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Original Paper

Prognostic Factors in Urothelial Renal Pelvis and Ureter Tumours: a Multicentre Rare Cancer Network Study*

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To assess the prognostic factors in patients with transitional-cell carcinoma of the renal pelvis and/or ureter, a series of 138 patients with transitional-cell carcinoma of the renal pelvis and/or ureter was collected in a retrospective multicentre study. 12 patients with distant metastases were excluded from the statistical evaluation. All but 3 patients underwent radical surgery: nephroureterectomy ($n = 71$), nephroureterectomy and lymphadenectomy ($n = 20$), nephroureterectomy and partial bladder resection or transurethral resection ($n = 20$), nephrectomy ($n = 10$), and ureterectomy ($n = 5$). Sixty-one per cent ($n = 77$) of the tumours were located in the renal pelvis, and 21% ($n = 27$) in the ureter (both in 22 [17%]). Following surgery, residual tumour was still present in 33 patients (16 microscopic and 17 macroscopic). Postoperative radiotherapy was given to 45 (36%) patients. The median follow-up period was 39 months. In a median period of 9 months, 66% of the patients relapsed (34 local, 7 locoregional, 16 regional, and 24 distant). The 5- and 10-year survival were 29% and 19%, respectively, in all patients. In univariate analyses, statistically significant factors influencing the outcome were Karnofsky index, pT-classification, pN-classification, tumour localisation, grade, and residual tumour after surgery. Multivariate analysis revealed that independent prognostic factors influencing outcome were pT-classification, the existence of residual tumour, and tumour localisation. In patients with urothelial renal pelvis and/or ureter tumours, a radical surgical attitude is mandatory; and the presence of tumour in the ureter is associated with a poorer prognosis. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: renal pelvis, ureter, transitional-cell carcinoma, radiotherapy, surgery, prognostic factors, Rare Cancer Network
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INTRODUCTION

TRANSITIONAL-CELL CARCINOMA of the renal pelvis and the ureter is a relatively rare cancer [1]. Its treatment is primarily surgical varying from conservative surgery 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 [2].

The role of adjuvant radiation therapy is not well established. In circumstances in which conservative resection is performed, postoperative radiation therapy is considered. A beneficial effect has been suggested by some [3–6] but questioned by others [7]. In this multicentre study, combining the experience of eight European institutions, the aims were to

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assess the prognostic factors, the extent of surgery, the role of adjuvant postoperative radiation therapy, and the outcome in patients with transitional-cell carcinoma of the renal pelvis and/or ureter.

PATIENTS AND METHODS

A series of 138 patients with transitional-cell carcinoma of the renal pelvis and/or ureter treated between 1971 and 1996 was collected in a retrospective multicentre study of the *Rare Cancer Network*. 12 patients with distant metastases were excluded from the statistical evaluation. In the remaining 126 patients, the median age was 66 years (range: 41–87). The male to female ratio was 2.5 (90:36). The median follow-up period was 39 months (range: 5–220).

Information concerning the performance status according to the Karnofsky index was available for 65 (52%) patients. It was < 80% in 14 patients, 80% in 17, 90% in 17, and 100% in 17. The most frequently occurring symptom was haematuria alone ($n = 55$) or combined with back pain ($n = 31$), back pain alone ($n = 12$) or combined with other symptoms ($n = 2$), urinary infections ($n = 4$), weight loss ($n = 3$), and hypertension in 1 patient. 18 patients presented initially without any clinical symptom.

The surgical treatment was nephroureterectomy ($n = 71$), nephroureterectomy and lymph node dissection ($n = 20$), nephroureterectomy and partial bladder resection or transurethral resection ($n = 20$), nephrectomy alone ($n = 10$), and ureterectomy ($n = 5$).

