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Original article

Lower ureteral lesion is an independent predictor of intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma

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Abstract

Objective: To elucidate whether the lower ureteral lesion can predict subsequent intravesical recurrence (IVR) in patients with upper tract urothelial carcinoma (UTUC) who underwent radical nephroureterectomy (RNU).

Patients and methods: We retrospectively reviewed 186 consecutive patients with UTUC who underwent RNU at our institution between 1996 and 2013. Associations of various clinicopathological factors with subsequent IVR were assessed. Lower ureteral lesion was defined as the pathologically confirmed lowest carcinoma component within 5 cm from the lower end of the ureter. The log-rank test and Cox proportional hazards model were used for univariable and multivariable analysis, respectively.

Results: Overall, 86 patients (46%) developed IVR during the follow-up, with a median follow-up period of 43 months (interquartile range: 17–79 mo). In all, 53 patients (28%) had lower ureteral lesions, and 34 (64%) of them developed IVR. Univariable analysis demonstrated that lower ureteral lesion was significantly associated with IVR, as well as tumor multifocality, lymphatic invasion, and history of bladder cancer. Multivariable analysis identified the lower ureteral lesion as a sole independent predictor of IVR ($P = 0.0304$, hazard ratio $= 1.74$).

Conclusions: Lower ureteral lesion was an independent predictor of IVR in patients with UTUC treated with RNU. Such patients may deserve prophylactic treatment and intensive follow-up.

Keywords: Bladder cancer; Intravesical recurrence; Nephroureterectomy; Upper tract urothelial carcinoma; Lower ureter

1. Introduction

Urothelial carcinoma (UC) of the renal pelvis and ureter (upper tract UC [UTUC]) is relatively rare, accounting for only 5% to 10% of all UCs, and has a poor prognosis [1,2]. Radical nephroureterectomy (RNU) is the gold standard treatment of UTUC, regardless of the tumor location in the upper urinary tract. However, 22% to 47% of the patients who underwent RNU for UTUC subsequently develop intravesical recurrence (IVR) [3–5]. Considering this high incidence of IVR, stringent follow-up for IVR is important, as well as for local recurrence and distant metastasis.

Several risk factors have been reported to be predictive of IVR after RNU. Among them, multifocality and history of bladder cancer are well-known risk factors and have been validated in several studies [6–10]. On the contrary, the effect of tumor location (renal pelvis vs. ureter) on IVR is still controversial. Several reports concluded ureteral location as a significant predictive factor of IVR [7,8,10], although others state that tumor location was not at all predictive [6,9].

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We hypothesized that the strength of correlation of tumor location with IVR may differ according to the precise area of the lowest tumor component within ureter, and that difference may result in the inconsistency among previous studies. The aim of our study was to elucidate risk factors for IVR after RNU, especially focusing on whether the location of the lowest cancer component is associated with subsequent IVR.

Materials and methods

This study was approved by the institutional review board (#3124). We retrospectively reviewed consecutive patients who underwent RNU at the university of Tokyo Hospital between January 1996 and December 2013. In all, 2 patients who underwent radiation therapy for bladder after RNU were excluded. Overall, 186 patients constituted the present study cohort, which included 65 cases from our previous study [11]. Medical records were reviewed and various clinical parameters were collected such as the following: age, sex, laterality, history of bladder cancer, history of intravesical therapy, type of surgery (open vs. laparoscopic), and use of adjuvant systemic chemotherapy.

Open ($n = 76$) or laparoscopic ($n = 110$) procedures were used, either with transperitoneal or with retroperitoneal approach. The distal ureter, including the intraluminal portion and the ureteral orifice, was removed en bloc by open surgical excision. The method of bladder cuff management was decided at the surgeon's discretion; most patients were managed with the extravesical technique. No patient underwent endoscopic approach.

Regional lymphadenectomy was not performed routinely. Use of adjuvant systemic chemotherapy was determined at each physician's discretion. No patients underwent prophylactic intravesical chemotherapy after RNU. Generally, follow-up examinations for IVR after RNU were performed as follows: cystoscopy and urine cytology every 3 months for the first 2 years, then every 6 months until 5 years, and annually thereafter.

All surgical specimens were reviewed by a dedicated genitourinary tract pathologist (T.M.). Tumors were restaged and graded according to the 2009 TNM classification [12] and the 2004 World Health Organization/International Society of Urological Pathology consensus classification [13]. Tumor location, pT stage, concomitant carcinoma in situ (CIS), grade, tumor multifocality, lymphatic invasion, microvenous invasion, and surgical margin status were reevaluated.

The primary outcome was clinically detected IVR, and the time to IVR was calculated from the date of RNU to the first evidence of IVR. Associations of various clinicopathological factors with subsequent IVR were assessed.

All statistical analyses were performed using JMP 11 (SAS Institute Inc., Cary, NC). IVR recurrence-free survival was estimated by the Kaplan-Meier method with differences assessed by the log-rank test. For multivariable analysis, Cox's proportional hazards regression model was used. The variables that were significant in univariable analyses were included in the multivariable analysis. $P < 0.05$ were considered statistically significant.

Results

Descriptive characteristics of the 186 patients are summarized in Table 1. The median follow-up after RNU was 43 months (interquartile range: 17–79 mo) for the entire cohort, and 51 months (interquartile range: 19–87 mo) for those alive and disease free at the last follow-up.

During follow-up, IVR occurred in 86 (46%) patients. The cumulative incidence of bladder recurrence at 1 and 5 years was 32% and 46%, respectively, and the median time to IVR was 7.5 months.

Univariable analyses showed that location of the lowest cancer component, tumor multifocality, lymphatic invasion, and history of bladder cancer were significant predictors for IVR (Table 2).

Then, the tumors of ureteral location were divided into 2 groups according to the precise location of the lowest cancer component. Comparisons between groups with cutoff values of 0, 1, and 2 cm from the lower end of the ureter showed no significant differences in correlation with IVR, whereas those with cutoff values of 3 to 8 cm showed significant differences, with the cutoff of 5 cm showing the most significant difference (Supplemental Table 1). Therefore, "lower ureteral lesion" was defined as the pathologically confirmed lowest carcinoma component within 5 cm from the lower end of the ureter. In all, 53 patients (28%) had lower ureteral lesion (Table 1), and they showed significantly higher IVR rate than those without it ($P = 0.0009$, Table 2). The Fig. shows Kaplan-Meier estimates of IVR-free survival stratified by the lowest tumor location. Multivariable analysis showed that only the lower ureteral lesion was a significant predictive factor for IVR ($P = 0.0304$, hazard ratio [HR] $= 1.74$, 95% CI: 1.05–2.83) (Table 3).

Even in a subanalysis of the patients without previous history of bladder cancer ($n = 150$), lower ureteral lesion was also a statistically significant predictor of IVR: on univariable analyses lower ureteral lesion ($P = 0.0004$) and lymphatic invasion ($P = 0.0022$) were statistically significant. Multivariable analysis showed that the lower ureteral lesion ($P = 0.0035$, HR $= 2.22$, 95% CI: 1.31–3.66) and lymphatic invasion ($P = 0.0149$, HR $= 1.96$, 95% CI: 1.14–3.26) were significant predictive factors for IVR.

Discussion

Surveillance of IVR after RNU is mandatory, considering its high incidence (22%–47%). Several risk factors of IVR have been reported: patient age, sex, multifocality, T stage, size, location, history of bladder cancer, concomitant CIS,