



## Original article

# Preoperative prognostic nutritional index is a significant predictor of survival in patients with localized upper tract urothelial carcinoma after radical nephroureterectomy

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## Abstract

**Background:** Patient's nutritional and immunological status have a potentially significant role in survival outcome in patients with malignant tumors. We investigated the prognostic value of preoperative prognostic nutritional index (PNI) in patients with localized upper tract urothelial carcinoma (UTUC) undergoing radical nephroureterectomy (RNU).

**Patients and methods:** A total of 425 patients with nonmetastatic UTUC (Ta-4N0/+M0) who underwent RNU were evaluated. PNI was calculated as  $10 \times$  serum albumin concentration (g/dl) +  $0.005 \times$  lymphocyte counts (number/mm<sup>3</sup>). The associations of preoperative PNI level with clinical and pathologic variables were analyzed.

**Results:** The optimal cutoff value of PNI for cancer-specific survival (CSS) stratification was determined to be 46.78. Multivariate analysis identified low PNI as an independent prognostic factor for CSS (HR = 1.98, 95% CI: 1.31–2.99,  $P = 0.001$ ) and overall survival (HR = 1.74, 95% CI: 1.20–2.53,  $P = 0.004$ ). The estimated *c*-index of the multivariate model for CSS and overall survival increased from 0.777 and 0.767 to 0.791 and 0.774, respectively, when PNI added, which was higher than hypoalbuminemia (albumin <37.75 g/l) or neutrophil-to-lymphocyte ratio >2.955 added.

**Conclusions:** Preoperative PNI was an independent prognostic factor for predicting survival in patients with UTUC undergoing RNU. Preoperative PNI may become a useful biomarker, particularly because of its low associated cost and easy accessibility. © 2017 Elsevier Inc. All rights reserved.

**Keywords:** Upper tract; Urothelial carcinoma; Albumin; Lymphocyte; Prognosis

## 1. Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon but aggressive malignant disease that accounts for only

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5% to 10% of all urothelial carcinomas [1]. Around 50% of UTUCs are muscular invasive at diagnosis and up to 30% of patients with UTUC already have lymph node involvement [2,3]. Even after radical nephroureterectomy (RNU) with bladder cuff excision, the prognosis for UTUC patients still remains poor. Currently, 5-year cancer-specific survival (CSS) ranging from 50% to 80% for UTUC patients after RNU has been reported [4,5].

Pathological T stage, tumor grade, lymph node metastasis, distant metastasis, lymphovascular invasion (LVI), tumor multifocality, and patient age are known to be well-established prognostic factors in patients with UTUC [1,6–8]. On the other hand, it might be relevant in the future to identify individual risk factors, which would benefit for outcome prediction and

individual patient treatment choices. But the potential prognostic preoperative factors are still limited in UTUC. In addition, more and more evidences proved that patients' nutritional and immunologic status could have an important role in perioperative data and long-term survival outcome of malignant tumors, such as renal cell carcinoma (RCC) [9], colorectal cancer [10], nonsmall cell lung cancer [11].

The effect of malnutrition on survival outcomes for UTUC and other malignancies has been reported. Morgan et al. [9] reported that preoperative nutritional status, defined as body mass index  $<18.5 \text{ kg/m}^2$ , albumin  $<3.5 \text{ g/dl}$ , or preoperative weight loss  $>5\%$  of body weight, is an independent prognostic factor of survival in patients for RCC. Ku et al. [12] demonstrated that preoperative hypoalbuminemia (albumin  $<35 \text{ g/l}$ ) is an independent prognostic factor of CSS and overall survival (OS) in UTUC patients.

To date, there is no standard well-established parameter that reflects preoperative nutritional and immunological status in patients with UTUC. The prognostic nutritional index (PNI) could be easily calculated on the basis of serum albumin level and lymphocyte counts in peripheral blood [11]. Recent studies have proved the prognostic value of PNI in a variety of malignant tumors including esophageal cancer, colorectal cancer, kidney cancer, and hepatocellular cancer [13–16]. However, the prognostic value of PNI for UTUC has not yet been reported. Thus, this study was designed to clarify the potential prognostic value of PNI in a large number of patients who have undergone RNU for localized UTUC.

## 2. Patients and methods

### 2.1. Patients

After obtaining institutional review board approval, we retrospectively reviewed 520 consecutive patients with nonmetastatic UTUC (pTa-4N0/+M0) who underwent RNU at the department of urology at our institution between January 2003 and June 2013. After excluding patients lost to follow-up within 3 months, patients without data on preoperative laboratory data, patients with an active infection, patients with concomitant carcinoma invading bladder muscle, and patients who underwent cisplatin-based neoadjuvant chemotherapy, there were 425 remaining patients who were included in the analyses.

### 2.2. Clinical and pathologic evaluation

Clinical features including patient age, sex, hypertension, diabetes mellitus, pathological diagnosis, and therapeutic information were obtained from the medical records. Pathological T and N stage were performed by using the 2009 TNM classification system [17]. M stage was assigned clinically before surgery. Tumor grade was assessed according to the 1998 WHO consensus classification [18].

Dissection of regional lymph nodes was performed in patients with lymph nodes enlarged in preoperative imaging. Multifocal tumors were defined as follows: the synchronous presence of 2 or more pathologically confirmed tumors in any location within the upper urinary tract [8]. Pretreatment complete blood cell counts, serum albumin were routinely measured 1 to 3 days before surgery. PNI was calculated using the following formula:  $10 \times \text{serum albumin concentration (g/dl)} + 0.005 \times \text{lymphocyte counts (number/mm}^3\text{)}$  in peripheral blood [19]. The neutrophil-to-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

Adjuvant chemotherapy (AC) would be offered as an option to patients with muscle invasive disease, lymph node positive disease, or pT1 disease with LVI, high-grade disease, or tumor multifocality after surgery. The patient would make a decision after the benefits and side effects of postoperative AC were explained by the treating urologist and oncologist together. The chemotherapy patients were administered  $1,000 \text{ mg/m}^2$  gemcitabine on day 1, and 8 and  $70 \text{ mg/m}^2$  cisplatin on day 2 for the gemcitabine and cisplatin regimen. Cisplatin was replaced by carboplatin if the glomerular filtration rate was less than  $40 \text{ ml/min/1.73 m}^2$ . About 4 to 6 cycles of chemotherapy were planned according to patient status.

### 2.3. Follow-up

Patients were assessed by urine cytology and cystoscopy 3 months and every 6 months for 3 years after RNU and every 12 months thereafter. Computed tomography and/or magnetic resonance imaging were also performed every 6 months for 3 years and annually thereafter. Duration of follow-up was calculated from the date of surgery to the last follow-up or death, which was valued as cancer related or not related to the tumor. Cause of death was determined by treating physicians and institutional cancer registries, by chart review corroborated by death certificates, or by death certificates alone. All patients who were coded as dead of cancer had previous disease progression.

### 2.4. Statistical analysis

For continuous variables, the Wilcoxon rank-sum test was used for the variables reported as median (range), for categorical variables, the chi-square and continuity corrected chi-square tests were used. Unlike most of the studies that used median or mean value as cutoff for PNI, and we chose minimum *P* value approach for CSS to determine our optimal cutoff value of PNI using a R software-engineered, web-based system designed by Budczies et al. [20] (<http://molpath.charite.de/cutoff/>). We also determined the cutoff point for NLR and hypoalbuminemia using the same method. To further identify a potential best threshold between different PNI, NLR, and hypoalbuminemia including the threshold previously reported (Table 1)

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