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ORIGINAL ARTICLE

Impact of diagnostic and treatment delay on survival in patients with renal pelvic and ureteral cancer

STEN HOLMÄNG[1] & SONNY L. JOHANSSON[2]

[1]*Department of Urology, Sahlgrenska University Hospital, Göteborg, Sweden, and* [2]*Department of Pathology and Microbiology and Eppley Cancer Center, Nebraska Medical Center, Omaha, Nebraska, USA*

Abstract

Objective. To investigate the relationships between diagnostic and treatment delay and tumour stage and survival among patients with malignant tumours in the renal pelvis and ureter. *Material and methods.* A clinical and histopathological review was performed on 943 patients with a primary malignant tumour in the renal pelvis and ureter. We selected 394 patients who had macrohaematuria as an initial symptom, had no previous history of bladder cancer, had undergone surgery and had adequate follow-up. We performed uni- and multivariate analyses of prognostic factors for disease-specific survival. *Results.* The median number of days between the first occurrence of macrohaematuria and surgery was 83.5 days (range 4–1770 days). Patients with advanced tumours had the shortest median delay. Advanced tumour stage, a solid growth pattern and vascular invasion were of prognostic importance for disease-specific survival in the multivariate analysis, but diagnostic and treatment delay were not. *Conclusions.* Although the delay was unacceptably long it still had no impact on survival, probably because macroscopic haematuria is a late symptom, in particular in high-grade tumours. New screening methods for the early detection of cancer and new treatment modalities are needed to improve the poor prognosis in stage pT3–pT4 tumours.

Key Words: *Delay, survival, renal pelvis, ureter, malignant tumours*

Introduction

Malignant tumours in the renal pelvis and ureter are unusual compared to bladder cancer, which is >10 times more common [1]. Renal pelvic and ureteral tumours usually present as large-sized tumours requiring radical surgical treatment. Non-organ-confined tumours (stages T3 and T4) have a poor prognosis, with 5-year survival rates of 16–33% and 0–5%, respectively [2]. The diagnosis is often difficult to establish and more than one radiological imaging study or endoscopic examination is often needed for diagnosis, thus increasing the time required to make the diagnosis. Thus, it is of clinical importance to study the prevalence and consequences of such a delay. The impact of diagnostic and treatment delay in patients with renal pelvic and ureteral tumours has, to our knowledge, not been studied previously. Herein we report on the delay among patients with macroscopic haematuria as the initial symptom. It is difficult to establish the exact onset of other initial symptoms, such as flank pain, weight loss or fatigue. Macroscopic haematuria is an alarming symptom for most patients, resulting in contact with the healthcare system within 1 week. This is why the exact date of the first occurrence of haematuria can generally be found in clinical records [3,4]. We measured the total delay from the day of initial macrohaematuria until surgery and correlated it with survival. We hypothesized that a long delay was associated with high stage at diagnosis and poor survival.

Material and methods

We used the Swedish Cancer Registry to identify all patients in Western Sweden diagnosed with a malignant ureteral or renal pelvic tumour between 1971 and 1998. A total of 943 patients were found. In

Correspondence: Sten Holmäng, MD, PhD, Department of Urology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden. Tel: +46 31 3421000. Fax: +46 31 414972. E-mail: sten.holmang@telia.com

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1998 the population of Western Sweden was 1.65 million. Patients with an upper urinary tract tumour underwent surgery at one of 18 hospitals in the region.

The clinical records from the hospitals at which the patients were treated and followed were reviewed. A histopathological review of upper urinary tract tumours was performed. New sections were made from the paraffin-embedded blocks and stained with haematoxylin–eosin if the original slides were unavailable or unreadable. Approximately 99% of the clinical records and 94% of the surgical pathology material were available for review. The tumours were restaged according to the TNM system of 1992 and graded according to both the WHO classification system of 1999 and the WHO/International Society of Urological Pathologists Consensus Classification of 1998, which is identical to the 2004 WHO classification system [5–8]. Information about tumour size was taken from the pathology report or, if absent, from the radiology reports. The diameter of the largest tumour was recorded in cases with multiple tumours.

