

## Urothelial Cancer

# Conditional Survival After Radical Nephroureterectomy for Upper Tract Carcinoma

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### Abstract

**Background:** Conditional survival (CS) provides better estimates of the survival probability at each follow-up time, and its usefulness has been proven in several solid malignancies.

**Objective:** To assess the changes in 5-yr CS rates after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC) and to determine how well-established prognostic factors evolve over time.

**Design, setting, and participants:** We analysed data from 3544 patients treated with RNU at 15 international academic centres between 1989 and 2012.

**Intervention:** RNU.

**Outcomes measurements and statistical analysis:** Conditional intravesical recurrence-free (IVRFS), cancer-specific survival (CSS), and overall survival (OS) estimates were calculated using the Kaplan-Meier method. A multivariable Cox regression model was used to calculate proportional hazard ratios for the prediction of mortality.

**Results and limitations:** The 5-yr bladder cancer recurrence-free survival, CSS, and OS rates were 54.9%, 72.2%, and 62.6%, respectively. Given a 1-, 2-, 3-, and 4-yr survivorship, the 5-yr conditional OS rates improved to 65.2%, 69.3%, 71.5%, and 73.0%, respectively. The 5-yr CS improvement was primarily noted among surviving patients with advanced-stage disease. The impact of pathologic parameters on CS estimates decreased over time for both CSS and OS, whereas the impact of age and gender increased with survivorship.

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No survival benefit was noted regarding the adjuvant chemotherapy status. Findings were confirmed upon multivariable analyses. Tumour location, the presence of carcinoma in situ, and the type of bladder cuff excision were continuously predictive for IVRFS whatever the survivorship. A limitation is the retrospective design.

**Conclusions:** CS analysis demonstrates that the patient risk profile evolves during the post-RNU follow-up. The probability of survival markedly increases over time in patients having high-stage disease. The impact of prognostic pathologic features decreases over time and can disappear for long-term CS.

**Patient summary:** In this study, we found that the risk of intravesical recurrence, cancer-specific survival, and overall mortality evolves over the follow-up after surgery. Taking into account the survivorship provides better estimates of the survival probability at each follow-up time.

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## 1. Introduction

Radical nephroureterectomy (RNU) with bladder cuff excision is the standard of care treatment in patients with upper tract urothelial carcinoma (UTUC) [1]. Despite this optimal treatment, the 5-yr cancer-specific mortality rates remain substantial ranging from 20% to 30% among series [2–4]. Although the oncologic outcomes are favourable in early-stage cancer patients with durable disease control despite a significant risk of intravesical recurrence, poor 5-yr overall survival (OS) rates are reported in non-organ-confined disease, ranging from 50% in pT3–4 disease to 30% in nodal metastatic disease [2,3,5]. In such settings, the benefit from adjuvant chemotherapy has been suggested without level 1 evidence available [6]. The prediction of disease recurrence may improve the post-RNU management of these patients. In clinical practice, 5-yr relative survival statistics are often used to measure cancer control and to assess international comparisons. Nomograms have been built to integrate all independent covariables and thus to better individualise patient prognosis [2,7]. Nevertheless, probabilities of disease recurrence and death evolve over time and decrease with increased survivorship. Thus initial cancer prognosis assessment at the time of surgery helps in the selection of adjuvant therapy and follow-up scheduling but provides a static view of risk without postoperative follow-up information. Conditional survival (CS) is derived from the concept of conditional probability [8]. CS measures the probability that a cancer patient will survive some additional number of years, given that the patient has already survived for a certain number of years. Thus it takes into account the survivorship and provides better estimates of the survival probability at each follow-up time. The usefulness of CS analysis has been proven in several solid malignancies including two studies in urothelial carcinoma of the bladder [9–16].

The aim of the current study was to determine the CS estimates in a large multicentre cohort of RNU patients and the evolution of the impact of well-known prognostic factors over time.

## 2. Materials and methods

### 2.1. Patient selection and data collection

This was an institutional review board-approved multicentre study involving 15 centres and 3544 patients who underwent RNU with

bladder cuff excision for nonmetastatic UTUC between 1989 and 2012. Data included clinical characteristics, pathologic features, postoperative chemotherapy status, perioperative ureteral management, surgery type (laparoscopy vs open), oncologic follow-up, and death and its underlying cause. All surgical specimens were processed according to standard pathologic procedures. Tumours were staged according to the 2002 American Joint Committee on Cancer TNM staging system. Grade was assigned according to the 2004 World Health Organisation grading system. Tumour location was defined as renal pelvic or ureteral. Multifocality was defined by the presence of two or more synchronous tumours. The extent of lymph node dissection was not standardised among centres and thus was not available for analysis. A median of four nodes were removed (Table 1). Overall, 2061 patients underwent a lymph node dissection (58.1%; Table 1). Adjuvant systemic chemotherapy was given at the surgeon's discretion based on patient preference and pathologic features ( $n = 375$ ). Intravesical cancer occurrences that were histologically proven were coded as intravesical recurrence.

### 2.2. Statistical analyses

Estimation of survival probabilities was performed using the Kaplan-Meier method. Intravesical recurrence-free survival (IVRFS), cancer-specific survival (CSS), and overall OS were assessed. The CS was estimated using the multiplicative law of probability [16]. That is, the 5-yr CS represents the probability of surviving an additional 5 yr, given that the person has already survived  $x$  years ( $x =$  time elapsed since RNU).

Patient survival was computed from the day of surgery until the most recent follow-up visit or until death. Variables significantly related to patient survival at Kaplan-Meier analysis were used for 5-yr CS calculation. Survival rates were then compared with the log-rank test and used in the calculation of the 5-yr CS.

Univariable and multivariable Cox regression models were used to calculate proportional hazard ratios for the prediction of mortality after adjustment on clinical (age, gender, adjuvant chemotherapy), operative (surgery approach, ureter management), and pathologic characteristics (pT stage, grade, node status, carcinoma in situ [CIS], multifocality, location). All tests were two sided with a statistical significance limit set at  $p < 0.05$ . Statistical analyses were performed using SPSS v.19.0 (IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1. Clinicopathologic features of the 3544 patients with upper tract urothelial carcinoma who underwent radial nephroureterectomy

Table 1 shows the patient characteristics. Urinary UTUC was staged pT3–4 in 26% of cases and node positive in 9.3%. The bladder cuff excision was predominantly performed using a

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