According to the UICC classification [8] there were 6 (5%) pTa (papillary non-invasive carcinoma), 22 (17%) pT1 (invasion of subepithelial connective tissue), 17 (14%) pT2 (invasion of the muscularis), 37 (29%) pT3 (invasion beyond the muscularis into peripelvic fat or renal parenchyma for renal pelvis tumours, or into the periureteric fat for ureter tumours), 37 (29%) pT4 (invasion of adjacent organs or through the kidney into perinephric fat), and 7 (6%) pTX (primary tumour cannot be assessed) tumours. The pN-classification was as follows: 69 (55%) pN0 (no regional lymph node metastasis), 8 (6%) pN1 (metastasis in a single lymph node ≤ 2 cm), 14 (11%) pN2 (metastasis in a single lymph node > 2 but ≤ 5 cm, or multiple lymph nodes < 5 cm), 4 (3%) pN3 (metastasis in a lymph node > 5 cm), and 31 (25%) pNX (regional lymph nodes cannot be assessed). Sixty-one per cent ($n = 77$) of the tumours were located in the renal pelvis, and 21% ($n = 27$) in the ureter. Renal pelvis and ureter localisation were present together in 22 (17%) patients. There were 4 (3%) grade 1, 37 (29%) grade 2, 42 (33%) grade 3 tumours; and the grade was not registered in 43 (34%) patients. Following surgery, microscopic ($n = 16$) or macroscopic ($n = 17$) residual tumour was detected in 26% of the patients. The characteristics of the patients according to different treatment modalities are presented in Table 1.

Postoperative radiotherapy was given using anterior–posterior portals in 45 (36%) patients with a median total dose of 50 Gy (range: 20–66) in median 25 fractions (range: 4–33). The postoperative target volume was mostly the kidney and the ureteral bed in 27 patients, or the same volume including the bladder ($n = 10$). Patients receiving postoperative radiation had significantly higher pT classification, ureteral localisation, and higher grade tumours after surgery compared with non-irradiated patients ($P < 0.0001$, $P = 0.02$, and $P = 0.06$; respectively) (Table 1). Adjuvant systemic chemotherapy was administered in 12 (10%) patients.

Means were compared by Student's *t*-test. Proportions were compared using the chi-square test for values greater than 5, and Fisher's exact test for those less than or equal to 5. Kaplan–Meier product-limit estimates were used to evaluate the survival, local control, and locoregional control [9]. The events were death (all causes of death included) for overall survival, and local or locoregional relapse for local and locoregional control (patients who died without local or locoregional relapse were censored at time of death), respectively. Differences between groups were assessed using the logrank test [10]. Bonferroni method was used to adjust the individual *P*-values in order to obtain overall significance levels depending on the number of parameters tested (*P*-adjusted equals individual *P*-value times number of parameters tested) [11]. Multivariate analyses were done

Table 1. *Characteristics of* 126 *patients with urothelial renal pelvis and/or ureter tumours*

	Surgery alone (%)	Postoperative RT (%)	*P*-value
Mean ± S.D. age (years)	66 ± 11	65 ± 9	0.47
Sex			
Female	21 (26)	15 (33)	0.38
Male	60 (74)	30 (67)	
Karnofsky index			
≥ 80%	33 (41)	18 (40)	0.32
< 80%	7 (8)	7 (16)	
Unknown	41 (51)	20 (44)	
Tumour localisation			
Renal pelvis	57 (70)	20 (45)	0.02
Ureter	13 (16)	14 (31)	
Both	11 (14)	11 (24)	
Type of surgery			
Nephroureterectomy (NU)	46 (57)	25 (56)	0.46
NU + lymphadenectomy (L)	14 (17)	6 (13)	
Nephrectomy + partial bladder resection (or TURB)	13 (16)	7 (15)	
Nephrectomy alone	6 (7)	4 (9)	
Ureterectomy alone	2 (3)	3 (7)	
pT-classification			
pTa	6 (7)	–	< 0.0001
pT1	21 (26)	1 (2)	
pT2	13 (16)	4 (9)	
pT3	21 (26)	16 (36)	
pT4	14 (18)	23 (51)	
pTX	6 (7)	1 (2)	
pN-classification			
pN0	45 (56)	24 (53)	0.14
pN1	4 (5)	4 (9)	
pN2	7 (9)	7 (16)	
pN3	1 (1)	3 (7)	
pNX	24 (29)	7 (15)	
Grade			
1	4 (5)	–	0.06
2	28 (34)	9 (20)	
3	25 (31)	17 (38)	
Unknown	24 (30)	19 (42)	
Residual tumour			
None	63 (78)	30 (67)	0.10
Microscopic	11 (14)	5 (11)	
Macroscopic	7 (8)	10 (22)	

RT, radiation therapy; TURB, transurethral resection, bladder.

