A Systematic Review And Meta-Analysis On Delaying Surgery For Urothelial Carcinoma Of Bladder And Upper Tract Urothelial Carcinoma: Implications For The COVID19 Pandemic and Beyond

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ABSTRACT

PURPOSE: The COVID-19 pandemic has led to competing strains on hospital resources and healthcare personnel. Patients with newly diagnosed invasive urothelial carcinomas of bladder (UCB) upper tract (UTUC) may experience delays to definitive radical cystectomy (RC) or radical nephro-ureterectomy (RNU) respectively. We evaluate the impact of delaying definitive surgery on survival outcomes for invasive UCB and UTUC.

METHODS: We searched for all studies investigating delayed urologic cancer surgery in Medline and Embase up to June 2020. A systematic review and meta-analysis was performed.

RESULTS: We identified a total of 30 studies with 32,591 patients. Across 13 studies (n=12,201), a delay from diagnosis of bladder cancer/TURBT to RC was associated with poorer overall survival (HR 1.25, 95% CI: 1.09-1.45, p=0.002). For patients who underwent neoadjuvant chemotherapy before RC, across the 5 studies (n=4316 patients), a delay between neoadjuvant chemotherapy and radical cystectomy was not found to be significantly associated with overall survival (pooled HR 1.37, 95% CI: 0.96-1.94, p=0.08). For UTUC, 6 studies (n=4,629) found that delay between diagnosis of UTUC to RNU was associated with poorer overall survival (pooled HR 1.55, 95% CI: 1.19–2.02, p=0.001) and cancer-specific survival (pooled HR of 2.56, 95%CI: 1.50-4.37, p=0.001). Limitations included between-study heterogeneity,

particularly in the definitions of delay cut-off periods between diagnosis to surgery.

CONCLUSIONS: A delay from diagnosis of UCB or UTUC to definitive RC or RNU was associated with poorer survival outcomes. This was not the case for patients who received neoadjuvant chemotherapy.

Keywords: Delay in Surgery, Delayed Treatment, Time-to-Treatment, Urinary Bladder Neoplasms, Ureteral Neoplasms, Urothelial Carcinoma

1. INTRODUCTION

Bladder cancer is the 11th most commonly occurring cancer worldwide, with almost 550,000 new cases in 2018 [1,2]. A comprehensive review in 2017 found that bladder cancer ranks 13th in terms of death ranks, with mortality rates decreasing mainly in the most developed countries [3]. In comparison, UTUC is much rarer, representing approximately 8.3% of all urothelial carcinoma [4].

At diagnosis, approximately 20% of patients have MIBC [5]. One of the factors thought to affect mortality for MIBC is the timing to definitive surgery following diagnosis. The 2020 EAU guidelines cited two studies, with one showing worse clinical outcome and poorer survival in patients who experienced a delay of RC by >3 months while the other showed no survival difference [6,7]. With regards to MIBC patients treated with neoadjuvant chemotherapy, the AUA recommends RC within 6-8 weeks of completion of chemotherapy, unless “medically inadvisable”, while acknowledging that there remains a void of prospective data regarding the optimal timing of RC following NAC [8]. Although low grade non-invasive UTUC can be treated endoscopically, RNU remains the treatment of choice for invasive and/ or high grade UTUC. The EAU recommends that RNU should not be delayed beyond 12 weeks as this increases the risk of disease progression [9].

This issue of delayed treatment for MIBC and invasive UTUC is especially pertinent in our current ongoing COVID19 pandemic. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic emerged in

December 2019 and has resulted in redistribution of healthcare resources to address the pandemic. This has resulted in cancelation of elective surgeries worldwide [10,11]. Many hospitals have deferred elective and non-cancer surgery, while prioritizing emergency cases and select high-risk oncological cases. To provide expert consensus, the EAU Guidelines Office Rapid Reaction Group recommend that RC should be performed within 3 months from MIBC diagnosis and RNU within 6 weeks of high-risk UTUC diagnosis [12].

The impact of the COVID-19 crisis on elective urological cancer surgery has been significant and disruptive worldwide and is compounded by the concerns of a second or third wave of COVID-19 cases. This invariably will result in the deferment of treatment of localized cancers, which may lead to disease progression and worse survival outcomes. In this study, we performed a systematic review and meta-analysis to evaluate the evidence and association of delayed RC and RNU for patients with MIBC and high-risk UTUC. These data should serve as a framework for decision making regarding timelines of definitive therapy in these disease entities.

