

Review – Urothelial Cancer

A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma

Thomas Seisen^{a,b}, Benjamin Granger^c, Pierre Colin^d, Priscilla Léon^{a,b}, Guillemette Utard^e, Raphaële Renard-Penna^f, Eva Compérat^g, Pierre Mozer^a, Olivier Cussenot^{a,b}, Shahrokh F. Shariat^h, Morgan Rouprêt^{a,b,*}

^aAcademic Department of Urology, Pitié-Salpêtrière Hospital, Paris, France; ^bUPMC Univ Paris 06, GRC5, ONCOTYPE-URO, Institut Universitaire de Cancérologie, Paris, France; ^cAcademic Department of Public Health and Biostatistics, Pitié-Salpêtrière Hospital, Paris, France; ^dDepartment of Urology, Hôpital Privé de La Louvière, Générale de Santé, Lille, France; ^eAcademic Library of Medicine, Paris Descartes University, Paris, France; ^fAcademic Department of Radiology, Pitié-Salpêtrière Hospital, Paris, France; ^gAcademic Department of Pathology, Pitié-Salpêtrière Hospital, Paris, France; ^hAcademic Department of Urology and Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Vienna, Austria

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Abstract

Context: There is an ongoing debate about the factors that influence intravesical recurrence (IVR) after radical nephroureterectomy (RNU) to treat upper tract urothelial carcinoma (UTUC).

Objective: To assess significant predictors of IVR after RNU from a systematic review of the literature and meta-analysis.

Evidence acquisition: A computerized bibliographic search of the Medline, Embase, and Cochrane databases was performed for all reports that included detailed results of multivariate analyses on the predictors of IVR. According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, we selected 18 retrospective studies that each included more than 100 patients treated exclusively with RNU between 2007 and 2014. Cumulative analyses of available hazard ratios (HRs) and their corresponding 95% confidence intervals were conducted using R software to assess the potential predictors of IVR.

Evidence synthesis: Among the 8275 patients included, 2402 (29%) were diagnosed with IVR within a median time of 22.2 mo (range 6.7–56.5). Patient-specific predictors were as follows: male gender (HR 1.37; $p < 0.001$), previous bladder cancer (HR 1.96; $p < 0.001$), and preoperative chronic kidney disease (HR 1.87; $p = 0.002$). Tumor-specific predictors were as follows: positive preoperative urinary cytology (HR 1.56; $p < 0.001$), ureteral location (HR 1.27; $p < 0.001$), multifocality (HR 1.61; $p = 0.002$), invasive pT stage (HR 1.38; $p < 0.001$), and necrosis (HR 2.17; $p = 0.02$). Treatment-specific predictors were as follows: a laparoscopic approach (HR 1.62; $p = 0.003$), extravesical bladder cuff removal (HR 1.22; $p = 0.02$), and positive surgical margins (HR 1.90; $p = 0.004$).

Conclusions: A meta-analysis of available data identified significant predictors of IVR that should be systematically assessed to propose a risk-adapted approach to adjuvant intravesical instillation of chemotherapy and cystoscopic surveillance after RNU.

Patient summary: In this report, we looked at the factors linked to intravesical recurrence after radical nephroureterectomy to treat upper urinary tract urothelial carcinoma. We identified patient-, tumor- and treatment-specific characteristics that should be systematically assessed to guide postoperative decision-making.

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* Corresponding author. Department of Urology, Pitié-Salpêtrière Hospital, 47–83 Boulevard de l'Hôpital, 75013 Paris, France. Tel. +33 1 42177150; Fax: +33 1 42175851.
E-mail address: morgan.roupret@psl.aphp.fr (M. Rouprêt).

1. Introduction

The pathogenesis of intravesical recurrence (IVR) after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC) is still unclear. Subsequent bladder tumors could theoretically result from either implantation of a single transformed cell after descendant intraluminal seeding [1] or a pan-urothelial field defect [2,3]. However, data to support a mixed monoclonal and oligoclonal origin of metachronous multifocal urothelial carcinoma have recently suggested that both mechanisms might be involved in the development of bladder cancer (BCa) following previous UTUC [4–7]. Accordingly, two prospective randomized clinical trials have demonstrated that the clearance of any residual tumor cells, using a single early intravesical instillation of mitomycin C (MMC) or pirarubicin (THP) after RNU, decreased the risk of IVR [8,9]. This strategy has now been advocated in the most recent European guidelines [10].