A total of 539 patients had macrohaematuria as the initial symptom. We excluded patients for whom the date of the initial episode of haematuria was lacking, patients who were not treated with surgery, patients with an unknown stage of cancer and patients with an earlier or concomitant bladder cancer. The remaining 394 patients constituted the study group for this report. The majority of patients ($n=287$; 73%) had a renal pelvic tumour, 78 (20%) had a ureteral tumour and 29 (7%) had tumours in both the renal pelvis and ureter. Urothelial cell carcinoma was seen in 340 patients (86%), squamous cell carcinomas in 22 (6%) and other histology in 12 (3%). The histopathological slides were unavailable for the remaining 20 patients (5%). The tumour had a solid or mixed solid/papillary growth pattern in 159 patients (40.4%), a papillary growth pattern in 206 (52.3%) and the growth pattern was not stated or unknown in 29 (7.4%). Vascular invasion was identified in routine histopathological stains in 132/234 (56.4%) invasive tumours. The median tumour size was 3 cm. Patients with stage pT3 and pT4 tumours had median tumour sizes of 3.8 and 5.5 cm, respectively. The majority of patients (346/394; 88%) were treated with nephroureterectomy or nephrectomy, 41 (10%) were treated with open local resection and six underwent surgical exploration only. One patient had bilateral tumours and was treated with nephroureterectomy on one side and resection on the other. Later, when a local recurrence or metastases developed, only three patients were treated with external-beam radiotherapy to the renal fossa and 16 were treated with systemic chemotherapy for metastases. Thus, the majority of patients were either not treated at all or treated only with palliative measures. The median follow-up period was 50 months (range 0–357 months).

Total diagnostic delay was defined as the interval from the first occurrence of macroscopic haematuria to surgery for the upper tract tumour. The patient-dependent delay was the interval between the first occurrence of macrohaematuria and the first contact with the healthcare system. The professional delay was the interval between the patient's first contact with the healthcare system and surgery. Neither the patient-dependent delay nor the professional delay could be calculated as the date of first contact with the general practitioner was unknown in many cases. The interval from macrohaematuria to urography includes the patient-dependent delay and the first part of the professional delay as urography was almost invariably the first radiological examination. The time from urography to surgery includes the second part of the professional delay.

Statistics

The mean, median and range were calculated for descriptive purposes. In order to predict survival the log rank test (for dichotomous variables) and Cox proportional hazard regression (for continuous variables) were used for univariate analyses. In multivariate survival analysis, stepwise multivariate Cox proportional hazard regression was used. Variables with a p-value of <0.1 in univariate analysis were included in stepwise analysis as possible predictors. When comparing groups, the Mann–Whitney U-test was used for continuous variables, Fisher's exact test for dichotomous variables, the χ^2 test for non-ordered variables and the Mantel–Haenszel χ^2 test for ordered categorical variables. Spearman's non-parametric correlation coefficient was used in all correlation analyses. All tests were two-tailed and conducted at a significance level of 5%.

Results

The median age, gender and tumour stage of the patients are shown in Table I. The total median delay was 83.5 days (range 4–1770 days). The median number of days between symptom and urography was 27 days and between urography and surgery 42 days. The median delay increased with each successive decade, being 64 days in the 1970s, 79.5 days in the 1980s and 103 days in the 1990s. The correlation between the year of diagnosis and delay was statistically significant ($r=0.18$; $p=0.0003$). I.v. urography was performed as the

Table I. The relationship between stage, age, delay and gender.

Tumour stage	Patients; *n* (%)	Median age (years)	Median delay (days)	No. of males	No. of females
Ta	164 (41.6)	69	88.5	103	61
T1	43 (10.9)	70	101	22	21
T2	14 (3.6)	68.5	78	9	5
T3	145 (36.8)	72	76	72	73
T4	28 (7.1)	71.5	56	15	13
All	394 (100)	70	83.5	221 (56%)	173 (44%)

initial diagnostic procedure in almost all patients. The frequency of additional diagnostic tests is shown in Table II. It can be seen that the frequency of angiography decreased between the 1970s and 1990s but that all other tests increased in frequency.

Patient age, gender, tumour side, tumour number and tumour location were not significantly related to the length of the delay (Table III). Patients who had tumours with vascular invasion had a shorter delay compared to those who had tumours without (72 vs 88.5 days; $p=0.0069$). Patients with stage pT4 tumours had the shortest total delay (56 days), as well as the shortest intervals from symptom to urography (18 days) and from urography to surgery (21 days).

