

Original article

High rates of advanced disease, complications, and decline of renal function after radical nephroureterectomy

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Abstract

Objectives: Recurrences remain common following radical nephroureterectomy (RNU) for locally advanced upper-tract urothelial carcinoma (UTUC). We review a cohort of RNU patients to identify the incidence of locally advanced disease, decline in renal function, complications, and utilization of adjuvant chemotherapy (AC).

Methods: Institutional databases from 7 academic medical centers identified 414 RNU patients treated between 2003 and 2012 who had not received neoadjuvant chemotherapy. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation. Complications were classified according to the modified Clavien system. Cox proportional hazard modeling and Kaplan-Meier analysis determined factors associated with cancer-specific survival.

Results: Of 414 patients, 177 (43%) had locally advanced disease, including 118 pT3N0/Nx, 13 pT4N0/Nx, and 46 pTanyN+. Estimated 3- and 5-year cancer-specific survival was 47% and 34%, respectively. Only 31% of patients with locally advanced UTUC received AC. Mean estimated glomerular filtration rate declined from 59 to 51 ml/min/1.73 m² following RNU, including a new-onset decline below 60 and 45 ml/min/1.73 m² in 25% and 15% of patients, respectively ($P < 0.001$ for both). Complications occurred in 46 of 177 (26%) patients, of which one-quarter were grade III or IV. Increasing age (Hazard Ratio (HR) 1.4, $P = 0.03$), positive surgical margins (HR 2.1, $P = 0.01$), and positive lymph nodes (HR 4.3, $P < 0.001$) were associated with an increased risk of death from UTUC, whereas receipt of AC (HR 0.85, $P = 0.05$) was associated with a decrease in UTUC mortality.

Conclusions: Under one-third of RNU patients with locally advanced UTUC cancers received AC. Perioperative complications and decline in renal function may have contributed to this low rate. Such data further underscore the need for continued discussion regarding the use of chemotherapy in a neoadjuvant setting for appropriately selected patients with UTUC. © 2014 Elsevier Inc. All rights reserved.

Keywords: Urothelial carcinoma; Locally advanced disease; Perioperative chemotherapy; Clavien complications; Renal-function changes

1. Introduction

Radical nephroureterectomy (RNU) remains the standard for managing upper-tract urothelial carcinoma (UTUC) [1]. Although oncologic outcomes with extirpative surgery are

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urable for many patients, adverse pathologic tumor features, such as nonorgan confined tumor stage and lymph node metastasis, portend a worse prognosis [2–4]. In particular, Hall et al. [2] observed that although a 5-year actuarial cancer-specific survival (CSS) was over 90% for non-muscle invasive tumors (<pT2), a decline to 40% occurred for pT3 lesions. Meanwhile, Brown et al. [3] demonstrated that despite contemporary improvements in staging and surgical treatment, patients with high-risk tumors continue to fare poorly, with no improvement in cancer outcomes over two decades. Collectively, such studies imply that radical surgery alone for locally advanced UTUC provides inadequate long-term oncologic control.

At the same time, urothelial carcinoma has been found to be a relatively chemosensitive malignancy [5]. Moreover, randomized clinical trials have demonstrated a survival advantage for neoadjuvant chemotherapy before radical cystectomy for patients with muscle-invasive bladder cancer [6–8]. In addition, the potential for tumor downstaging with neoadjuvant chemotherapy before RNU has been suggested in limited series of patients to date [9,10]. Despite such observations, neoadjuvant chemotherapy is infrequently utilized before RNU with proposed arguments being (1) RNU alone may cure patients with organ-confined disease; (2) neoadjuvant chemotherapy may delay surgery and introduce unnecessary toxicity for patients with localized cancers; and (3) adjuvant chemotherapy (AC) can be employed if needed in the postoperative setting. Studies to date regarding AC, however, for high-risk UTUC are conflicting with respect to delivery, oncologic efficacy, and survival benefit [11–14].

Here then, we report the clinicopathologic outcomes of a large, contemporary cohort of patients undergoing RNU without prior chemotherapy. In particular, we evaluated the incidence of locally advanced disease (pT3N0/Nx, pT4N0/Nx, or pTanyN+) and the subsequent utilization of AC in these patients. Furthermore, we review factors such as complication rates and change in perioperative renal function, which may have affected the delivery of chemotherapy following RNU. Finally, we sought to assess factors associated with survival in these patients.

2. Patients and Methods

Data from 414 patients, who underwent an RNU at one of 7 academic medical centers between January 2003 and December 2012, with suspected organ-confined UTUC as determined by preoperative axial imaging (Computed Tomography or Magnetic Resonance Imaging) were combined following Institutional Review Board approval. RNU was performed via open or minimally invasive techniques with regional lymphadenectomy occurring in 60% of patients in this cohort (median LN yield 7, range 2–23). Patients who received neoadjuvant radiation or chemotherapy were excluded from analysis.

All specimens were histologically confirmed to be urothelial carcinoma. Tumor classification was assigned according to the 2002 American Joint Committee on Cancer-International Union Against Cancer TNM classification, whereas grading was assessed by the 2004 World Health Organization/International Society of Urological Pathology consensus classification. In general, patients were followed every 3 to 4 months for the first year following RNU, every 6 months from the second through the fifth year, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation via cross-sectional imaging of the abdomen and pelvis.

Median follow-up for this cohort with advanced disease was 16.0 months (range, 2–120). AC was defined as treatment received within 3 months of nephroureterectomy utilizing previously published definition [11]. No patients included in this cohort had evidence of disease recurrence on imaging performed before initiating AC. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone [15].

Estimated GFR was calculated using the Modification of Diet in Renal Disease equation: Estimated glomerular filtration rate (eGFR) = $186 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]$. Serum creatinine used for preoperative eGFR calculation was drawn within 4 weeks of surgery, whereas postoperative creatinine was collected between 4 and 12 weeks following RNU. eGFR change was evaluated as both a continuous variable as well as categorically, as new-onset decline below 60 and 45 ml/min/1.73 m² (thresholds that may affect the type of chemotherapy offered).

The modified Clavien-Dindo classification system was used to categorize perioperative complications [16]. Clavien grade III and IV complications were considered major complications, and were grouped together for analysis.

Chi-square or Fisher exact test evaluated the association between categorical variables, and the Mann-Whitney U test assessed for differences in continuous variables. CSS was calculated using the Kaplan-Meier method. Cox proportional hazard regression models determined factors associated with cancer survival. All reported *P*-values are 2-sided and statistical significance was set at ≤ 0.05 . Statistical analysis was performed with S-Plus Professional version 4.5 (MathSoft Inc., Seattle, Washington).

3. Results

A total of 414 RNU patients with a median age of 70 years (range, 27–96) were included. Characteristics of the cohort are provided in Table 1. Consistent with other urothelial cancer surgical series, most patients were male, Caucasian, and had an Eastern Cooperative Oncology Group performance status of 0 to 2. Notably, over

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