



Original article

Impact of surgical waiting time on survival in patients with upper tract urothelial carcinoma: A national cancer database study

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Abstract

Purpose: To evaluate the impact of surgical waiting time (SWT) on the survival outcome in patients with upper tract urothelial carcinoma (UTUC).

Materials and methods: We identified patients with nonmetastatic UTUC who underwent radical nephroureterectomy (RNU) between 2004 and 2013 in the National Cancer Database. The association between SWT and overall survival (OS) was evaluated using Cox proportional hazards regression. SWT was categorized into 6 groups: SWT ≤ 7 days, SWT 8 to 30 days, SWT 31 to 60 days, SWT 61 to 90 days, SWT 91 to 120 days, and SWT 121 to 180 days. Multivariable analyses were adjusted for patient, tumor, and facility-related factors.

Results: A total of 3,581 patients were included in the final overall cohort and 2,397 (66.9%) patients had the higher-risk disease (high-grade or $\geq pT2$). Multivariable Cox regressions showed that patients in the groups of SWT 31 to 60 days, SWT 61 to 90 days, and SWT 91 to 120 days had similar OS compared with patients who had SWT of 8 to 30 days in the overall cohort and higher-risk cohort. Patients with SWT 121 to 180 days had worse OS (HR = 1.61, 95% CI: 1.19–2.19, $P = 0.002$ in the overall cohort; HR = 1.56, 95% CI: 1.11–2.20, $P = 0.010$ in the higher-risk cohort).

Conclusions: Increased SWT from diagnosis to RNU appears to be not associated with worse OS within 120 days after the diagnosis of UTUC but SWT > 120 days may be associated with worsened survival. These findings might have important implications for trial design in the evaluation of neoadjuvant chemotherapy for UTUC and future clinical practice. © 2017 Published by Elsevier Inc.

Keywords: Upper tract urothelial carcinoma; Ureter; Renal pelvis; Time factors; Survival; Outcome assessment

1. Introduction

Upper tract urothelial carcinoma (UTUC) is a rare malignancy accounting for 5% to 7% of all renal cancers and 5% to 10% of all urothelial carcinomas [1]. Although selected low-risk disease can be managed with kidney-sparing surgery, radical nephroureterectomy (RNU) (with bladder cuff removal) remains the standard of care for the majority of nonmetastatic UTUCs [2–4]. Despite radical surgery, high-risk UTUCs usually have a poor prognosis

and the long-term survival for UTUC has not improved very much for the past 20 to 30 years [2,5–7]. There is an imperative need to further investigate the role of perioperative therapies, particularly chemotherapy, in the management of UTUC.

Although there is a lack of level 1 evidence for neoadjuvant chemotherapy (NAC) in patients with UTUC, NAC appears to be a promising approach for selected patients with high-grade or muscle-invasive disease [8–10]. Also, with advances in imaging and diagnostic ureteroscopy technology, our ability to clinically stage UTUC has improved. However, the lack of level 1 evidence for NAC in UTUC and the potential for delaying definitive surgical therapy in patients who may not respond continues to be a significant concern.

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It is intuitive that excessive SWT for cancer surgery may cause disease progression and result in unfavorable prognosis. It is also likely that different cancers have different growth rates and biological behavior. Therefore, it is currently unknown as to whether there is a potential “safe window” of SWT for specific cancers [11,12]. Some would argue that definitive surgery for aggressive cancers such as UTUC should be performed with the shortest SWT possible and it is a moot point to investigate the so-called “safe window” [3]. However, in the modern health care system, SWT may be inevitable and the fact that UTUC is potentially aggressive raise the need to evaluate the impact of SWT on survival outcomes. The results may provide guidance regarding the preoperative assessment timeline. Also, if the “safe window” is long enough, it may partially alleviate the concerns regarding delaying RNU for legitimate reasons such as NAC in practice and clinical trials. It can also add valuable information for institutions and health care policy makers in setting parameters for wait times in various clinical conditions.

There is limited data regarding the impact of SWT on the survival outcomes in patients with UTUC [13–15]. Due to small sample sizes, previous studies categorize patients into only 2 groups (early RNU vs. delayed RNU), which can potentially bias the results. Given these drawbacks, there remains no consensus about the “safe window” or cutoff for removal of tumors after diagnosis [2–4]. Given the fact that UTUC is a relatively rare malignancy, the current question is unlikely to be answered in a prospective trial or single-institution retrospective study. We hypothesized that there may be a “safe window” in terms of the effect of SWT on UTUC outcome and the question should be answered with the nonbinary categorization of SWT. We, therefore, investigated the association of SWT and outcome using the National Cancer Database (NCDB). NCDB is a well-validated database for cancer outcomes research including the effect of SWT on survival [16–18]. In this study, we took the advantages of prospectively collected data and large sample size of NCDB analyzing the impact of SWT on survival after UTUC.

2. Materials and methods

2.1. Data source

Data of current study was derived from the NCDB. The NCDB is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons. The NCDB, established in 1989, is a nationwide, hospital-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually. NCDB contains comprehensive data about reporting facility, patient demographics, cancer identification, disease stage, treatments, short-term outcomes, and

long-term survival [18]. This study used de-identified data and institutional review board approval was not required.

2.2. Study population and variables

All patients with UTUC in the NCDB from 2004 to 2013 were identified. Urothelial histology was determined via International Classification of Diseases for Oncology, Third Edition, codes 8120 to 8139. The study population was defined as patients who underwent RNU (Code 40 in the NCDB). We excluded patients with metastatic disease at the time of diagnosis, those with other cancer diagnoses, those who died within 90 days of RNU, those who had NAC, those who had other treatments other than chemotherapy, and those with missing data in relevant co-variables or outcomes of interest. SWT was defined as the number of days between the date of initial diagnosis and the date on which the RNU was performed. We also excluded cases with RNU occurred on the same day as the diagnosis and patients who had SWT more than 180 days considering the rare occurrence in the database.

Co-variables included age, sex, race, reporting facility type, income level, education level, comorbidity status measured by the Charlson/Deyo score (CDS, categorized as 0, 1, and ≥ 2), tumor location (renal pelvis vs. ureter), tumor grade, pT stage, pN stage, lymph node dissection (LND), and adjuvant chemotherapy (AC). We used the general cancer grading system (grade 1—well differentiated, grade 2—moderately differentiated, grade 3—poorly differentiated, and grade 4—undifferentiated) in our study. Although both general grading system and 2004 World Health Organization/International Society of Urological Pathology (WHO/ISUP) system (low-grade vs. high-grade) were included in the NCDB recently, WHO/ISUP grading system had significantly more missing values. As described and confirmed by previous studies, grades 1 to 2 can be considered as WHO/ISUP low-grade tumors and grades 3 to 4 as WHO/ISUP high-grade tumors [19–21]. The primary outcome of interest was overall survival (OS). Follow-up time was defined as the number of months between the date of diagnosis and the date on which the patient was last contacted or died.

2.3. Statistical analysis

The primary objective of the study was to assess the association between SWT and OS. Time intervals between the date of initial diagnosis and date of RNU were set at 30-day increments, with the last 2 intervals combined owing to smaller numbers in each. Also, the first interval was separated into 2 groups with the consideration that small SWT may indicate nonelective surgery and may have worse outcomes [22]. Our a priori analysis also showed less favorable OS in patients who had $SWT \leq 7$ days vs. patients who had SWT of 8 to 30 days. Therefore, SWT

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