

Original article

De Ritis (aspartate transaminase/alanine transaminase) ratio as a significant predictor of recurrence-free survival in patients with upper urinary tract urothelial carcinoma following nephroureterectomy

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Abstract

Background: To evaluate the prognostic significance of preoperatively assessed aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and the AST/ALT (De Ritis) ratio in patients with upper urinary tract urothelial carcinoma (UUTUC).

Methods: This study included a total of 109 consecutive patients with clinically localized UUTUC who underwent nephroureterectomy. Effects of preoperative levels of AST, ALT, and the De Ritis ratio in addition to conventional clinicopathological parameters on the extravesical recurrence-free survival (eRFS) in these 109 patients were retrospectively analyzed.

Results: Despite the lack of a significant correlation of AST or ALT with any of the factors examined in this study, the elevation of the De Ritis ratio was significantly correlated with several unfavorable parameters, including elderly age, high pathological stage, high tumor grade, and lymphovascular invasion. During the observation period of this series (median = 40.8 mo), extravesical disease recurrence developed in 39 (35.8%) of the 109 patients, with a 5-year eRFS rate of 56.8%. Of several factors examined, the tumor location, De Ritis ratio, pathological stage, lymph node metastasis, tumor grade, lymphovascular invasion, surgical margin status, and adjuvant chemotherapy were shown to be significantly correlated with eRFS by univariate analysis. Of these, the De Ritis ratio, pathological stage, lymph node metastasis, and tumor grade were identified as independent predictors of eRFS on multivariate analysis.

Conclusions: These findings suggest that preoperative assessment of the De Ritis ratio may provide useful information with respect to the clinical course of patients with clinically localized UUTUC who are scheduled to be treated with nephroureterectomy. © 2016 Elsevier Inc. All rights reserved.

Keywords: De Ritis ratio; Upper urinary tract urothelial carcinoma; Nephroureterectomy; Recurrence

1. Introduction

Upper urinary tract urothelial carcinoma (UUTUC) is a rare disease that accounts for approximately 5% of all tumors derived from the urothelium [1]. Although nephroureterectomy with bladder cuff removal is currently considered as the gold standard treatment for localized UUTUC, high incidences of postoperative systemic disease recurrence in patients with UUTUC have been reported [2,3]. Therefore, it is important to precisely predict the clinical course following surgery in counseling to determine the best treatment and follow-up strategies for individual

patients with UUTUC. However, it remains challenging to guide physicians and patients in the management of UUTUC based on high-quality data for several reasons, such as the low incidence of this disease, the varied UUTUC biology and associated prognosis, and the presence of different therapeutic options [4].

Aminotransaminases, including aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT), are enzymes released from liver cells into the blood stream, representing hepatocellular damage; thus, these are recognized as a part of the commonly requested panel, assessing the liver function [5]. In 1957, the ratio of the serum activities of AST and ALT was initially described by De Ritis, and has been known as the De Ritis ratio [6]. Although originally being proposed as a characteristic of

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viral hepatitis, this ratio has subsequently been shown to be a useful biomarker for other hepatic diseases [7]. In recent years, there have been several studies showing that different levels of aminotransaminases, including the De Ritis ratio, could be useful prognostic biomarkers in patients with certain types of malignant tumor [8–11]. For example, Bezan et al. [11] reported that the preoperative De Ritis ratio was an independent prognostic factor in patients with nonmetastatic renal cell carcinoma. To our knowledge, however, the prognostic significance of aminotransaminases in UUTUC remains largely unknown. Considering these findings, we retrospectively reviewed clinicopathologic data from a total of 109 consecutive Japanese patients with clinically localized UUTUC who underwent nephroureterectomy, focusing on the prognostic significance of aminotransaminases in this cohort of patients.

