Editorial

Are all metachronous multifocal urothelial carcinoma created equal?

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Metachronous multifocal urothelial carcinoma could theoretically result from intraluminal seeding implantation (monoclonal), pan-urothelial field change (oligoclonal) or mixed mechanisms (1). While not completely elucidated, different potential mechanisms might impact clinical behavior, course, biological characteristics and eventually the response to intravesical Bacillus Calmette-Guérin (BCG), especially when comparing primary and subsequent non-muscle-invasive bladder cancer (NMIBC) after radical nephroureterectomy for upper urinary tract urothelial carcinoma (UTUC).

A recent study in the BJU international by Miyake *et al.* (2) has head to head compared in a retrospective multicenter collaborative study the clinical outcomes of patients treated by intravesical BCG due to UTUC-NMIBC versus a propensity score-matched primary NMIBC cohort.

Propensity score-matched analysis was introduced to adjust the control cohort for confounding variables such as sex, T category, and tumor multiplicity for the UTUC-NMIBC (n=75) and primary NMIBC (n=352), resulting in an even distribution of the patient baseline characteristics in the UTUC-NMIBC (n=75) and primary NMIBC (n=75) groups. Interestingly, after the adjustment, there were no significant differences between the two groups with regard to bladder progression-related survival and death, though patients with UTUC-NMIBC had a worse intravesical recurrence-free survival rate compared with patients with primary NMIBC (2).

Some might overestimate the recurrence difference, even in the absence of more robust endpoints such as cancer progression and death. Among many potential confounding aspects, at least two might affect intravesical recurrence in the Miyake *et al.* study: smoking status (3,4) not assessed (possibly related to significantly increased recurrence) and immediate post-TURBT chemotherapy instillation (5) given to a subset of the cohort (possibly related to significantly decreased recurrence), no patient with UTUC-NMIBC has received it.

The authors have recognized that adjuvant intravesical BCG was underutilized when considering NMIBC guidelines, as well as the inherent limitations related to the study design concerning selection bias, inconsistencies in surgical skills, follow-ups, clinical interpretations, pathological diagnosis, adjuvant intravesical therapy criteria, dosage and scheme that were not consistent and depended on the physician's decision (2).

Though still an open question, challenged by the relative rarity of UTUC, one might interpret the Miyake *et al.* results as supportive of not significant different response to intravesical BCG between UTUC-NMIBC and primary NMIBC, to be revisited in bigger cohorts, different ethnicities, and better-controlled studies. Such intriguing interrogation is fueled by the diverse natural history of UTUC and bladder cancer, certainly beyond the mono- and oligo-clonal paradox. A clear definition of distinct clinical,

etiological, epidemiological and genetic urothelial entities is still controversial and warrants further understanding, despite many similarities (6).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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