Table 2. Distribution of relapses (99 sites of relapse in 81 patients) according to treatment modality

	Surgery alone ($n=81$)			Postoperative RT ($n=45$)		
	NU ± L (%) ($n=60$)	NUB (%) ($n=13$)	N/U (%) ($n=8$)	NU ± L (%) ($n=31$)	NUB (%) ($n=7$)	N/U (%) ($n=7$)
Urothelial						
Bladder	16 (27)	5 (38)	1 (13)	4 (13)	2 (29)	–
Renal	4 (7)	1 (8)	1 (13)	2 (6)	–	1 (14)
Ureter	1 (2)	–	–	2 (6)	–	–
Contralateral ureter	–	1 (8)	–	1 (3)	–	–
Regional						
Paraaortic	11 (18)	3 (23)	1 (13)	3 (10)	–	–
Iliac	2 (3)	–	–	–	1 (14)	–
Inguinal	–	–	–	–	1 (14)	–
Distant						
Liver	7 (12)	1 (8)	1 (13)	4 (13)	1 (14)	–
Bone	4 (7)	–	1 (13)	3 (10)	–	–
Lung	2 (3)	–	–	–	–	1 (14)
Skin	–	–	–	1 (3)	–	–
Brain	–	–	–	1 (3)	–	–
Adrenal gland	–	–	–	–	–	1 (14)
Supraclavicular	1 (2)	–	–	–	–	–
Bone + liver	1 (2)	–	–	2 (6)	–	–
Bone + lung	1 (2)	–	–	–	–	–
Lung + liver	1 (2)	–	–	1 (3)	–	–

RT, radiation therapy; NU ± L, nephroureterectomy with or without lymphadenectomy; NUB, NU + partial bladder resection (or transurethral bladder resection); N/U, nephrectomy or ureterectomy alone.

using the Cox stepwise-regression analysis to determine the independent contribution of each prognostic factor [12].

RESULTS

In a median period of 9 months (range: 1–141), 64% ($n=81$) of the patients relapsed (local in 34, locoregional in 7, regional in 16, and distant in 24). The distribution of relapses is presented in detail in Table 2. The 5- and 10-year overall survival (± S.D.) were 29 ± 5% and 19 ± 5%, respectively in all patients. The 5- and 10-year local control rates were 46 ± 7% and 36 ± 8%, and the locoregional control rates were 37 ± 5% and 29 ± 7%, respectively (Figure 1).

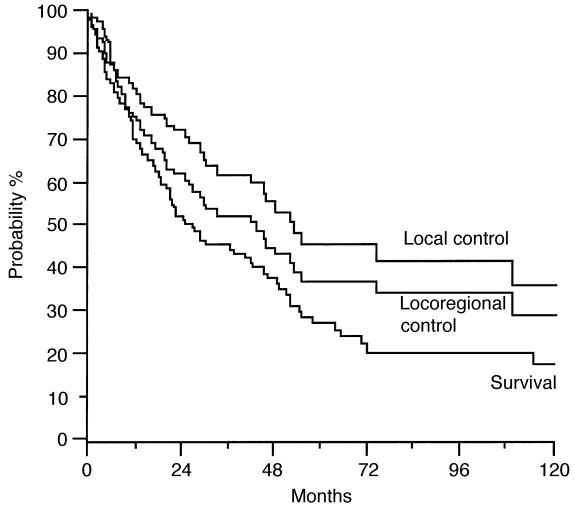

Figure 1. 10-year projected probabilities of local control, locoregional control and overall survival in 126 patients.

