Iatrogenic Causes of Urothelial Cancer of the Upper Urinary Tract and Bladder

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The bladder and the upper urinary tract (UUT) are both lined by urothelium, and have cancer characteristics that are histologically and molecularly similar. Aside from inherited (e.g. Lynch family tumor syndrome) [1] or unusual exposures (e.g. phenacetin or herbal remedies with Aristolochia fanchi) [2, 3], upper tract urothelial cancer (UTUC) represents 5–10% of all UCs [4] (Sountoulides) and presents with concomitant UC of the bladder (BC) in 20% of cases [5]. Moreover about 30% of patients with UTUC have prior histories of BC [6, 7] and as many a 30% of patients with newly diagnosed UTUC without prior BCs will experience a recurrence in the bladder over the 12 months following radical nephron-ureterostomy (RNU) and bladder cuff excision [8]. Clearly, finding ways to prevent both UTUC and BC is worthwhile. Thus, it is of interest that two articles recently published in the Journal of Urology look at ways to reduce recurrences that are potentially iatrogenically induced.

In one, the authors queried The Mayo Clinic database to determine if certain preoperative investigations of the UUT led to a greater likelihood of recurrence of UC in the bladder after RNU [7]. They also performed a meta-analysis of other studies to determine if any preoperative evaluative studies predisposed for post RNU recurrences in the bladder.

In the second, authors from Greece performed a systematic review and meta-analysis to determine whether ureteral stenting during a transurethral resection of a bladder tumor (TURBT) contributes to the development of metachronous, ipsilateral UTUCs [4].

Sharma and colleagues used The Mayo Clinic database from 1995-2019 to review 834 cases of patients who underwent RNU who did not undergo prior or concomitant cystectomy [7].

Patients were divided into four groups: 1. No ureteroscopy or tumor biopsy, going straight to RNU based on findings on imaging with or without positive cytology, 2. Percutaneous biopsy without ureteroscopy, 3. Ureteroscopy without biopsy, 4. Ureteroscopy with ureteroscopic biopsy.

Numerous tumor factors (including size, grade, multiplicity, location, prior BC and its treatment, bladder cuff excision technique, surgical margin status, use of neoadjuvant or adjuvant systemic chemotherapy, and post RNU intravesical chemotherapy) and patient characteristics (age, gender, body mass index, smoking status) were analyzed for a median of 29 months follow up, for biopsy confirmed intravesical recurrence, although for over one-third, bladder surveillance and treatment were not done at The Mayo Clinic. The authors found that patients undergoing ureteroscopic biopsy (group 4) had the highest likelihood of having an intravesical recurrence (21.9%), and recurrences occurred...
in their review and meta-analysis determined that stenting placed patients at increased risk for developing subsequent ipsilateral UTUC [4]. In the case of imperative drainage (with pre-existing hydronephrosis) no increased likelihood of UTUC was seen with stenting vs nephrostomy tube vs no drainage (presumably because the hydronephrosis was very mild or it was believed that ipsilateral renal impairment was so severe that it was unlikely to improve with drainage). However, when stenting was done to protect an orifice from TURBT induced scarring, metachronous ipsilateral UTUC was more likely in patients who underwent stenting (OR 3.49 95% CI 1.43-8.48) than no stenting (either no drainage or nephrostomy), or stenting vs no upper tract drainage (OR 3.37 95% CI 1.49 -7.63). However, when stenting was compared with nephrostomy drainage, the difference in developing metachronous UTUC was no longer significant (OR 3.07 95% CI 0.41-22.98), because the 95% CIs crossed 1. This was primarily because of the relatively small number of patients having nephrostomy tubes placed (N=131) compared with those being stented (N=225), and because all of the nephrostomy tube patients had pre-existing hydronephrosis (where means of drainage did not significantly influence the development of metachronous UTUC).

The authors acknowledge that the robustness of their results were low since the retrospective observational studies (no randomized prospective clinical trial has been performed on this topic) used in their review/meta-analysis “enrolled different populations and did not adequately control for potential confounding factors”. Data about prior manipulations and treatments, tumor multifocality in the bladder or upper tracts, and size of the index bladder tumor were not reported. Moreover, how often TURBT near an orifice causes ureteral damage is unknown. Given these limitations, whether to place a stent to “protect a ureter” at the time of TURBT is uncertain, but in view of the low incidence of metachronous upper tract recurrence (7.7% in the stented patients), the sample size needed to answer this question definitively in a randomized study is prohibitively large – and such a trial is very unlikely to ever be conducted. That said, caution about stenting a ureter at TURBT in the absence of pre-existing hydronephrosis should at least be considered.

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.
REFERENCES


