# A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract

GRANT D. STEWART, SIMON V. BARIOL, KEN M. GRIGOR*, DAVID A. TOLLEY and S. ALAN McNEILL
*Departments of Urology and *Pathology, Western General Hospital, Edinburgh, UK.*

Accepted for publication 8 December 2004

## OBJECTIVE

To clarify the histopathological patterns of upper and lower urinary tract transitional cell carcinomas (TCCs), as previous reports suggest that upper urinary tract TCCs have a greater tendency towards high-grade disease than bladder TCCs, of which most are low-grade and low-stage tumours.

## PATIENTS AND METHODS

All patients presenting with TCC of bladder or upper urinary tract between February 1991 and December 2001 at one institution were identified. Further patient information was obtained from the hospital database and case-note review.

## RESULTS

In all, 164 patients with upper urinary tract TCC and 2197 with bladder TCC were identified. There was a correlation between grade and stage of both upper urinary tract and bladder TCCs. 35% of the upper tract TCCs were classified as grade 2 and 44% as grade 3, while for bladder TCCs, 31% of lesions were classified as grade 2 and 35% as grade 3 ($P = 0.003$). Of the upper urinary tract lesions 33% were stage pT2–T4, compared with only 20% of bladder TCCs ($P = 0.001$).

## CONCLUSIONS

Upper urinary tract TCC is a higher grade and stage disease than bladder cancer, a finding that emphasizes the need for aggressive treatment of upper urinary tract TCC. If endourological management of upper urinary tract TCC is considered, histopathological determination of tumour grade before treatment is essential.

## KEYWORDS

carcinoma, transitional cell, bladder, kidney, ureter, TCC

## INTRODUCTION

It has been previously stated that most TCCs are low-grade (G1 and G2) and low-stage tumours (pTa and pT1), even when the upper tract is affected [1], but several published studies have shown a varying distribution of grade and stage of upper urinary tract TCC. Most studies have shown a preponderance of high-grade (G3) and stage (pT2–4) disease when the upper urinary tract is affected [2–6]. Mazeman [2], in a review of 893 patients with upper urinary tract TCC, found that 55.3% of tumours were high-grade. Hall *et al.* [4], in a cohort of 252 patients with upper urinary tract TCC, found that 42.5% had high-grade disease and 43.8% had high-stage tumours. By contrast, Anderström *et al.* [7] found that 75% of patients with upper urinary tract TCC had low-stage and -grade tumours.

There is an established correlation between the grade and stage for TCC affecting the upper and lower urinary tract [6,8–12]. Furthermore, advanced grade and stage is associated with a poorer prognosis, which influences management decisions [1]. Keeley *et al.* [13] showed that accurate grading and staging is possible from specimens obtained by ureteroscopic biopsy of upper urinary tract TCC, as information obtained from these biopsies correlated well with that of the final pathological specimen.

Although endourological management is indicated for patients with a single kidney, synchronous bilateral disease, chronic renal failure or those unfit for major surgery [14], there is a trend towards endourological management of patients with a normal contralateral kidney. However, this recommendation is confined to the management of small, low-grade lesions [14–16].

We sought to evaluate the stage and grade of upper and lower urinary tract TCC using a large series over a 10-year period, to assess differences in the pathology of the disease affecting the different parts of the urinary tract.

## PATIENTS AND METHODS

All patients with TCC of the bladder or upper urinary tract presenting to the Department of Urology at the authors' institution between February 1991 and December 2001 were identified from a prospectively collected pathology database. Histological material was reviewed by one uropathologist (K.M.G.); data from patients' initial pathology were included in the analysis. Most of the bladder TCCs in this study were resected endoscopically, and we are confident that these patients have not been understaged because of inadequate muscle in the specimen. The experienced pathologist who reviewed all the specimens gave a staging of pTx if there was any doubt of the stage from the specimen. Further data were obtained from the hospital database and patient notes, which included patient demographics, anatomical location of the tumour and method of resection. Data on disease recurrence, disease-specific survival and overall survival were not collected, as it was not the aim of the study to evaluate these factors. Independent statistical advice was obtained. The Pearson chi-square test was used for analysis unless otherwise stated, and $P < 0.05$ taken to indicate significance.

