

Management of transitional-cell carcinoma of the renal pelvis and ureter

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Summary

Transitional-cell carcinoma of the renal pelvis or ureter is a relatively rare disease. Several risk factors are smoking, occupational carcinogens, analgesic abuse or Balkan nephropathy. The grade and stage of the disease have the most significant impact on the outcome. The treatment of renal pelvis and ureter tumours is open or laparoscopic surgery varying from conservative to more extensive surgical procedures, i.e. radical nephroureterectomy including removal of the contents of Gerota's fascia with ipsilateral ureter

and a cuff of bladder at its distal extent. Most available data are from retrospective studies and surgery is the mainstay of treatment. Chemotherapy and/or radiation therapy are possible adjuvant or primary treatment for selected patients; however, prospective studies are needed to confirm their use.

Key words: transitional-cell carcinoma; renal pelvis carcinoma; ureter carcinoma

Introduction

Primary transitional-cell carcinoma (TCC) of the renal pelvis or ureter is a relatively rare disease. It accounts for less than 1% of genitourinary neoplasms and 5–7% of all urinary tract tumours [1]. Its incidence increases with age, the peak diagnosis being in the sixth and seventh decades of life [2]. Male gender is a factor in increased incidence [1, 2]. TCC arises from the lining surface

epithelium [3]. Adverse prognostic factors are high grade pathology and/or advanced stage. Most available data are from retrospective studies and surgery is the mainstay of treatment. Chemotherapy and/or radiation therapy are possible adjuvant or primary treatment for selected patients; however, prospective studies are needed to confirm their use.

Aetiology and pathology

The aetiology of primary TCC of the renal pelvis or ureter is similar to that reported for TCC of the bladder [4]. Heavy cigarette smoking and chronic use of laxatives or non-steroidal anti-inflammatory drugs such as phenacetin are reported to be closely associated with this cancer [5, 6]. Occupational exposure to organic chemicals has been associated with a higher risk of developing upper urinary tract urethelial cancers in workers in the chemical, petrochemical or plastics industries [6]. The surface epithelium of the urinary tract exposed to potential carcinogens may develop a "field cancerisation" resulting in synchronous or metachronous involvement of multifocal areas [7]. Endemic nephropathies, such as Balkan nephropathy, an indolent inflammatory process occurring in the Balkan countries, or nephropathy from China secondary to the ingestion of Chinese

herbs containing *Aristolochia fangchi*, used for weight reduction, are associated with the development of TCC of the renal pelvis or ureter [8, 9]. Environmental factors such as radon inhalation or minerals in drinking water are reported to increase the risk of TCC of the renal pelvis or ureter [6]. Genetic factors such as Lynch syndrome are also reported to increase the risk of upper urinary tract cancers [10, 11].

The most common type of renal pelvis and ureter cancers is TCC [7, 12]. Squamous-cell carcinoma, adenocarcinoma or sarcoma are uncommon [13]. Morphologically, TCC of the renal pelvis and ureter, like bladder TCC, can be papillary or solid and associated with carcinoma *in situ*. The prognosis of TCC is better than in other histological subtypes [14].

Clinical presentation

Macroscopic or microscopic haematuria is present in 75–90% of patients. Flank pain, occurring in 20–40% of patients secondary to an obstructive tumour mass, may mimic a ureteral calculus [15]. Urinary symptoms (dysuria, pollaki-

uria, etc) may occur in 25–50% of patients [14, 15]. Physical examination is generally normal, with the exception of a palpable flank mass in fewer than 10% of patients.

Staging and diagnostic workup

Table 1

Definition of TNM staging for tumours of renal pelvis and ureter [16].

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades the muscularis
T3	For renal pelvis only: tumour invades beyond muscularis into peripelvic fat or the renal parenchyma
For ureter only: tumour invades beyond muscularis into periureteric fat	
T4	Tumour invades adjacent organs, or through the kidney into the perinephric fat
Regional lymph nodes (N)*	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
MO	No distant metastasis
MI	Distant metastasis

* Note: laterality does not affect the N classification.