2. EVIDENCE ACQUISITION

2.1. Protocol registration

Our protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) registry (CRD42020190882).We performed this study according to the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Since most of the included studies were retrospective in nature, we also adhered to guidelines from the “Meta-analysis Of Observational Studies in Epidemiology” (MOOSE) group [14].

2.2. Literature Search

We performed a systematic search of PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews to identify studies up to June 2020. Different variations of key words and MESH terms for urothelial carcinoma were combined with various combinations of survival outcomes in delaying surgery to identify articles that focused on the issue of delayed surgery. Our complete search strategy is shown in **Supplementary Table 1**.

Objective

The primary objective was to evaluate if delays to RC and RNU would affect the overall survival of patients with MIBC and high-risk UTUC, respectively.

Eligibility criteria, manuscript screening, data abstraction, and study quality

We evaluated studies for inclusion and exclusion based on a pre-defined PICOS approach where the population (P), intervention (I), comparator group (C), outcome (O), and study design (S) were considered. This is summarized in **Table 1**.

2.3. Screening and data extraction

Search results were screened by two independent reviewers. Any conflicts were resolved by a third reviewer Finally, eligible articles were identified for full text review (**Figure 1**). Data extraction was then performed by two authors (JJL, JT) with any discrepancy resolved by a third author (WST). Data on the paper (first author, year, center, country, study design), participant demographics and oncologic characteristics, treatment characteristics, and outcomes, and results were extracted.

2.4. Statistical methods

Descriptive statistics using median and interquartile range were used to summarize demographic and baseline data of eligible patients. Sample size of individual studies, demographic values were calculated based on percentages and summed up to obtain the values used for this cohort. Pooled averages were estimated using fixed and random-effects model when indicated. The I^2 statistic was used to quantify heterogeneity. Statistical analyses were performed using STATA/SE 14.2 (StataCorp, College Station, Texas, USA).

2.5. Risk of bias assessment

We performed risk of bias assessment using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (**Supplementary Table 2**) [15].

3. EVIDENCE SYNTHESIS

3.1. Search Results

Our literature search initially revealed 1858 articles after removing duplicates. After screening them based on our pre-defined PICOS criteria, we identified 136 articles which were further reviewed in detail and categorized by type of cancer (**Figure 1**).

3.2. Meta-Analysis for Bladder Cancer Studies

We identified a total of 30 studies with 32,591 patients (**Table 2**). There were varied definitions of delay to RC, with 11 studies identifying the "start point" as "diagnosis of bladder cancer" [16-26], while another 10 used "time of transurethral resection of bladder tumour" (TURBT) [6,7,27-34]. Five studies evaluated the delay between neoadjuvant chemotherapy and RC [27,35-38]. Four other studies evaluated delay from time of diagnosis prompting BCG therapy to RC [39], time from RC to starting adjuvant chemotherapy [40], time from referral to first treatment [41], and time from first clinic appointment to definitive treatment (radiotherapy or RC) [42].

Given that the diagnosis of bladder cancer is confirmed upon histology obtained from TURBT, it can be safe to assume that these two "events" are synonymous. Although each study's exact cut-off duration varies from 60 to

90 days, we considered this “delay” the exposure variable for our meta-analysis. Across 13 studies (n=12,201), a delay from diagnosis of bladder cancer / TURBT to RC was associated with poorer overall survival (HR 1.25, 95% CI: 1.09-1.45, p=0.002) (**Figure 2**). There was substantial heterogeneity with an I^2 value of 76.9% (Cochrane p-value <0.001), so a random-effects model was used. Influence analysis showed that the two most influential studies [36,42] had the greatest effects on the pooled HR if omitted.

For patients who underwent neoadjuvant chemotherapy prior to radical cystectomy, across the five studies (n=4316 patients), a delay between neoadjuvant chemotherapy and radical cystectomy was not found to be significantly associated with overall survival (pooled HR 1.37, 95% CI: 0.96-1.94, p=0.08). There was substantial heterogeneity with an I^2 value of 70% (Cochrane p-value 0.01), so a random-effects model was used. Three studies representing patients treated at Johns Hopkins[38], Michigan[35] (ref) and Mayo [37] reported 3 cycles of neoadjuvant chemotherapy administered and received by patients. The other 2 studies did not have such granular data as they were analyses of the National Cancer Data Base (records only whether patients received single or multi-agent chemotherapy)[36] and SEER-Medicare database (provider billing data utilized to determine receipt and timing chemotherapy).[27]

3.3. Meta-Analysis for Upper Tract Urothelial Carcinoma Studies

There were six studies evaluating the effect of delay to radical nephroureterectomy on survival for UTUC with a total of 4629 patients.[43-48] When evaluating the delay between diagnosis of UTUC and RNU, the meta-

analysis revealed a pooled HR of 1.55 (95% CI: 1.19–2.02, p=0.001) for overall survival (**Figure 3**) and a pooled HR of 2.56 (95%CI: 1.50-4.37, p=0.001) for cancer-specific survival (**Figure 4)**. There was no evidence of heterogeneity so fixed-effects models were used. Influence analysis showed that Alva et al [35] had the greatest effect on the result if omitted.

