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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.

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
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

| Authors                  | Study design | Sample size | Treatment                                                                 | Outcome                                                                 | Level of evidence |
|--------------------------|--------------|-------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------|
| **Kidney**               |              |             |                                                                           |                                                                         |                   |
| 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 thombus to level 3 thrombus with 1 month delay in surgery | C                 |
| **UTUC**                 |              |             |                                                                           |                                                                         |                   |
| 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 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**                |              |             |                                                                           |                                                                         |                   |
| 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 vs. 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 |
|------------------------|--------------|-------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Parker et al. (2014)   | Retrospective| 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) respectively | 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)
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
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 metaanalysis revealed 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 multivariable analysis, Gleason grade \( \geq 7 \), PSA \( \geq 20 \), 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 \( \geq 7 \), PSA \( \geq 10 \), or clinical stage \( \geq T2a \), 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 asymptomatic 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.

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