Most patients (267/394; 68%) were operated on in one of the five largest hospitals. There were considerable differences in delay and tumour stage (pathological stage) between these hospitals. The total median delay varied between 59 and 99 days ($p=0.0362$). The median number of days from symptom to urography varied between 12 and 30 days ($p=0.1830$) and the median delay between urography and surgery varied between 23 and 57 days ($p=0.0001$). The proportion of non-invasive tumours varied between 25% and 61%. The proportion of stage pT3+pT4 tumours varied between 24% and 68% and the shortest delay was seen in those hospitals with the largest proportion of advanced tumours. The 5-year disease-specific survival rate varied from 47% to 72%. The shortest survival was found in the hospital with 68% stage pT3–pT4 tumours.

At the end of the study, 138/394 patients (35%) had died of cancer and 141 (36%) of other diseases, while 115 (29%) were alive. The univariate analysis identified a number of variables with prognostic significance for disease-specific survival (Table III). A short delay between urography and surgery was associated with short survival. Delay had no prognostic significance in the multivariate analysis (Table IV).

The statistical analyses were also performed with patients divided into two groups, as follows: a delay of >90 days ($n=212$) and a delay of ≤ 90 days ($n=182$). Patients with a total delay of ≤ 90 days had an inferior disease-specific survival compared to those with a longer delay ($p=0.0478$).

Discussion

The median total delay between the first episode of macrohaematuria and surgery for patients with tumours of the renal pelvis and ureter was 84 days, which is comparable to the delay for bladder cancer patients in Sweden, Denmark and the UK [4,9,10]. Although this delay may seem long, it is comparable to that for other malignancies, such as colorectal cancer [11].

Table II. Diagnostic tests used in the two periods 1971–79 ($n=100$) and 1990–98 ($n=141$). The values shown represent numbers of patients, with percentages in parentheses. Information is incomplete for some patients.

	Period		
Test	1971–79	1990–98	p (χ^2)
Angiography	70/99 (70.7)	9/141 (6.4)	0.0001
CT	1/100 (1)	86/141 (61)	0.0001
Ultrasound	4/97 (4.1)	79/140 (56.4)	0.0001
Retrograde pyelography			
on the suspected tumour side	63/98 (64.3)	104/141 (73.8)	0.1164
on the presumed healthy side	12/98 (12.2)	36/140 (25.7)	0.0108
Ureteroscopy	0/100	20/141 (14.2)	0.0001

Table III. Univariate analysis of factors of possible prognostic value for delay and disease-specific survival. Survival was calculated from the date of surgery until the last follow-up.

Variable	Hazard ratio	CI	p
Age	1.018	1.001–1.034	0.0351
Gender	1.056	0.758–1.472	0.7477
Side	1.250	0.898–1.741	0.1825
Tumour in ureter	1.007	0.699–1.453	0.9681
No. of tumours	1.471	0.794–2.725	0.2143
Tumour size	1.027	1.021–1.034	<0.0001
Carcinoma in situ	1.535	1.273–1.852	<0.0001
Stage	2.113	1.846–2.419	<0.0001
Grade (WHO 1999)	3.961	2.857–5.491	<0.0001
Grade (WHO/ISUP 1998)	5.717	2.739–11.933	<0.0001
Papillary vs solid tumour	3.611	2.917–4.471	<0.0001
Urothelial vs non-urothelial	3.215	2.092–4.950	<0.0001
Vascular invasion	9.408	6.346–13.948	<0.0001
Delay between symptom and urography	1.000	0.998–1.001	0.4629
Delay between urography and surgery	1.002	1.000–1.005	0.0440
Delay between symptom and surgery	1.001	1.000–1.002	0.0779

We found that the overall delay for patients with ureteral and renal pelvic tumours had no significant impact on prognosis, which is similar to what other authors [4,9,10] found for patients with bladder cancer. The delay among patients with advanced renal pelvic and ureteral tumours was shorter than that for patients with non-invasive tumours. Both Gulliford et al. [12] and Wallace et al. [4] suggested that urologists actively hastened the work-up process when a large bladder tumour was first seen at cystoscopy. We suspect that a large tumour seen on the initial urogram prompts the urologist to perform surgery as soon as possible. Another possibility may be that haematuria is more severe and continues for a longer time in patients with large, high-stage tumours, leading to a more rapid work-up and earlier surgery.