3.4. Discussion

The SARS-CoV-2 epidemic has resulted in the cancelation of elective cancer surgeries worldwide, resulting in delay of cares for patients with invasive urothelial carcinoma. We performed a systematic review and meta-analysis to evaluate the evidence and the effect of delayed RC and RNU for patients with MIBC and high risk UTUC. Our study suggests that for patients who underwent upfront RC, a delay between bladder cancer diagnosis and undergoing definitive RC was associated with significantly poorer overall survival. Similarly, for UTUC, a delay between UTUC diagnosis to RNU was associated with worse overall and cancer-specific survival.

On the contrary, we found that a delay in RC following neoadjuvant chemotherapy did not impact survival outcomes. This finding is particularly pertinent because increasingly more patients with MIBC are receiving neoadjuvant chemotherapy, backed by level one evidence [49]. This provides some reassurance to patients who face treatment delays due to chemotherapy related adverse events. Even among a relatively healthy study population in the SWOG-8710 trial, 33% of patients had grade 4 (severe) granulocytopaenia, and 17% had grade 3 (moderate) nausea, vomiting, stomatitis, diarrhoea, or constipation after neoadjuvant chemotherapy [50].

However, during the COVID-19 pandemic it is important to acknowledge the theoretical competing risk of succumbing to COVID-19 due to an impaired immune system secondary to chemotherapy [51], particularly among the unvaccinated. This may lead to patients or clinicians electing to avoid peri-operative chemotherapy despite guideline recommendations.

Guidelines and societies have risen to the challenge during the COVID pandemic and came up with suggestions on how to overcome and reduce delay in definitive surgery for urology patients. The Urology Research Network from Italy has strategized how best to reorganize routine urologic practice and recommended how to facilitate the process of rescheduling both surgical and outpatient activities during the COVID-19 pandemic, and in subsequent phases[52]. For muscle-invasive bladder cancer, radical cystectomy was categorized in the list of urological surgical procedures strongly recommended to continue during the pandemic, as delay can jeopardise cancer-related outcomes. Caution is advised in case of bowel resection due to high prevalence of high virus load in stool. Preoperative staging is suggested to be simplified to CT chest, abdomen and pelvis, omitting diagnostic ureteroscopy which was optional with weak strength rating in the 2020 EAU guidelines[52,53]. For high-risk UTUC, radical nephro-ureterectomy with template-based lymphadenectomy is also strongly recommended to continue, with preoperative staging simplified to CT urogram and flexible urethrocystoscopy alone, omitting diagnostic ureteroscopy[52,53]. These recommendations are a key referendum for all to resume routine urologic practice and can help as this pandemic evolves with time. Another helpful strategy to improve access for patients with haematuria is to use telehealth services to expedite workup with

upper tract imaging and flexible cystoscopy, as described in more detail in a review article highlighting practical ways of how telehealth services can be useful during and after the COVID pandemic[54]

The effect of delays in RC has been investigated previously for MIBC. A recent systematic review (19 studies) and meta-analysis (10 studies) was performed for papers up to August 2019, although we found that there were some methodological errors (e.g. hazard ratio for progression-free survival used in overall survival meta-analysis) [55]. Our study has updated the literature search up to June 2020 and includes a total of 30 studies in all, representing the latest available evidence for this topic.

Established dogma would suggest that delays in radical surgery for localised cancer carries the risk of disease progression, resulting in patients missing the opportunity to be cured of their cancer [56]. Efforts to minimise treatment delays have led to countries such as the United Kingdom establishing cancer targets for providers to initiate treatment within 31 days from the time decision to treat is established [57]. However, it is worth bearing in mind that not all cancer types have the same natural history and prognosis, and in the era of the COVID-19 pandemic, a tailored approached based on cancer disease risk should be adopted in terms of prioritising the urgency of each case. Invasive urothelial carcinoma, in the absence of treatment, progresses quickly. Those who decline treatment with curative intent have a 75% chance of dying from bladder cancer and a 40-50% chance of doing so within 1 year[58]. It may also

be possible that delay in surgery could lead to more advanced disease, and could lead to more postoperative complications.