In univariate analyses (Table 3), statistically significant factors influencing survival were pT-classification ($P<0.00001$; P-adjusted <0.0001), pN-classification ($P=0.001$; P-adjusted <0.01), tumour localisation (renal pelvis versus ureter ± renal pelvis; $P=0.003$; P-adjusted <0.05) (Figure 2), histological grade ($P<0.00001$; P-adjusted <0.0001), and the existence of residual tumour after surgery ($P<0.00001$; P-adjusted <0.0001) (Figure 3). The only factor influencing the local or locoregional control probability was the presence or not of a residual tumour following surgery (Table 4).

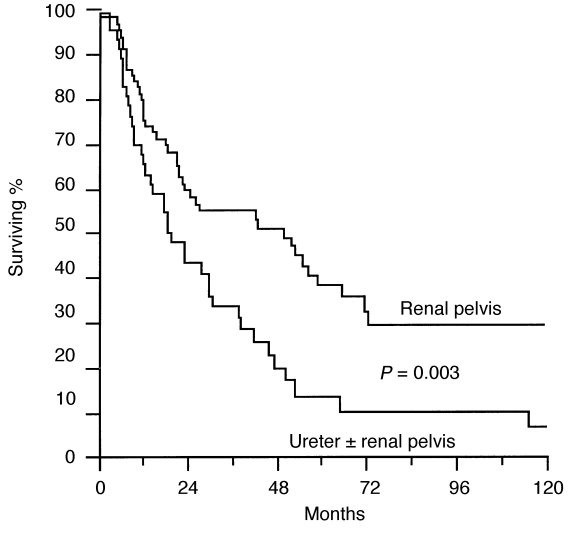

Figure 2. 10-year overall survival rates according to tumour localisation: renal pelvis ($n=78$) versus ureter ± renal pelvis ($n=48$); $P=0.003$; P-adjusted <0.05.

Table 3. Univariate analyses in 126 patients (overall survival)*

		Overall survival (%)			
	n	5-yr.	10-yr.	*P*-value	Adjusted *P*-value**
All patients	126	29 ± 5	19 ± 5		
Karnofsky index					
≥ 80%	50	35 ± 8	29 ± 9	0.009	NS
< 80%	13	12 ± 10	–		
Tumour localisation					
Renal pelvis	78	39 ± 6	29 ± 7	0.003	< 0.05
Ureter ± renal pelvis	48	14 ± 6	7 ± 5		
Type of surgery					
Nephroureterectomy (NU) ± lymphadenectomy	91	29 ± 6	18 ± 6	0.91	NS
NU + partial bladder resection (or TURB)	20	29 ± 12	19 ± 11		
Nephrectomy or ureterectomy alone	15	23 ± 14	23 ± 14		
pT-classification					
pTa	6	56 ± 25	–	< 0.00001	< 0.0001
pT1	22	45 ± 13	33 ± 14		
pT2	17	61 ± 13	41 ± 19		
pT3	37	15 ± 7	5 ± 5		
pT4	37	16 ± 7	6 ± 5		
pTX	7	0	0		
pN-classification					
pN0	69	32 ± 6	25 ± 6	0.001	< 0.01
pN1	8	25 ± 15	–		
pN2	14	8 ± 8	8 ± 8		
pN3	4	0	0		
pNX	31	32 ± 12	16 ± 13		
Grade					
1	4	67 ± 27	–	< 0.00001	< 0.0001
2	37	52 ± 10	35 ± 12		
3	42	16 ± 6	11 ± 6		
Unknown	43	17 ± 6	14 ± 6		
Residual tumour					
None	93	37 ± 6	24 ± 6	< 0.00001	< 0.0001
Microscopic	16	9 ± 8	9 ± 8		
Macroscopic	17	0	0		
Postoperative RT					
No	81	33 ± 6	24 ± 6	0.04	NS
Yes	45	21 ± 7	13 ± 6		

*Logrank test [10]; **Bonferroni correction [11]; NS, not significant; TURB, transurethral resection, bladder; RT, radiation therapy.

