

Paper Alert

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

Edward M. Messing*

University of Rochester Medical Center, Rochester, NY, USA

Received 13 July 2021

Accepted 14 July 2021

Pre-press 27 July 2021

Published 31 August 2021

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 pre-disposed 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

*Correspondence to: Edward M. Messing, University of Rochester Medical Center, Rochester, NY, USA. E-mail: Edward.Messing@urmc.rochester.edu.

3.3 to 7.7 months earlier than for the other three groups. In the meta-analysis, ureteroscopy (usually no data on ureteroscopic biopsy was provided in the studies reviewed) was found to be significantly more likely associated with intravesical recurrence after RNU than after no ureteroscopy. In univariate analysis older age, prior BC, tumor multifocality on the excised RNU specimen, and a positive margin at the bladder cuff were all associated with increased likelihood of intravesical recurrences ($p < 0.05$), but on multivariate analysis, besides undergoing ureteroscopy + biopsy, only smoking status, advanced age, and positive ureteral/bladder margin were. The authors acknowledge limitations to their study including being uncertain about how many diagnostic procedures patients had undergone before undergoing RNU, and what monitoring and treatment regimens the third of patients not receiving follow up care at The Mayo Clinic received. Moreover details of the pre-RNU procedures, including whether ureteral access sheaths were used, ureteral dilations performed, and postoperative J stents were placed (see below), all of which are far more traumatic than the other diagnostic procedures, and are more likely to be used in those undergoing ureteroscopic biopsy compared to ureteroscopy only or percutaneous biopsy, may have contributed to the development of BC recurrences. These procedures as well as ureteroscopy + biopsy can all facilitate downstream passage of malignant cells. However, use of ureteroscopy (with or without biopsy) made it much less likely to have benign findings on RNU pathology ($p < 0.02$). Because of this greater diagnostic accuracy and the limitations of this study, I agree with the authors' recommendations to consider instilling post RNU single dose intravesical chemotherapy, whenever ureteroscopy, especially with biopsy, has been performed; but of course, this probably should be done in all patients undergoing RNU who's bladder is to remain [8, 9].

And what about placing an ureteral stent at the time of TURBT? This is primarily employed for patients with pre-existing hydronephrosis, or to "protect" the ureteral orifice from scarring from the tumor resection or fulguration, or in the rare circumstance that subsequent ureteroscopic inspection is planned, but not performed (for any numbers of reasons) at the time of the TURBT. Because the last situation is unusual, it won't be discussed further. However, for the first two circumstances, Sountoulides and colleagues 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 preexisting 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

- [1] Lim A, Rao R, Martin SF. Luynch Syndrome and Urologic Malignancies: A Contemporary Review, *Current Opin Urol*. 2019;29:357-63.
- [2] Johansson S, Wahlquist L. Tumors of the Urinary Bladder and Ureter Associated with Abuse of Phenacetin-containing Analgesics. *Acta Pathol Microbiol Scand*. 1977;85:768-74.
- [3] Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial Carcinoma Associated with the Use of a Chinese Herb (*Aristolochia fangchi*). *N Engl J Med*. 2000;342:1686-92.
- [4] Sountoulides P, Pyrgidis N, Brookman May S, Mykoniditis I, Karasavoudis T, Hatzichristou D, Does Ureteral Stenting Increase the Risk of Metachronous Upper Tract Urothelial Carcinoma in Patients With Bladder Tumors? A systematic review and meta-analysis. *J Urol*. 2021;205:956-66.
- [5] Cosentino M, Palou J, Gaya JM, et al. Upper Urinary Tract Urothelial Cell Carcinoma: location as a predictive factor for concomitant bladder carcinoma. *World J Urol*. 2013;31:141.
- [6] Singla N, Fang D, Su X, et al. A Multi-Institutional comparison of Clinicopathological Characteristics and Oncologic Outcomes of Upper Tract Urothelial Carcinoma In China and the United States. *J Urol*. 2017;197:1208.
- [7] Sharma V, Miest TS, Juvet TS, Toussi A, Packiam V, Chamic K, Matin SF, Boorjian SA, Thompson RH, Tollefson MK, Potretzke AM. The Impact of Upper Tract Urothelial Carcinoma Diagnostic Modality on Intravesical Recurrence after Radical Nephroureterectomy: A single-institution series and updated meta-analysis. *J. Urol*. doi:10.1097/JU.0000000000001834, JU21-97, 2021
- [8] O'Brien T, Ray E, Singh R, et al. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). *Eur Urol*. 2011;60:703.
- [9] Ito A, Shintaku I, Satoh M, Ioritani N, Aizawa M, Tochigi T, Kawamura S, Aoki H, Numata I, Takeda A, Namiki S, Namima T, Ikeda Y, Kambe K, Kyan A, Ueno S, Orikasa K, Katoh S, Adachi H, Tokuyama S, Ishidoya S, Yamaguchi T, Arai Y. Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP Monotherapy Study Group Trial. *J Clin Oncol*. 2013;31:1422.