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Original article

Gender as a significant predictor of intravesical recurrence in patients with urothelial carcinoma of the upper urinary tract following nephroureterectomy

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Abstract

Objectives: To retrospectively assess the significance of gender as a predictor of intravesical recurrence following nephroureterectomy for urothelial carcinoma of the upper urinary tract (UC-UUT).

Materials and methods: This study included 502 consecutive patients (360 male and 142 female) who were diagnosed as having clinically localized UC-UUT and underwent nephroureterectomy. Clinicopathologic outcomes of these patients were analyzed focusing on the impact of gender.

Results: The incidence of intravesical recurrence in male patients (41.9%) was significantly greater than that in female patients (27.5%). Despite the lack of significant differences in cancer-specific and overall survivals with respect to gender, the intravesical recurrence-free survival in male patients was significantly worse than that in female patients. Of several parameters examined, univariate analysis identified gender, tumor site, and tumor focality as significant predictors of intravesical recurrence following nephroureterectomy. Of these, only gender and tumor site appeared to be independently associated with intravesical recurrence-free survival on multivariate analysis. Furthermore, there was a significant difference in intravesical recurrence-free survival according to positive numbers of these two independent factors; that is, intravesical recurrence occurred in 12 of 55 patients who were negative for both risk factors (21.8%), 96 of 280 positive for a single risk factor (34.3%), and 82 of 167 positive for both risk factors (49.1%).

Conclusions: The incidence of intravesical recurrence following nephroureterectomy for UC-UUT is comparatively high. Therefore, it would be potentially important to perform careful follow-up targeting intravesical recurrence for such patients, particularly for male patients and/or patients with tumor located at the ureter.

Keywords: Urothelial carcinoma of the upper urinary tract; Intravesical recurrence; Nephroureterectomy; Gender

1. Introduction

Urothelial carcinoma of the upper urinary tract (UC-UUT) is a relatively rare malignancy, accounting for approximately 5% of all UCs. Although the current mainstay for the treatment of patients with nonmetastatic UC-UUT is complete surgical resection of tumors by nephroureterectomy [1], 15% to 50% of patients who underwent surgical management of UC-UUT have been reported to develop postoperative intravesical recurrence [1–6]. Because of this high incidence of recurrence following surgical resection of UC-UUT, several previous studies attempted to identify possible risk factors for predicting intravesical recurrence [1–8]. However, most of these studies included a comparatively small number of patients, and these outcomes remained controversial.

It has been well documented that gender has a significant association with clinical features in patients with UC [9–15]. For example, UC has been shown to be two to three times more common in men than in women [9], while

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several investigators have reported the poor prognosis of female patients with bladder cancer compared with that of male patients [10,11]. As for UC-UUT, recent studies addressed the impact of gender on the prognosis of patients with this disease [6,12–15]. However, the findings of these studies were not consistent, particularly those associated with the relation between gender and the probability of intravesical recurrence following surgical management of UC-UUT [13–15]. Considering these findings, we retrospectively reviewed clinicopathologic data from a total of 502 consecutive patients with UC-UUT who underwent nephroureterectomy in order to clarify the significance of gender as a predictive factor for postoperative intravesical recurrence.

2. Patients and methods

This study included a total of 502 consecutive patients who were diagnosed as having clinically localized UC-UUT without any suspicious lesions suggesting the presence of metastatic diseases, and subsequently underwent nephroureterectomy at Kobe University Hospital or related hospitals between January 2000 and December 2009, after excluding patients with a history of previous and/or concurrent bladder cancer or those with a follow-up period less than 6 mo after surgery. Hospital medical records from these 502 patients were retrospectively reviewed to assess the significance of several clinicopathologic factors as predictors of subsequent intravesical recurrence, and written informed consent was obtained from all patients to use their data for the objectives of this study. The mean follow-up period of this series was 39.0 mo (range, 6.0 134.8 mo).

In this study, the upper urinary tract was divided into four sites, including the renal pelvis, upper, middle, and lower ureter, based on the previous study reported by Hisataki *et al.* [7], and the focality of diseases in the upper urinary tract in each case was classified as either a single site or multiple sites. Tumor location was divided into either the renal pelvis or ureter based on the location of the dominant tumor as identified in the final pathologic specimen. Of 502 patients included in this study, open and laparoscopic nephroureterectomy were performed in 320 and 182 patients, respectively. In this series, it was basically the decision of the patient whether an open or laparoscopic approach would be selected as the surgical procedure for resecting the kidney and ureter. Each of these procedures was carried out using standard methods as described previously [16]. The distal ureter was managed by open surgical excision of the bladder cuff with or without an anterior cystotomy in both methods. Pathologic examinations of resected specimens were carried out based on the International Union against Cancer TNM classification system.

In general, adjuvant cisplatin-based combination chemotherapy was administered in patients with pT3 or pT4 diseases and/or nodal involvement. As a rule, follow-up examinations of patients after nephroureterectomy was carried out as follows: cystoscopy and urinary cytological examination were performed every 3 mo for 2 years after surgery, then every 6 mo until 5 y after surgery; intravenous urography and computed tomography were performed every 6 mo until 3 y after surgery and then annually until 5 y after surgery. Five years after surgery, follow-up examinations were performed depending on each patient's request.

All statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Berkley, CA). Clinicopathologic factors were analyzed using χ^2 test or unpaired *t*-test. The subsequent intravesical recurrence-free rate was determined by the Kaplan-Meier method. For univariate and multivariate analyses, Cox proportional hazards regression model was used. Probability (*P*) values <0.05 were considered significant.

3. Results

Of 502 patients included in this study, 360 (71.7%) and 142 (28.3%) were male and female patients, respectively. Table 1 presents clinicopathologic characteristics of these patients as stratified by gender. Male patients were significantly younger than female patients. In addition, female patients were significantly more likely to have multifocal tumors compared with male patients, and the proportion of male patients with tumor located at the ureter was significantly smaller than that of female patients. As shown in Table 1, however, there were no significant differences in the remaining factors between male and female patients, including laterality, urinary cytology, surgical modality, pathologic T stage, lymph node metastasis, tumor grade, microvenous invasion, lymphatic invasion, and surgical margin status.

In this series, intravesical recurrence developed in 190 patients (37.8%), consisting of 151 male and 39 female patients. The mean interval from nephroureterectomy to intravesical recurrence was 15.2 mo (range, 1.2–71.5 mo). As shown in Fig. 1A, A 1-, 3-, and 5-y intravesical recurrence-free survival rates of all patients were 69.7%, 61.2%, and 58.2%, respectively. The incidence of intravesical recurrence in male patients (41.9%) was significantly greater than that in female patient (27.5%), and the intravesical recurrence-free survival in male patients was significantly worse than that in female patients (Fig. 1B). However, there were no significant differences in either cancer-specific or overall survival between male and female patients (data not shown).

To identify factors associated with the development of subsequent intravesical recurrence following nephroureterectomy, univariate and multivariate analyses using the Cox proportional hazards regression model were performed. Of several factors examined, gender, tumor focality, and tumor