Original article

# Utilizaton of perioperative systemic chemotherapy in upper tract urothelial carcinoma

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## Abstract

**Introduction:** Evidence for the use of perioperative chemotherapy (PC) in upper tract urothelial carcinoma (UTUC) is largely derived from level I evidence for invasive urothelial carcinoma of the bladder (UCB). There has been an increase in PC for urothelial carcinoma of the bladder, as it has disseminated into clinical practice. Therefore, we sought to not only analyze trends in the utilization of PC in UTUC, but also assess factors associated with its use in a large cancer registry database.

**Methods:** The National Cancer Database was queried for patients with UTUC who underwent extirpative surgery from 2004 to 2013. Predictors of receiving PC were identified using univariate and multivariate logistic regression. Temporal trends in the utilization of PC were also analyzed using a general analysis of variance linear model.

**Results:** From 2004 to 2013, there was significant increase in PC for UTUC from 9.6% to 13.8% ($P = 0.0003$). Neoadjuvant chemotherapy increased from 0.7% to 2.1% ($P = 0.0018$), whereas adjuvant chemotherapy remained relatively stable at 11.3%. Significant predictors of receiving PC on multivariate analysis were private insurance, ureter as the primary site, poorly differentiated and undifferentiated grade, lymphovascular invasion, positive margins, clinical T3 or T4 disease, nodal metastasis, and reporting from an academic research program. Patients who were $\geq 70$ years old, $>50$ miles to treatment center, had tumor in the kidney, or had an increased Charlson-Deyo Score were significantly less likely to receive PC.

**Conclusions:** Over the time period studied, there has been an increase in the use of PC, primarily from increased administration of neoadjuvant chemotherapy. Its use is mostly associated with advanced pathologic characteristics. The study also highlights key demographic and socioeconomic differences that can help identify barriers to receiving PC and aid in making improvements in delivery of health care to patients with UTUC. Published by Elsevier Inc.

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## 1. Introduction

Unlike urothelial carcinoma of the bladder (UCB), there are no randomized controlled trials proving the benefit of neoadjuvant chemotherapy (NAC) in upper tract urothelial carcinoma (UTUC). Many urologists and medical oncologists have

extrapolated data from the bladder literature as evidence for systemic treatment in UTUC. Since the landmark 2003 SWOG study showing a survival benefit of MVAC + cystectomy vs. cystectomy alone [1] and the subsequent study showing non-inferiority of the better tolerated gemcitabine plus cisplatin regimen [2], NAC has disseminated into clinical practice and is now considered standard of care for muscle-invasive UCB.

Representing $<5\%$ of all urothelial carcinoma, UTUC is a relatively rare disease, and thus most studies examining

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either cisplatin-based NAC or adjuvant chemotherapy (AC) have been small retrospective studies. Attempted prospective trials for NAC or AC in UTUC have been limited by poor accrual. Despite similar morphology, UCB and UTUC have underlying genetic differences [3] and also differ in their natural disease course. A higher percentage of UTUC is invasive at presentation [4], and there is more upstaging after extirpative therapy than in UCB [5]. The aggressiveness and advanced presentation of this disease suggest a role for perioperative chemotherapy (PC), although key differences from UCB may limit direct comparisons and indiscriminate application of evidence for PC. Difficulties in accurate clinical staging and limitations of renal function after nephroureterectomy give UTUC a unique set of challenges that may affect decisions to administer PC. Despite these differences, most major urologic and oncologic associations do not have separate guidelines for UTUC [6].

Thus far, there have been no studies examining the utilization of PC in UTUC. Therefore, using a large cancer registry database, we sought to assess temporal trends in the utilization and associated clinical, pathological, and demographical factors of PC for UTUC.

## 2. Materials and methods

### 2.1. Cohort definition

The National Cancer Database (NCDB) is a nationwide, facility-based, comprehensive cancer registry, established in 1989, that currently captures approximately 70% of all newly diagnosed malignancies in the United States annually. The NCDB draws data from over 1,500 commission accredited cancer programs in the United States and Puerto Rico. The database is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons. No institutional review board approval was necessary, as the NCDB is a de-identified database.

The cohort was selected from the NCDB for diagnoses between 2004 and 2013 for patients 18 years or older with urothelial carcinoma histology of the kidney, renal pelvis, or ureter. Patients were only included if UTUC was their primary malignancy with no previous malignancy and no metastatic disease. Patients who underwent extirpative surgery of the upper tract (ureterectomy, nephrectomy/nephroureteretomy) were included in the analysis. Patients who underwent NAC and AC were identified based on the NCDB surgery and systemic sequence codes. PC was defined as NAC or AC or both. From 2004 to 2005, the NCDB did not differentiate between NAC and AC, so patients in these years were included in the PC group but were excluded from the NAC and AC analyses. Patients diagnosed but not treated at a facility participating in the NCDB were excluded because of lack of data.

Patient characteristics such as age, sex, race, year of diagnosis, insurance status, distance from treatment facility, and Charlson-Deyo Score were collected. Disease variables included primary site, grade, lymphovascular invasion (LVI), surgical margins, and clinical/pathological stage. Treatment characteristics included facility type (academic/research program, community cancer program, comprehensive community cancer program, integrated network cancer program, and others), days from diagnosis to treatment, multiagent vs. single-agent chemotherapy, and other treatments (radiation, immunotherapy, and hormone).

### 2.2. Statistical analysis

Descriptive statistics were used to characterize the cohort. Univariate and multivariate linear and logistic regression analyses were conducted to determine associations between clinical, pathological, and demographical covariates and the use of PC, NAC, and AC. Trend analyses by analysis of variance linear models were performed to assess the utilization of PC, NAC, and AC over the time period. Analysis was performed for PC from 2004 to 2013 and for NAC and AC from 2006 to 2013 owing to the change in coding by the NCDB in 2006. A trend for median age over time was also examined for PC, NAC, and AC. All statistical analyses were performed using SAS software.

## 3. Results

### 3.1. Patient characteristics

We identified 17,837 patients who underwent extirpative surgery for UTUC from 2004 to 2013. Of those, 2,148 (12.0%) patients underwent PC, and 182 (1.0%) and 1,640 (9.2%) underwent NAC and AC, respectively. During 2004 and 2005, when NAC and AC were not differentiated in the NCDB, 289 patients had NAC or AC. The median age for those receiving PC was 67 years and the median age for patients not receiving any chemotherapy was 72 years. The characteristics of each group are listed in Table 1.

### 3.2. Trends in PC

The use of PC increased from 9.6% to 13.8% from 2004 to 2013 ($P = 0.003$) (Fig.). From 2006 to 2013, NAC increased from 0.7% to 2.1% ($P = 0.0018$). During the same time period, AC was stable from 11.3% to 11.3% ($P = 0.6$). The median age for patients receiving PC, NAC, or AC appeared to stay stable over the time period studied, and there was no significant effect on age over time.

### 3.3. Predictors of PC

On multivariate analysis, age, distance, Charlson-Deyo Score, insurance type, primary site, clinical stage, pathologic