Possible implications for active surveillance from the SEARCH database. Prostate 2013;73(4):409–17.
[31] Graefen M, Walz J, Chun KHF, Schlomm T, Haese A, Huland H. Reasonable delay of surgical treatment in men with localized prostate cancer - Impact on prognosis? Eur Urol 2005;47(6):756–60.
[32] Khan MA, Mangold LA, Epstein JI, Boitnott JK, Walsh PC, Partin AW. Impact of surgical delay on long-term cancer control for clinically localized prostate cancer. J Urol 2004;172(5):1835–9.
[33] Korets R, Seager CM, Pitman MS, Hruby GW, Benson MC, McKiernan JM. Effect of delaying surgery on radical prostatectomy outcomes: A contemporary analysis. BJU Int 2012;110(2):211–6.
[34] Boorjian SA, Bianco FJ, Scardino PT, Eastham JA. Does the time from biopsy to surgery affect biochemical recurrence after radical prostatectomy? BJU Int 2005;96(6):773–6.
[35] Morini MA, Muller RL, de Castro Junior PCB, de Souza RJ, Faria EF. Time between diagnosis and surgical treatment on pathological and clinical outcomes in prostate cancer: does it matter? World J Urol 2018;36(8):1225–31.
[36] Van Den Bergh RCN, Albertsen PC, Bangma CH, et al. Timing of curative treatment for prostate cancer: A systematic review. Eur Urol 2013;64(2):204–15.
[37] Ries L, Melbert D, Krapcho M, et al. SEER cancer statistics review, 1975-2003 2006.
[38] Derrick FC, Lynch KM, Kretkowski RC, Yarbrough WJ. Epidermoid carcinoma of the penis: computer analysis of 87 cases. J Urol 1973;110(3):303–5.
[39] Hardner GJ, Bhanalaph T, Murphy GP, Albert DJ, Moore RH. Carcinoma of the penis: analysis of therapy in 100 consecutive cases. J Urol 1972;108(3):428–30.
[40] Lucky MA, Rogers B, Parr NJ. Referrals into a dedicated British penile cancer centre and sources of possible delay. Sex Transm Infect 2009;85(7):527–30.
[41] Abi-Aad AS, DeKernion JB. Controversies in ilioinguinal lymphadenectomy for cancer of the penis. Urol Clin North Am 1992;19(2):319.
[42] Leijte JAP, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence Patterns of Squamous Cell Carcinoma of the Penis: Recommendations for Follow-Up Based on a Two-Centre Analysis of 700 Patients. Eur Urol 2008;54(1):161–9.
[43] Chipollini J, Tang DH, Gilbert SM, et al. Delay to Inguinal Lymph Node Dissection Greater than 3 Months Predicts Poorer Recurrence-Free Survival for Patients with Penile Cancer. J Urol 2017;198(6):1346–52.
[44] WISHNOW KI, JOHNSON DE, PRESTON WL, TENNEY DM, BROWN BW. Prompt Orchiectomy Reduces Morbidty and Mortal from Testicular Carcinoma. Br J Urol 1990;65(6):629–33.
[45] Moul JW, Paulson DF, Dodge RK, Walther PJ. Delay in diagnosis and survival in testicular cancer: Impact of effective therapy and changes during 18 years. J Urol 1990;143(3):520–3.
[46] Moul JW. Timely Diagnosis of Testicular Cancer. Urol Clin North Am 2007;34(2):109–17.
[47] Spermon JR, Roeleveld TA, Van der Poel HG, et al. Comparison of surveillance and retroperitoneal lymph node dissection in Stage I nonseminomatous germ cell tumors. Urology 2002;59(6):923–9.