Multivariate analysis (Table 5) revealed that independent prognostic factors influencing survival were pT-classification (Ta, T1, T2 versus T3, T4, TX; $P < 0.00001$), the existence of residual tumour after surgery (no residual tumour versus micro- or macroscopic rest; $P < 0.00001$), and tumour localisation (renal pelvis versus ureter ± renal pelvis; $P = 0.007$). Residual tumour was found to be the only independent factor for either local ($P = 0.002$) or locoregional ($P = 0.0008$) control.

DISCUSSION

Tumours of the renal pelvis and ureter have a significantly high local recurrence rate after nephroureterectomy, particularly in patients with high grade tumours or deep invasion [13, 14]. The biology of these tumours is similar to transitional-cell carcinoma of the bladder. The major prognostic factors in patients with renal pelvis or ureter carcinoma are initial stage, grade of the tumour, and extent of surgery [14–17]. Clinical computed tomography (CT) staging may enhance our ability to make a clinically relevant distinction between minimally invasive and deeply invasive tumours thus predicting the extent of surgery [18]. High grade tumours are associated with a higher incidence of metastases and worse survival [15]. No survival difference was found for patients with papillary versus solid tumours [14]. Multifocal lesions have a worse prognosis than the unifocal lesions at time of initial diagnosis [15]. Flow cytometry, by determining the DNA pattern (diploid versus aneuploid) has also been reported to be an important prognostic indicator for long-term prognosis [15, 19].

In our series, among the factors analysed (Table 3) univariate analyses revealed that the significant factors influencing the survival were Karnofsky performance index, pT- and pN-classification, ureteral localisation, histological grade, and existence of residual tumour after surgery. Independent prognostic factors found to be significant following multivariate analysis (Table 5) were pT-classification, existence of residual tumour, and ureteral localisation. Residual tumour

Table 4. Univariate analyses in 126 patients (local and locoregional control)*

	n	5-yr.	10-yr.	*P*-value	Adjusted *P*-value**
Local control (%)					
All patients	126	46 ± 7	36 ± 8		
Tumour localisation					
Renal pelvis	78	51 ± 8	51 ± 8	0.30	NS
Ureter ± renal pelvis	48	35 ± 12	18 ± 11		
Type of surgery					
Nephroureterectomy (NU) ± lymphadenectomy	91	47 ± 8	35 ± 10	0.80	NS
NU + partial bladder resection (or TURB)	20	35 ± 14	35 ± 14		
Nephrectomy or ureterectomy alone	15	68 ± 15	68 ± 15		
Residual tumour					
No	93	50 ± 8	38 ± 10	0.0003	0.001
Yes	33	34 ± 16	34 ± 16		
Postoperative RT					
No	81	48 ± 8	36 ± 10	0.84	NS
Yes	45	39 ± 13	39 ± 13		
Locoregional control (%)					
All patients	126	37 ± 5	29 ± 7		
Tumour localisation					
Renal pelvis	78	44 ± 7	44 ± 7	0.20	NS
Ureter ± renal pelvis	48	24 ± 9	12 ± 7		
Type of surgery					
Nephroureterectomy (NU) ± lymphadenectomy	91	39 ± 7	29 ± 8	0.40	NS
NU + partial bladder resection (or TURB)	20	26 ± 11	26 ± 11		
Nephrectomy or ureterectomy alone	15	57 ± 16	57 ± 16		
Residual tumour					
No	93	41 ± 7	31 ± 8	0.0002	< 0.001
Yes	33	27 ± 13	27 ± 13		
Postoperative RT					
No	81	38 ± 7	29 ± 8	0.92	NS
Yes	45	33 ± 12	33 ± 12		

*Logrank test [10]; **Bonferroni correction [11]; NS, not significant; TURB, transurethral resection, bladder; RT, radiation therapy.

was the only significant factor in either univariate (Table 4) or multivariate analyses for either local or locoregional control.