2. Materials and methods

Of consecutive patients who were newly diagnosed with clinically localized UUTUC and subsequently underwent nephroureterectomy without any neoadjuvant therapies between 2005 and 2014 at our institution, this study included a total of 109 patients fulfilling the following criteria: (1) pure UUTUC was pathologically confirmed, (2) clinical T stage was less than T3, (3) neither nodal nor distant metastasis was found by any diagnostic imaging modality, (4) patients did not have a history of previous or concurrent bladder cancer, (5) hepatitis or severe fatty liver was not present; that is, this study included the patients, not showing symptoms and physical findings as well as blood tests for viral antibodies or not consisted of moderate and severe fatty liver on ultrasound. In this study, upper limit of normal of aminotransaminases were set at 30 and 32 IU/l in AST and ALT, respectively. Informed consent for performing the present study was obtained from all these patients, and the study design was approved by the Research Ethics Committee of our institution.

Information on the clinicopathological characteristics of the included patients was retrieved from their medical records. The clinicopathological examinations were assessed based on the 2009 American Joint Committee on Cancer TNM classification system. Before surgery, all patients were evaluated with computed tomography of the chest, abdomen, and pelvis, whereas bone scintigraphy or brain magnetic resonance imaging was done only in patients with accompanying clinical symptoms. All laboratory data, including plasma AST and ALT, were measured in each patient by standard clinical testing methods within a week before surgical intervention.

In this series, nephroureterectomy was performed through a retroperitoneal approach in both open and laparoscopic surgeries using the standard methods [12]. The distal ureter was managed by open surgical excision of the bladder cuff with or without anterior cystotomy in both

methods. Lymphadenectomy was generally performed in patients judged to be physiologically tolerant; that is, the extent of lymphadenectomy was renal hilum for tumors of the renal pelvis, the ipsilateral side of the great vessels and for upper and middle ureter and the ipsilateral pelvic lymph nodes for tumors of the lower ureter. However, the range of dissection was not strictly determined. As a rule, adjuvant cisplatin-based combination chemotherapy was conducted in patients with pT3 or pT4 disease or those positive for nodal involvement. Follow-up of patients after surgery was conducted as follows: cystoscopy and urinary cytological examination were performed every 3 months for 2 years after surgery, then every 6 months until 5 years after surgery; intravenous urography and computed tomography were performed every 6 months until 3 years after surgery and then annually until 5 years after surgery. Further, 5 years after surgery, it depended on each patient's request whether or not follow-up examinations were continued.

All statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Berkeley, CA), and $P < 0.05$ were considered significant. Optimal threshold of the De Ritis ratio for the estimation of extravesical recurrence was defined using the Youden index [14]. The ability of the De Ritis ratio to predict the occurrence of extravesical recurrence was analyzed using receiver operating characteristics and the area under curve (AUC). The chi-square test was used to evaluate effects of AST, ALT, and the De Ritis ratio on several parameters. Extravesical recurrence-free survival (eRFS) rates were calculated employing the Kaplan-Meier method, and differences were determined by the log-rank test. The prognostic significance of certain factors was assessed using the Cox proportional hazards regression model.

3. Results

In this study, 1.30 was selected as an optimal threshold value for the De Ritis ratio using the Youden Index (Fig. 1A). Based on this cutoff value, receiver operating characteristics analysis was conducted to evaluate the association between the De Ritis ratio and eRFS, and the AUC of this case was 0.55 (Fig. 1B). Table 1 shows the clinicopathological characteristics of 109 patients with clinically localized UUTUC who underwent nephroureterectomy according to the preoperative values of AST, ALT, and the De Ritis ratio. Median value (range) of each parameters were as follows: AST = 21 IU/l (8–64 IU/l), ALT = 16 IU/l (5–70 IU/l), and De Ritis ratio 1.24 (0.49–3.59), respectively. There was no significant effect of AST or ALT on any factors examined in this study, whereas the elevation of the De Ritis ratio was significantly correlated with several parameters suggesting an unfavorable prognosis, including elderly age, high pathological stage, high tumor grade, and lymphovascular invasion.

During the observation period of this study (median = 40.8 mo), extravesical disease recurrence was detected in 39

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