The question of what constitutes an 'acceptable' time to treatment delay is often a subject of investigation. A SEER-Medicare analysis of patients with T2 bladder cancer who underwent RC between 1992-2001 identified 441 patients. Patients who experienced a delay of 8-12 weeks had a similar mortality risk compared to those who underwent RC within 4-8 weeks of diagnosis. However, patients who experienced a delay of 12-24 weeks had significantly worse mortality (HR 2.0) [25]. Similar findings were demonstrated in an analysis of 2,535 patients who underwent RC for bladder cancer in Ontario, Canada between 1992-2004 where the hazard ratio of death gradually increased in a step-wise manner with an increase in waiting times. The risk of death exponentially increased when time to treatment was more than 150 days [30].

Causes of treatment delays can be multifactorial. Patients undergoing RC or RNU are often elderly and may have cardiovascular and respiratory comorbidities following years of exposure to cigarette smoking [1,2]. Hence, it is likely this patient cohort requires a multidisciplinary evaluation and a period of 'prehabilitation' prior to radical surgery which may result in a delay in time to treatment [59]. Patients initially diagnosed in community hospitals may also experience delays when referred to a tertiary unit if referral pathways are not efficient. This is increasingly encountered due to the centralisation of complex cancer surgery. These factors add to the complexities of treatment delays secondary to the COVID-19, where limited healthcare personal, availability of

intensive care beds and ventilators, and efforts to minimise staff and patients from contracting COVID-19 significantly impair the ability to provide prompt surgical treatment. As the world moves on from the COVID-19 pandemic, healthcare systems can learn from the gaps exposed and put together comprehensive plans to remedy shortcomings in healthcare inefficiencies, particularly those related to delay in definitive treatment for cancer.

For example, delay in time to treatment following cancer diagnosis only represents part of the treatment pathway. In our current study, we could not account for delays between the interval that a patient experiences symptoms suggestive of possible cancer until the time they seek medical care [60]. This may be addressed with bladder health awareness campaigns such as those from the Bladder Cancer Advocacy Network (BCAN), Action Bladder Cancer UK, or World Bladder Cancer Patient Coalition, just to name a few. In addition, delays exist between the time from initial consultation until the completion of investigations, such as staging tests and histopathological confirmation of cancer. Such delays can also influence cancer outcomes and are likely as important to identify and address.

Despite the strengths of our study, it is not devoid of limitations. These include the varying definitions and cut-offs used in individual studies' analysis of delay, with most studies using a cut-off of 84-93 days. Despite the EAU guideline's recommendations of 12 weeks, numerous studies chose to use different cut-offs to define delays. Additionally, there were insufficient granular data from each study, which limited our ability to perform subgroup meta-regression analysis by T or N stages, for example. Additionally, our meta-

analysis was limited to studies published up to June 2020. Finally, there was substantial heterogeneity across different studies, although our meta-analysis attempted to overcome this with random effects models.

4. CONCLUSION

Our study revealed that a delay between bladder cancer diagnosis and RC was significantly associated with poorer overall survival outcomes, but this was not the case among patients who underwent neoadjuvant chemotherapy prior to RC. Similarly, a delay between UTUC diagnosis and RNU was significantly associated with worse overall and cancer-specific survival. In the COVID-19 era where hospital resources may be limited, we need to continue to provide prompt definitive treatment for our patients with urothelial cancers in order to achieve the best oncologic outcomes for them.

DISCLOSURES

The authors declare no conflict of interest.

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FIGURES

Figure 1. PRISMA flow chart

Figure 2. Forrest plot for meta-analysis on effect of delayed radical cystectomy on overall survival in bladder cancer

Figure 3. Forrest plot for meta-analysis on effect of delayed radical nephro-ureterectomy on overall survival in upper tract urothelial carcinoma

Figure 4. Forrest plot for meta-analysis on effect of delayed radical nephro-ureterectomy on cancer-specific survival in upper tract urothelial carcinoma

TABLES

Table 1. Population, intervention group, comparator group, outcomes and study design (PICO) of studies included in this systematic review and meta-analysis.

Table 2. Characteristics of included studies evaluating delayed radical cystectomy on survival in bladder cancer and upper tract urothelial carcinoma, based on various definitions of delay: **(A)** Delay between diagnosis of BC and RC; **(B)** Delay between NAC and RC; **(C)** Other definitions of delay

Supplementary Table 1. Search strategy

Supplementary Table 2. Risk of bias assessment using Newcastle-Ottawa Quality Assessment Scale for Cohort Studies