## RESULTS

In all, 164 patients with an upper urinary tract TCC and 2197 with bladder TCC were reviewed, and Table 1 shows the demographic details; 102 patients with upper urinary tract TCC (62%) had an open nephroureterectomy, 45 (27%) had a

laparoscopic nephroureterectomy, five (3%) had ureteroscopic resection of TCC and 12 (7%) had other procedures (anterior exenteration, distal ureterectomy or percutaneous treatment). Most patients with bladder TCC had a transurethral resection, 214 (10%) with muscle-invasive disease had a cystectomy, and the rest were treated with radiotherapy. Follow-up data were not evaluated.

Of the patients with upper urinary tract TCCs, 92 (56%) were found to have had a bladder TCC either before or after the diagnosis of the upper urinary tract lesion, 14 (8.5%) had synchronous bladder TCC, and 70 (43%) had metachronous bladder TCCs (data missing for the remaining eight patients). Tumours in the calyces or renal pelvis were found in 97 patients (59%), and 13 (8%), nine (6%) and 40 patients (24%) had TCC of the upper, mid and lower ureter, respectively. In 11 patients (7%) with ureteric tumours the site was not specified. Six patients (4%) had multifocal tumours, and are included in two of the above groups.

Table 1 shows the distribution of the grade and stage of TCCs. There were significant differences between the groups in tumour stage and grade; 35% of upper urinary tract TCC lesions were graded as G2 (moderately differentiated, low-grade) and 44% as G3 (poorly differentiated, high-grade), compared with only 31% and 35%, respectively, for patients with bladder TCC ($P = 0.003$). Of upper urinary tract lesions, 33% were stage pT2–T4 lesions compared with only 20% of bladder TCCs ($P = 0.001$). The incidence of high-grade deeply invasive disease was significantly higher in the upper urinary tract than in the bladder (Table 1). Correspondingly, the proportion of low-grade (G1 and G2) superficial (pTa/pT1) TCC was significantly higher in the bladder than in the upper urinary tract ($P = 0.021$).

There was an association between stage and grade in all cases (Pearson correlation coefficient, $r = 0.7$). Of all patients, 1229 (56%) had low-grade and pTa/pT1 disease, and 641 tumours (29%) were high-grade and deeply invasive. Only 217 patients (10%) with low-grade disease had deeply invasive tumours, and 123 (6%) had high-grade superficial tumours ($P < 0.001$). This relationship was the same when grade and stage of upper urinary tract and bladder TCC were analysed separately.

*TABLE 1*
*Comparison of TCCs of the bladder and upper urinary tract*

| Variable | Bladder TCC | Upper urinary tract TCC | P |
|---|---|---|---|
| Demographic characteristics | | | |
| Number | 2197 | 164 | NA |
| Sex, *n* (%) | | | 0.02 |
| Male | 1519 (69) | 100 (61) | |
| Female | 678 (31) | 64 (39) | |
| Mean (SD): | | | |
| age, years | 77.3 (12) | 76.9 (11) | 0.359† |
| months from surgery | 95.3 (40) | 81.0 (42) | <0.001† |
| Grade of tumour, *n* (%) | | | 0.003 |
| CIS | 45 (2) | 1 (0.6) | |
| G1 | 704 (32) | 32 (20) | |
| G2 | 683 (31) | 58 (35) | |
| G3 | 762 (35) | 72 (44) | |
| Gx | 3 (0.1) | 1 (0.6) | |
| Stage of tumour, *n* (%) | | | 0.001 |
| Tis | 45 (2) | 1 (0.6) | |
| Ta | 1228 (60) | 79 (50) | |
| T1 | 370 (18) | 25 (16) | |
| T2–T4 | 411 (20) | 52 (33) | |
| Relationship between grade and stage*, *n* (%) | | | |
| Low-grade: | | | |
| superficial | 1155 (56) | 74 (47) | |
| deeply invasive | 202 (10) | 15 (10) | |
| High-grade: | | | |
| superficial | 117 (6) | 6 (4) | |
| deeply invasive | 579 (28) | 62 (40) | |