Nevertheless, there are huge discrepancies around the world regarding indiscriminate postoperative administration of chemotherapy into the bladder immediately after RNU. Clinical concerns have been raised with regard to the side effects of such a systematic strategy and, notably, the risk of painful extravasation into extraperitoneal tissues or potentially lethal intraperitoneal leakage, both of which are related to the hypothetically delayed healing of the bladder cuff removal area [8]. Therefore, accurate prediction of IVR for each patient might pinpoint those who are the best candidates for such an adjuvant local treatment. However, there are sparse data regarding predictors that could be used, not only to guide a risk-stratified approach to the adjuvant intravesical instillation of chemotherapy but also to adapt the frequency of cystoscopies during follow-up. Most studies attempting to identify the risk factors for IVR are limited by their single-center nature, small sample size, and heterogeneous population, including patients treated with either RNU or kidney-sparing surgery [11–15]. Although a nomogram has recently been developed to accurately assess the risk of IVR after RNU [16], external validation of this tool is still required before its routine use [17]. Therefore, our purpose was to assess significant predictors of IVR after RNU for UTUC from a systematic review of the literature and a meta-analysis of the available data.

2. Evidence acquisition

2.1. Search strategy

Two authors (T.S. and G.U.) together performed a computerized bibliographic search of the Medline, Embase, and Cochrane databases in August 2014. The following search terms (“Intravesical recurrence” OR “Bladder recurrence” OR “Bladder cancer” OR “Bladder tumor”) AND (“Nephroureterectomy”) AND (“Upper tract” OR “Upper urinary tract” OR “Renal pelvis” OR “Ureter”) AND (“Urothelial carcinoma” OR “Transitional cell carcinoma” OR “Carcinoma” OR “Cancer”) were used according to a free text protocol that

applied only “Humans” and “English language” filters without a time period restriction.

2.2. Inclusion criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, we used the Population, Intervention, Comparator, Outcome, and Study design (PICOS) approach to define study eligibility [18]. Records were considered relevant to this systematic review and meta-analysis if they compared patients diagnosed with BCa (P) after RNU to treat UTUC (I) to patients without BCa (C) to determine independent clinicopathologic predictors of IVR (O) using multivariate logistic regression analyses (S). Case reports, editorials, letters, review articles, and meeting abstracts were excluded during the systematic review process.

Studies were selected according to the following criteria:

- (1) Only large studies that included more than 100 patients who had been treated exclusively with RNU.
- (2) Only studies that defined IVR as a pathologically confirmed occurrence of BCa after RNU.
- (3) Only studies that excluded patients with previous BCa, or that used previous BCa as a variable for adjustment in multivariate analysis.
- (4) Only studies that provided hazard ratios (HRs) from multivariate logistic regression analyses with their corresponding 95% confidence intervals (CIs).

Finally, if two or more studies reported results of overlapping surgical series (eg, by the same team), we selected the one with the largest sample size.

2.3. Systematic review process

After duplicates were removed, two authors (T.S. and P.C.) completed an independent review of 597 abstracts to ultimately select 102 studies for separate full-text evaluation. Any discrepancies in study inclusion were resolved by consulting the senior author (M.R.), who was in charge of supervising the systematic review process. In accordance with all previously mentioned inclusion criteria, a final selection of 18 articles published between 2007 and 2014 was made [19–36]. The PRISMA flow chart depicting the process for the systematic literature search and selection of the studies is shown in Figure 1.

2.4. Quality of data assessment

The 18 included studies were limited by their retrospective design. However, they were all considered to be of high methodological quality according to the Newcastle-Ottawa Scale, which is recommended by the Cochrane Collaboration [37]. This tool has been developed to assess the quality of nonrandomized studies to incorporate quality assessments in the interpretation of meta-analytic results. Using a star system ranging from 0 to 9, each study was independently judged by two authors (T.S. and P.L.)

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