The present report, as well as published retrospective reports on macrohaematuria and delay, must be viewed with caution as the date of the initial episode of macrohaematuria may be erroneous and may also have another origin, such as infection or prostatic hypertrophy. Reports on delay in bladder cancer are further confounded by the staging method as it is based on bimanual palpation and transurethral resection, which is known to be less reliable than staging based on pathological examination of the cystectomy specimens [13]. Chang et al. [14] reported on 153 patients with muscle-invasive disease in the transurethral resection specimen. The authors found a significantly higher proportion of non-organ-confined disease when the interval from transurethral resection to cystectomy was >90 days compared to when it was shorter. Furthermore, interpretation of reports on the impact of delay is hampered by the fact that the initial tumour stage was not known. If it had been known, it would have been easy to determine the number of patients who progressed in stage between the onset of symptoms and surgery. In a study on lung cancer, O'Rourke and Edwards [15] compared the diagnostic CT scan with the subsequent radiotherapy planning scan. The median delay between these two imaging studies was 54 days. The median increase in cross-sectional tumour area was 19%. Six out of 29 patients became clinically incurable while waiting.

A reasonable assumption is that a urinary tract tumour which is non-invasive (stage pTa) will increase in diameter but is unlikely to acquire invasive properties, even during a long delay. One can assume that there is a higher risk that an invasive but organ-confined tumour (pT1–pT2) will become

Table IV. Multivariate analysis of factors of possible prognostic value for disease-specific survival. Survival is calculated from the date of surgery until the last follow-up.

Variable	Hazard ratio	CI	p
Tumour size	1.017	1.009–1.026	<0.0001
Tumour stage	1.526	1.148–2.027	0.0036
Vascular invasion	2.160	1.137–4.104	0.0187
Papillary vs solid tumour	1.587	1.064–2.365	0.0235
Age at diagnosis	1.023	1.002–1.045	0.0346

non-organ-confined during a long delay. The risk seems particularly high for invasive tumours of the upper urinary tract as the lamina propria and muscle layers are much thinner than those in the urinary bladder. The much lower incidence of stage T1–T2 tumours in the upper urinary tract compared to the urinary bladder may be indirect evidence for the hypothesis that a delay in treatment is of importance. We cannot rule out the possibility that a number of our stage pT3 tumours were actually stage T1–T2 tumours at the time when the patients had their first episode of macrohaematuria. Subgroup analyses must be viewed with caution but it is interesting that three groups of authors [4,9,10] reported a trend towards improved survival with short delay in stage T1 bladder tumours. One can speculate whether the delay was related to the depth of invasion in the lamina propria, which has prognostic importance, but the depth of invasion was not determined in any of the three studies [4,9,10,16].

There were considerable differences between the largest hospitals in the region regarding the length of delay. The disease-specific survival rates differed between hospitals, which was due to a large difference in the percentage of advanced tumours. This difference cannot be explained by a difference in delay as the delay was shortest in the hospital with the highest proportion of advanced tumours. We could not identify any particular factor responsible for delay at the hospital. A well-designed haematuria diagnostic service can significantly reduce unnecessary delays between presentation of cases of haematuria and the delivery of appropriate treatment [17]. Such an organization was not available at any of the studied hospitals.

It may seem surprising that a delay as long as 5 years was found. Soloway et al. [18] studied the growth of small bladder tumours and determined the average monthly increase in size, which was 1.77 mm. Some tumours, however, showed no growth at all during the observation period. Some small low-grade tumours in our study were most likely overlooked at the time of the first episode of macrohaematuria due to the poor sensitivity of urography for the diagnosis of small-sized tumours [19]. In patients with high-grade or solid tumours, however, it seems that macroscopic haematuria is a late symptom which occurs at a time when many tumours are of large size and high stage.

Screening for bladder cancer among men aged >60 years using commercially available haematuria dipsticks is realistic because bladder cancer is not uncommon in this age group, in particular among smokers [20]. Renal pelvic and ureteral cancers are so rare that screening could only be considered if a new screening tool with very high sensitivity and specificity was invented.

The delay increased for each successive decade, which is very worrisome. One possible explanation is that patients with macrohaematuria are increasingly managed as outpatients, which means that a lower priority is given to cystoscopic and radiological studies compared to when the work-up is done with the patient hospitalized. The number of diagnostic examinations increased during the study period, which may have contributed to a longer delay. The increase in delay may be a general trend; an increasing delay and an increasing number of diagnostic examinations were recently reported among Danish patients with squamous cell carcinoma of the larynx and pharynx [21]. Primdahl et al. [21] found that an extra pre-treatment delay of 3 weeks among patients with laryngeal and pharyngeal cancer could theoretically lead to a 10% lower tumour control probability in 2002 compared to 1992. There is an urgent need to put treatment delays on the agenda, although other measures, such as new screening methods and new treatment modalities, are also needed to improve the poor prognosis of upper tract tumours.

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