**Low-grade = G1, G2; high-grade = carcinoma in situ, G3; superficial = Tis, Ta, T1; deeply invasive = T2, T3, T4.*
*†Mann-Whitney U test.*

## DISCUSSION

The anatomical location of upper urinary tract TCCs in the present study conforms with that described by Mazeman [2], who also reported that there were almost twice as many pelvicalyceal as ureteric tumours (60% and 40%, respectively, in the present study). Of the present patients with upper urinary tract TCC, 43% had metachronous bladder cancer, a proportion similar to that reported previously [14]. The pattern of pathology of the bladder tumours is consistent with standard teaching that ≈70% of tumours are superficial [1]. It is well established that 70% of superficial lesions present as stage pTa, 20% as pT1 and 10% as pTis, which was also reflected in the present findings. There was a strong correlation between grade and stage of TCC for both upper urinary tract and bladder TCCs; most low-grade tumours were noninvasive or superficially invasive, and high-grade tumours were predominantly deeply invasive (muscle or renal parenchyma), which is in good agreement with published data [6,8–12].

The main aim of the present study was to establish any differences in the pathology of TCC of the bladder and upper urinary tracts. Upper urinary tract TCC was significantly more aggressive and deeply invasive than TCC affecting the bladder. Although this has been alluded to previously, particularly in studies of patients with synchronous upper urinary tract and bladder TCC [5,17], this difference has not, until now, been well established. The more aggressive nature of upper urinary tract cancer might be a consequence of the higher-grade lesions found, or might represent anatomical differences between the bladder and ureter or renal pelvis and earlier transmural spread.

In the present study, 44% of upper urinary tract TCCs were grade G3; upper urinary tract TCC should therefore be regarded as an aggressive, high-grade cancer unless proven otherwise. These findings are important for managing upper urinary tract TCC, particularly as nephron-sparing procedures are redefining the management of these

lesions. Endourological techniques, which were until recently used for clearly defined situations (note above) are now more widely applied to patients with normal contralateral kidneys. However, indications for endourological management should be related to tumour rather than patient factors, i.e. small (<2.0 cm) solitary low-grade superficial lesions. Under these circumstances endourological management is safe and effective [14]. As upper urinary tract TCC appears to be potentially more aggressive than bladder tumours, a rigorous surveillance programme should be followed after initial conservative treatment. Patients must also be aware of the risk of recurrence and possible future requirement for nephroureterectomy [14]. Patients with multifocal disease, larger tumours, high-stage (pT2–T4) or grade 3 TCC should be offered nephroureterectomy [18], but the outcome after radical nephroureterectomy in patients with locally advanced disease (stage pT3–T4, N1–N2) is poor, with a 5-year survival rate of 23% [19]. In these patients, consideration might be given to adjuvant therapies such as local or systemic chemotherapy. However, these treatments have not been evaluated in prospective randomized trials, as this would be difficult given the low prevalence of upper urinary tract TCC [20].

The present study clearly shows that upper urinary tract TCC is a more aggressive tumour than that of the bladder. The clinical significance of this finding is important. If tumours of the upper urinary tract are automatically assumed to be of low grade and stage, as some reviews have suggested, and are fulgurated without previous biopsy, a patient with high-grade disease could potentially be denied curative surgery, in the form of a nephroureterectomy. Ureteroscopic biopsies should be mandatory if endourological management is to be used, as it cannot be assumed that TCC of the upper urinary tracts is of low grade and stage.

## CONFLICT OF INTEREST

None declared.

