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Carcinoma of the Renal Pelvis and Ureter

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ABSTRACT

Objective: To assess the occurrence of upper urinary tract urothelial tumors (UUTT) in Brazil.
Materials and Methods: We performed a clinical and histopathologic study of 33 patients who were diagnosed with a malignant neoplasm in the renal pelvis or ureter in the period of 1994 to 2004, in a single institution.
Results: Among the patients with upper urinary tract carcinoma, 70% were males and 30% females, with mean age of 65 ± 16 years (ranging from 31 to 91 years). Nineteen patients presented renal pelvis tumor (58%), 9 ureteral tumor (27%) and 5 synchronic pelvic and ureteral tumors (15%). Renal pelvis tumors represented 2.8% of all the urothelial neoplasms, and 11.4% of all renal neoplasms treated in the same period. Ureteral tumors represented 1.6% of all the urothelial malignancies surgically managed in these 11 years. Tobacco smoking was the most common risk factor, and analgesic abuse was not reported by those patients. Most carcinomas were high-grade and muscle-invasive. Mean time to diagnosis was 7 months, being hematuria the most common symptom.
Conclusions: A high association was also found between UUTT and bladder urothelial carcinoma. UUTT were mostly seen in men in their seventies and related to a high overall and cancer-related mortality rate.
The overall disease-specific survival was 40%, much lower than found in most of the reported series.

Key words*: kidney; ureter; neoplasms; transitional cell; epidemiology; Brazil*
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INTRODUCTION

Upper urinary tract tumors involving the renal pelvis and ureter are relatively uncommon. The great majority of these are epithelial, 80% are malignant and 90% are urothelial carcinomas. Renal pelvis tumors account for approximately 7 to 10% of all renal tumors and about 5% of all urothelial tumors (1-9). Ureteral tumors are even more uncommon, occurring in one fourth of the incidence of renal pelvis tumors (1,10).

Many factors contribute to the development of upper urinary tract urothelial tumors (UUTT), some of them similar to bladder cancer associated factors, and the most common of these are tobacco smoking and analgesics abuse, particularly phenacetin (2,3,5,11-13). Other risk factors include papillary necrosis, chronic urinary infections, renal calculi, occupational exposure, Balkan nephropathy, thorium containing radiologic contrast medium and family associated cancer syndromes (2,3,5,12-14). The behavior of the UUTT is also similar to the bladder urothelial carcinoma, presenting high recurrence rates and usually is multicentric (2,3,9).

In the bladder, however most urothelial carcinomas are superficial at diagnosis (3,5). In these

cases, organ-sparring procedures are the treatment option. For UUTT, nephroureterectomy with bladder cuff removal has been the conventional treatment. More recently, with the introduction of endourological techniques, approaches that are more conservative have been advocated in selecting patients in an effort to salvage kidneys. However, different from bladder carcinoma, radical surgery is more often used in UUTT cases, as the diagnosis is commonly made at advanced stages and management by conservative measures is problematic (3).

Among the North-American population, there has been an increase in women affected, and it tends to occur at an older age (3,5,15). Large demographic studies have been undertaken in several countries (2,4,6-9,15-19) but to our knowledge, there is no study analyzing data about UUTT in the Brazilian population.

The aim of the present study is to assess the occurrence of UUTT in 33 patients who underwent surgery from 1994 to 2004 in a single institution.

MATERIALS AND METHODS

Surgical pathology files of all patients who underwent surgery for primary UUTT at the Division of Urology of the authors' institution from 1994 to 2004 have been retrospectively reviewed (33 subjects).

Macroscopic data were obtained from the pathological reports. The hematoxylin and eosin stained slides were reviewed by one pathologist with special expertise in the field of uropathology (MGC). Slides on each case were collected and reclassified using the criteria of the 2004 WHO grading system (5). All tumors were restaged based on TNM (tumor node metastasis) staging system, 2002 (20). All urothelial and renal tumors surgically treated during the same period in the referred institution were also revised in order to calculate disease-related prevalence.

Further data were obtained from the hospital database and patients notes, including patients' demographics, anatomical location of the tumor, surgery outcomes, disease recurrence, specific survival and overall survival. Contact was established with the patient and/or family whenever possible, and the district death registry was consulted for the remaining cases.

Disease-specific survival was assessed by the Kaplan-Meier method and compared by the Log-Rang test.

The institutional medical ethics committee approved the present study.

RESULTS

Among patients with UUTT, 70% were males and 30% females, with a mean age of 65 ± 16 years (ranging from 31 to 91 years). Ninety-one per cent of the patients were white and 9% black. The left side was affected in 61% of the cases and the right side in 39% (Table-1).

Nineteen patients had only renal pelvis tumor (58%), 9 had ureteral tumor (27%) and 5 had both pelvic and ureteral tumors (15%). Renal pelvis urothelial carcinomas represented 2.8% of all the urothelial neoplasms surgically treated in our institution during this period, and 11.4% of all renal tumors. Ureteral tumors represented 1.6% of all the urothelial malignancies surgically managed. In 50% of the patients the distal ureter was affected, middle and proximal ureter were respectively affected in 29% and 21% of the patients.

Association with bladder cancer was present in 30% of the patients. In 17% of them, there had been a previously treated bladder cancer (mean of 4 years previously) and in 23%, there had been a synchronous bladder neoplasm. In 15% of the cases, there had been synchronous ureteral and pelvic neoplasm

Table 1 – *Clinical features of upper urinary tract urothelial tumors.*

Feature	Value
Male / Female	70% / 30%
Mean age (years)	65 ± 15
Right / Left	39% / 61%
Bilateral	3%
Mean follow-up (range)	7 ± 3 (1-11 years)

and in 3% of the patients, bilateral disease had been found.