TCC of the renal pelvis or ureter may spread locally by direct extension to adjacent anatomical structures, or may be disseminated by lymphatic or haematogenous pathways [16]. The primary tumour is detected by urinary cytology, intravenous pyelography and/or ureteroscopy. Routine staging includes chest radiograph and/or thoraco-abdominal CT combined with assessment of hepatic, renal and haematological chemistry. To determine the staging procedure it is essential to ascertain the distribution of simultaneous tumours of the urinary tract. Multifocal tumours are frequent, and may arise in the ureter, bladder, or on the contralateral side. Radionuclide bone scan is also recommended to exclude bone metastases in locally advanced disease. The UICC (Union Internationale Contre le Cancer) staging system classifies this disease according to tumour (T), nodes (N), and metastases (M) (table 1) [17].

Treatment of non-metastatic disease

The treatment of renal pelvis and ureter tumours is open or endoscopic/laparoscopic surgery [18] varying from conservative to more extensive surgical procedures, i.e. radical nephroureterectomy including the removal of the contents of Gerota's fascia with ipsilateral ureter and a cuff of bladder at its distal extent [19]. Nephron sparing approaches in well-selected patients with low-stage and low-grade disease can be treated endoscopically by ureteroscopy and percutaneous renal surgery [18]. Lymphadenectomy should be considered in locally advanced non-metastatic disease but its therapeutic effect on the outcome needs further prospective investigation [20]. The entire ipsilateral ureter should be removed as 20–50% of

patients with residual ureteral stumps develop tumours within the stump [21, 22]. Following surgery, locoregional failure is reported in 9–15% of patients with low grade and low stage disease, and in 30–50% of those with high grade and advanced disease [23, 24].

In bladder cancer an organ-preserving approach using combined chemo- and radiotherapy has proved successful [25–28]. The same approach can also be applied in upper urinary tract tumours if surgery is not possible.

Despite aggressive primary surgery, locoregional failure remains frequent. Adjuvant radiation therapy has been advocated by some authors [15, 29–33] but its benefit is unclear. Some studies

Table 2

Postoperative radiotherapy in urothelial renal pelvis and/or ureter tumours: data from the literature.

Author [ref]	n	Dose (Gy)	Residual tumour after surgery	Results
Babaian [30]	8	18.25–59	8 out of 8	Control: 4 of 8; local control: 7 of 8
Brookland [29]	9	40–60	4 of 9	Control: 5 of 9; local control: 8 of 9
	11	–	1 of 11	Control: 3 of 11; local control: 8 of 11
Brady [31]	2	40–50	2 of 2	Control: 1 of 2
Cozad [21]	10	37.4–56	3 of 10	Local control: 9 of 10
Czito [37]	31	46.9	5 of 31	Control: 15 of 31; local control: 24 of 31
Maulard-Durdux [32]	26	45	?	Local control: 21 of 26
Ozsahin [22]	45	20–66	15 of 45	Local control: 33 of 45
	81	–	18 of 81	Local control: 51 of 81
Zhang [33]	17	42 (IORT)	5 of 17	Local control: 12 of 17

IORT: Intraoperative radiotherapy

suggest no benefit from adjuvant radiotherapy, but data from clinical experience are limited without conclusive results from prospective studies [29, 33]. Data from the literature are summarised in table 2. Generally speaking, in patients with adverse factors such as a high grade or advanced stage, close or positive surgical margins or positive lymph nodes, postoperative radiotherapy may be considered. The role of adjuvant chemotherapy is also unproven. Recent retrospective results show that modern cytotoxic agents, combined

with radiotherapy or alone, appear to be associated with a better outcome [34–37]. In this setting, prospective studies are warranted in large collaborative groups.

According to data from the National Cancer Institute SEER programme [3], 5-year overall survival in TCC of the upper urinary tract is 95% for *in situ* tumors, 89% in localized disease, 63% in node positive patients and 17% in metastatic disease.

Treatment of advanced disease

Many treatment options exist for the management of advanced or metastatic disease, including surgery, radiation therapy and/or chemotherapy, depending on the patient's performance status and comorbidities. Urothelial cancers are reported to

be responsive (39–65%) to cisplatin-based chemotherapy regimens [38, 39]. Taxanes and/or gemcitabine have also been used in this setting [40, 41].

Conclusion

In patients with TCC of the renal pelvis and/or ureter, radical surgery should be carried out whenever possible. Locoregional failure rate remains high. With the introduction of more sophisticated treatment planning, conformal techniques and intensity modulation, the role of postoperative radiation therapy remains to be reassessed. Adjuvant chemotherapy using novel drugs and/or targeted agents should also be evaluated prospectively.

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