Urothelial Cancer

Prediction of Intravesical Recurrence After Radical Nephroureterectomy: Development of a Clinical Decision-making Tool

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Article info

Abstract

Background: Intravesical recurrence after radical nephroureterectomy (RNU) is a frequent event requiring intense cystoscopic surveillance. Recently, a prospective randomized clinical trial has shown that a single intravesical postoperative dose of mitomycin C (MMC) reduces the absolute risk of intravesical recurrence after RNU.
Objective: The aim of the current study was to identify predictors of intravesical recurrence and to develop a tool to allow a risk-stratified approach supporting patient counseling for cystoscopic surveillance and postoperative intravesical MMC administration.
Design, setting, and participants: We performed a retrospective analysis of 1839 patients with upper tract urothelial carcinoma (UTUC). The data set was split into a development cohort of 1261 patients from North America and a validation cohort of 578 patients from Europe.
Interventions: RNU with bladder cuff excision was performed. The surgical approach was open in 1424 patients (77.4%) and laparoscopic in 415 patients (22.6%).

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Outcome measurements and statistical analyses: Univariable and multivariable Cox regression models addressed time to intravesical recurrence after RNU. We developed a nomogram for prediction of the probability of intravesical recurrence at 3, 6, 9, 12, 18, 24, and 36 mo. Predictive accuracy was quantified using the concordance index. Decision curve analysis was performed to evaluate the clinical benefit associated with the use of our nomograms.

Results and limitations: With a median follow-up of 45 mo, intravesical recurrence occurred in 577 patients (31%). The probability of intravesical recurrence-free survival at 6, 12, 24, and 36 mo was $85\% \pm 1\%$, $78\% \pm 1\%$, $68\% \pm 1\%$, and $47\% \pm 2\%$, respectively. In multivariable Cox regression analysis, advanced age, male gender, ureteral tumor location, laparoscopic surgical technique, endoscopic distal ureteral management, previous bladder cancer, higher tumor stage, concomitant carcinoma in situ, and lymph node involvement were all significantly associated with intravesical recurrence (p values ≤ 0.04). The nomograms were highly accurate for predicting intravesical recurrence in the external validation cohort (concordance index of 67.8% and 69.0% for the reduced model and the full model, respectively), and calibration plots revealed only minor overestimation beyond 24 mo. If one decided to perform postoperative instillation based on the risk of intravesical recurrence of 15% at 24 mo, one would spare 23% of the patients while not preventing only 0.3% of intravesical recurrences. The lack of information on the stage and grade of the intravesical recurrences is the main limitation of the study.

Conclusions: Intravesical recurrence after RNU is a common event in patients with UTUC. We developed nomograms that predict intravesical recurrence after RNU with reasonable accuracy. Such nomograms could improve the clinical decision-making process with regard to cystoscopic surveillance scheduling and postoperative intravesical instillations of MMC after RNU.

1. Introduction

Intravesical recurrence after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC) is a frequent event, occurring in 30–50% of patients, with the majority of tumors occurring in the first postoperative year [1–5]. Recently, a prospective randomized trial demonstrated that a single postoperative administration of 40 mg of intravesical mitomycin C (MMC) reduces the probability of intravesical recurrence following RNU [6], with an absolute risk reduction of 11%, and nine patients needed to be treated to prevent one intravesical recurrence. Although this can be considered a step toward improved outcomes, the number of patients that need to be treated, the cost of the treatment in some countries, and the side-effect profile of this drug make this rate too high to implement use indiscriminately [7].

Improved risk stratification and accurate individualized prediction of intravesical recurrence after RNU could help tailor cystoscopic surveillance and guide administration of postoperative MMC to those who are likely to benefit from it while sparing those who are not likely to benefit. Several studies have tried to identify predictors of intravesical recurrence based on clinicopathologic features [1,2,5]. However, conclusions from these studies are limited by their single-center nature, relatively small sample size, homogeneous study populations, and lack of integration of both tumor- and surgery-specific characteristics in multivariable analysis. Therefore, the aim of the current study was to identify predictors of intravesical recurrence and to develop a tool for guidance of a risk-stratified approach to cystoscopic surveillance and postoperative intravesical MMC instillation.

2. Methods

2.1. Patients

In this institutional review board–approved study, all participating sites provided necessary institutional data-sharing agreements prior to the initiation of the study. A total of 15 centers worldwide provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Prior to final analysis, the database was frozen and the final data set was produced for the current analysis.

From 1987 to 2007, 1839 patients underwent RNU with bladder cuff excision for UTUC. None of patients received preoperative chemotherapy or radiotherapy. No patients had previous muscle-invasive bladder cancer or high-grade non–muscle-invasive disease (no previous instillations). Adjuvant systemic chemotherapy was administered at the clinician's discretion based on tumor stage and overall health status as well as patient's preference ($n = 196$).

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the 2002 American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification [8]. Tumor grade was assessed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus classification [9]. Tumor location was defined as either renal pelvic or ureteral [10]. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any location (renal pelvicalyceal system or ureter) [11]. Lymphovascular invasion was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [12].