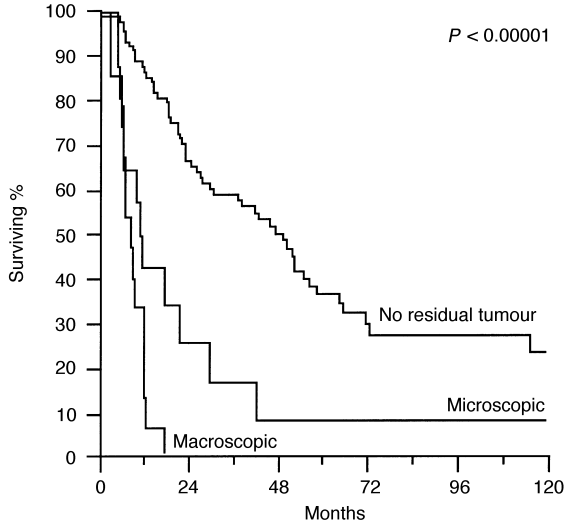

Figure 3. 10-year overall survival rates according to residual tumour following surgery: no residual tumour (*n*=93), microscopic (*n*=16), and macroscopic (*n*=17); *P*<0.00001; *P*-adjusted<0.0001.

Few data support the routine use of adjuvant postoperative radiation therapy in transitional-cell carcinoma of the renal pelvis or ureter (Table 6). It may be helpful in selected cases with high tumour stage, high tumour grade, and/or in patients with lymph node metastases, and it remains an unproven adjunct for the control of residual tumour. Using postoperative radiation therapy, some retrospective series suggest a decreased local relapse rate in patients with high

Table 5. Multivariate analysis (overall survival)*

Covariable	Relative risk (confidence interval)	*P*-value
pT-classification (a, 1, 2 versus 3, 4, X)	5.96 (2.7–14.5)	< 0.00001
Residual tumour (no versus yes)	8.33 (3.5–19.6)	< 0.00001
Tumour localisation (renal pelvis versus ureter ± renal pelvis)	1.69 (1.2–2.5)	0.007
pN-classification (0, X versus 1, 2, 3)	2.85 (1.0–7.7)	0.06
Postoperative radiotherapy (no versus yes)	1.36 (0.9–2.1)	0.15
Grade (1, 2 versus 2, 3)	1.88 (0.7–5.9)	0.25

*Cox model [12].

Table 6. 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 [3]	8	18.25–59.0	8 of 8	control: 4 of 8; local control: 7 of 8
Brookland [4]	9	40.0–60.0	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 [5]	2	40.0–50.0	2 of 2	control: 1 of 2
Cozad [6]	10	37.4–56.0	3 of 10	local control: 9 of 10
Maulard-Durdux [7]	26	45.0	?	local control: 21 of 26
Present series	45	20.0–66.0	15 of 45	locoreg. control: 28 of 45; local control: 33 of 45
	81	–	18 of 81	locoreg. control: 28 of 81; local control: 51 of 81

stage and/or high grade tumours with or without positive lymph nodes [3–6]. Others did not observe any advantage of adjuvant radiation therapy [7].

In this multicentre retrospective study, we could not show any benefit of postoperative radiation therapy. One should note that patients given postoperative radiation therapy had significantly higher pT-classification, ureteral localisation, and higher grade tumours (Table 1) compared with non-irradiated patients. However, no statistically significant difference was found in terms of local or locoregional control between patients receiving postoperative radiotherapy and those not (Table 4), whilst the latter showed a better survival (Table 3). In their series including 41 patients, Brookland and Richter [4] reported that local recurrence was less, although distant failure was about the same with postoperative radiation therapy (Table 6).

In our series, the rate of distant failures was relatively high (19%), which was also reported as high as 54% by Maulard-Durdux and colleagues [7]. For this reason, adjuvant systemic chemotherapy should be investigated because good objective responses are observed in a palliative setting [20, 21].

We conclude that, in patients with transitional-cell carcinoma of the renal pelvis and/or ureter, a radical surgical attitude is mandatory; and presence of tumour in the ureter is associated with a poorer prognosis. Nevertheless, with the introduction of more sophisticated treatment planning, conformal techniques, and intensity modulation, the role of postoperative radiotherapy remains to be reassessed.

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