## REFERENCES


1 **Messing EM.** Urothelial tumours of the urinary tract. In Walsh PC, Retik AB, Vaughan ED, Wein AJ eds, *Campbell's Urology*, 8th edn, Vol. 4 Chapt 76. Philadelphia: WB Saunders, 2002: 2732–84

2 **Mazeman E.** Tumours of the upper urinary tract calyces, renal pelvis and ureter. *Eur Urol* 1976; **2**: 120–6

3 **McNeill SA, Chrisofos M, Tolley DA.** The long-term outcome after laparoscopic nephroureterectomy: a comparison with open nephroureterectomy. *BJU Int* 2000; **86**: 619–23

4 **Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG.** Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology* 1998; **52**: 594–601

5 **Auld CD, Grigor KM, Fowler JW.** Histopathological review of transitional cell carcinoma of the upper urinary tract. *Br J Urol* 1984; **56**: 485–9

6 **Huben RP, Mounzer AM, Murphy GP.** Tumor grade and stage as prognostic variables in upper tract urothelial tumors. *Cancer* 1988; **62**: 2016–20

7 **Anderström C, Johansson SL, Pettersson S, Wahlqvist L.** Carcinoma of the ureter: a clinicopathological study of 49 cases. *J Urol* 1989; **142**: 280–3

8 **Jewett HJ, Strong GH.** Infiltrating carcinoma of the bladder: relation of depth of penetration of the bladder wall to incidence of local extension and metastases. *J Urol* 1946; **55**: 366–72

9 **Charbit L, Gendreau M-C, Mee S, Cukier J.** Tumors of the upper urinary tract: 10 years of experience. *J Urol* 1991; **146**: 1243–6

10 **Nielsen K, Ostri P.** Primary tumors of the renal pelvis: evaluation of clinical and pathological features in a consecutive series of 10 years. *J Urol* 1988; **140**: 19–21

11 **Murphy DM, Zincke H, Furlow WL.** Primary grade 1 transitional cell carcinoma of the renal pelvis and ureter. *J Urol* 1980; **123**: 629–31

12 **Murphy DM, Zincke H, Furlow WL.** Management of high grade transitional cell carcinoma of the upper urinary tract. *J Urol* 1981; **125**: 25–9

13 **Keeley FX, Kulp DA, Bibbo M, McCue PA, Bagley DH.** Diagnostic accuracy of ureteroscopic biopsy in upper tract transitional cell carcinoma. *J Urol* 1997; **157**: 33–7

14 **Gettman MT, Segura JW.** Endourological management of upper tract transitional cell carcinoma. *BJU Int* 2003; **92**: 881–5

15 **Elliot DS, Blute ML, Patterson DE, Bergstralh EJ, Segura JW.** Long-term follow-up of endoscopically treated upper urinary tract transitional cell carcinoma. *Urology* 1996; **47**: 819–25

16 **Elliot DS, Segura JW, Lightner DJ, Patterson DE, Blute ML.** Is nephroureterectomy necessary in all cases of upper tract transitional cell carcinoma? Long-term results of conservative endourological management of upper tract transitional cell carcinoma in individuals with a normal contralateral kidney. *Urology* 2001; **58**: 174–8

17 **Kang CH, Yu TJ, Hsieh HH *et al.*** The development of bladder tumours and contralateral upper urinary tract tumors after primary transitional cell carcinoma of the urinary tract. *Cancer* 2003; **98**: 1620–6

18 **Jarrett TW, Sweetser PM, Weiss GH, Smith AD.** Percutaneous management of transitional cell carcinoma of the renal collecting system: 9-year experience. *J Urol* 1995; **154**: 1629–35

19 **Batata MA, Whitmore WF, Hilaris BS, Grabstald H.** Primary carcinoma of the ureter: a prognostic study. *Cancer* 1975; **35**: 1626–32

20 **Oosterlinck W, Solsona E, van der Meijden AP *et al.*** EAU Guidelines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. *Eur Urol* 2004; **46**: 147–54


Correspondence: Mr S. Alan McNeill, Department of Urology, Western General Hospital, Edinburgh, EH4 2XU, UK.
e-mail: alan.mcneill@luht.scot.nhs.uk