

# The complex relationship between upper urinary tract and bladder cancer: clinical and predictive issues

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Miyake *et al.* (1) analyzed the outcome of a series of Bacillus Calmette-Guérin (BCG)-treated non-muscle invasive bladder cancer (NMIBC) occurring after upper tract urothelial carcinoma (UTUC) in comparison to a “control” group of primary NMIBC. Their results, as well as the study concept itself, raise some intriguing issues on a quite controversial topic.

## UTUC and urothelial bladder cancer (UBC): disparate and/or Siamese twins?

First of all, UTUC has traditionally been considered the twin tumor of UBC, since both stem from the same tissue, i.e., the transitional lining of the urinary tract (2). Such consideration, along with its very low frequency (almost 5–10% of all UC), have resulted in outlining treatment strategies for UTUC on the basis of UBC (3).

Recently, several attempts have been made to better understand the complex nature of UTUC, inducing some authors to define UTUC and UBC “disparate twins” due to the coexistence of both similarities (i.e., cell of origin, histology types, biological features) and discrepancies (diagnostic and prognostic role of gender, limitations in staging and treatment) between them (4). On a molecular basis, a prospective assessment of cell cycle and proliferative tissue markers disclosed close resemblance between UTUC and UBC (5). A recent comprehensive genomic

characterization of UTUC (6) conversely revealed novel mutations and mutation frequencies in comparison to UBC, and identified four expression subtypes with unique molecular profiles and clinical correlates with features that were similar but did not overlap those of the established bladder subtypes (7).

While “disparate” on a pathological and biological basis, UTUC and UBC can be “Siamese” due to their close clinical connections. Upper tract recurrence (UTR) in UBC as well as intravesical recurrence (IVR) in UTUC may occur as well-known complications of the surgical management in both tumors. In this setting, UTR typically arises after a longer than 3 years’ disease-free survival (8), with urethral tract involvement at radical cystectomy (RC) being a significant predictor of UTR in both sexes. Although uncommon, such complication may be dismal due to its frequent detection at a symptomatic stage, despite the patients’ adherence to follow-up protocols (8).

## UTUC and UBC: who is the cat and who is the tiger?

Another common feature shared by UTUC and UBC is difficulty in predicting disease outcome.

Most efforts have initially been driven towards factors predicting the outcome of UBC, particularly non-muscle invasive BC (NMIBC). The European Organization for

Research and Treatment of Cancer (EORTC) risk tables and the Spanish Urological Club for Oncological Treatment (CUETO) scoring model remain a standpoint in this issue but research is strongly moving towards the identification of molecular markers that could better predict disease outcome (9,10).

Since UTUC is considered an aggressive disease with >60% of cases presenting with invasion at diagnosis, risk stratification is advisable in order to choose the proper surgical and/or medical treatment option (11). Similarly to NMIBC, clinical and pathological parameters (i.e., tumor multifocality, size, stage and grade, patient's gender, and so on) continue to play a role even though studies addressing their role have yielded conflicting results and limited evidence overall (12,13). A large multicentric Canadian study described old age, tumor location in both the renal pelvis and the ureter, treatment with adjuvant systemic chemotherapy and extravesical ureterectomy or laparoscopic radical nephroureterectomy (RNU) as independent risk factors for IVR (14). As opposed to these findings, a meta-analysis of 40 studies including 12,010 patients failed to confirm such statistical association, rather suggesting that gender, location (renal pelvis *vs.* ureteral), stage, tumor size and concomitant BC are significantly correlated to subsequent IVR after RNU (15). In the last decade, several studies have been published addressing the role of different markers to predict IVR, such as cell inflammation-based parameters (12,16), the gross hematuria and the preoperative serum creatinine level (17), and diagnostic ureteroscopy (18). Their results have been biased by intrinsic limitations, namely the retrospective nature and relatively small number of cases in single center studies. Further attempts of risk stratification for IVR have been made, taking into account from time to time the above-mentioned parameters along with additional ones, such as papillary tumor architecture and lymphovascular invasion (19), and even the impact of different chemotherapy regimens (20). Current guidelines from the European Association of Urology (21) suggest a risk stratification based on three categories of predictors of increased risk for IVR namely, (I) patient-specific factors (i.e., male gender, previous BC, smoking and preoperative chronic kidney disease), (II) tumour-specific factors (i.e., positive preoperative urinary cytology, ureteral location, multifocality, invasive pT stage, and necrosis), and (III) treatment-specific factors (i.e., laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins). However, so far there are no validated

nomograms.

Strategies to prevent IVR after treatment for UTUC mostly focus on the use of postoperative prophylactic intravesical chemotherapy. In view of the intraluminal seeding hypothesis, it finds a rationale in the putative ability of the chemotherapeutic agent to prevent tumor cells implantation. Evidence has been provided that a significant decrease in IVR is achieved under such strategy (22), and intravesical chemotherapy seems to be even more effective in peculiar pathological and molecular settings (i.e., lack of EGFR, low-level Ki67, pre-operative positive cytology) (23).

### Post-UTUC NMIBCs: are they really different and why?

IVR usually develop in up to 50% of patients during surgical follow-up after RNU (12) with cumulative incidence rates at 1 and 5 years after treatment as high as 31.0% and 48.4%, respectively, in one series (24), the most frequent site being around the excised bladder cuff. Furthermore, post-surgical IVR may be a significant predictor of later urethral recurrence (25). In order to find parameters able to predict the outcome of such IVRs, Tanaka *et al.* examined a series of 241 IVRs after RNU for UTUC; according to their analysis, multiplicity, pT1 stage, concomitant carcinoma in situ (CIS) and lack of BCG treatment were independent risk factors for subsequent IVR and/or progression (24). Miyake *et al.* (1) report that NMIBC occurring after RNU for UTUC carry a worse prognosis after intravesical BCG than their primary bladder counterpart, suggesting that such patients are inherently poor responders to BCG exposure, and this is a very novel finding providing a ground for further research in this field.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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