Hematuria was the most common symptom, seen in 45% of the patients. Other presenting manifestations included anemia (43%), flank pain (30%), weight loss (27%), fever (17%) pyelonephritis (17%) and palpable mass (10%). Diagnosis due to incidental finding during follow-up of previous urothelial carcinoma occurred in 10% of the patients. In the cases that weight loss, the mean loss observed was 5 Kg.

Mean duration of symptoms prior to diagnosis was 6.9 ± 4.3 months. Initial diagnosis was UUTT in 85% of the cases. In 6% of the cases, renal cancer was suspected and in 9% of the cases, the surgery was undertaken with the diagnosis of pyonephrosis, and the presence of cancer was confirmed during pathologic exam.

Regarding risk factors, tobacco smoking was referred by 66% of the patients and 33% had recurrent urinary tract infections or calculi. In one patient there was an hereditary nonpolyposis colorectal cancer syndrome associated (3%). Analgesic abuse was not referred to as risk factor in any patient.

Surgical treatment consisted of radical nephroureterectomy and bladder cuff removal in 65% of the patients; in 6% radical cistectomy was also performed; in 16% only distal ureterectomy and reimplant was performed, and in 13% only nephrectomy. Radiation therapy and chemotherapy were respectively combined in 6% and 12% of the cases.

Pathological exam demonstrated high-grade malignancies in 58% of the renal pelvis neoplasms and in 86% of the ureteral neoplasms. Regarding renal pelvis neoplasms, pT3 was the most common stage, observed in 37% of the patients; pTa was observed in 29%, pT1 in 12%, pT2 in 12% and pT4 in 8% (Table-2). In ureteral neoplasms, pTa was the most common stage, observed in 28% of the cases. Stages pTis, pT1, pT2, pT3 and pT4 occurred respectively in 7%, 14%, 21%, 14% and 14% of the cases (Table-2). In 93.9% of the patients there was an urothelial tumor, and in 6.1% a squamous cell carcinoma. Squamous cell differentiation was observed in 9.7% of the urothelial carcinomas (3 cases). In all the cases with squamous cell differentiation, pathological stage was pT3, and for pure squamous cell carcinomas, one had a pT3 stage and the other a pT4. All the patients with squamous cell differentiation or squamous cell carcinoma had renal calculi and/or infection associated. In terms of lymph node status, 85% of the tumors were at NX, 6% at N0 and 9% at N1-3.

During follow-up (mean 7 ± 3 years, ranging from 1-11 years), 10% were alive, 30% died due to other causes, 5% died due to surgical complications and 55% died due to the malignancy. Three patients presented bladder cancer (treated endoscopically) and one patient that had a previous renal pelvis neoplasm underwent a contra-lateral distal ureterectomy 2 years later due to UUTT. Adequate follow-up was possible in 61% of the patients.

Disease-specific survival was not related to tumor grade ($p = 0.31$) neither to pathologic stage ($p = 0.51$) in the present series.

COMMENTS

In the present series, UUTT prevalence related to renal and bladder cancer was similar to that

Table 2 – *Distribution of renal pelvis and ureteral tumors according to histologic grade and stage.*

		Ta	Tis	T1	T2	T3	T4	Total
Renal pelvis	LG	7 (29%)	0	1 (4%)	1 (4%)	1 (4%)	0	10 (43%)
	HG	0	0	2 (8%)	2 (8%)	8 (33%)	2 (8%)	14 (57%)
Ureter	LG	2 (14%)	0	0	0	0	0	2 (14%)
	HG	2 (14%)	1 (7%)	2 (14%)	3 (21%)	2 (14%)	2 (14%)	12 (84%)

LG = low-grade; HG = high-grade.

previously reported in other studies (1,2,21). The anatomical location of UUTT in the present study conforms to that previously described, with almost twice as many pelvicalyceal as ureteric tumors (22). Ureteric tumors were also more common in the distal third, followed by the middle and proximal portions of the ureter, as reported in other series (22). The incidence of bilateral synchronous tumors was similar to other series (1,2).

UUTT has also been found to be primarily a disease of white individuals (91% of the cases), and mostly affecting elderly men (15). The demographic characteristics of our patients showed a peak incidence in the seventh decade of life and male-to-female ratio of 2.3:1. This is different from the lower tract disease in which the male-to-female ratio is 3 to 4:1 (3).

In the American population, Munoz et al. observed that patients with UUTT are being diagnosed at an older age, and a higher proportion of female and nonwhite individuals have been diagnosed. In our patients, such variation has not been noticed. Even though the number of patients is limited, age, ethnics and gender characteristics of the patients with UUTT remained the same during the last decade (15).

According to the WHO 2004 grading system, tumors are grading as papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade and high-grade carcinomas. There were few studies that used this system (2-4,18,19). We did not identify any PUNLMP, similarly to Olgac et al. It seems that differently from what occurs in the bladder, PUNLMP occur less frequently in upper urinary tract (19). In the present study, 86% of ureteral carcinoma and 58% of renal pelvis carcinoma were high-grade. These findings are similar to others investigators' data (3,6,7,9,17-19,23), confirming that most of the patients treated for UUTT present a high-grade disease.

Squamous cell carcinoma has accounted for 6.1% of the UUTT, close to previously reported in other series (4,24,25). Also, as reported by Blacher et al. in our patients all the squamous cell carcinomas and the urothelial carcinoma with squamous cell differentiation occurred within the renal pelvis, and all of them were high grade and high stage diseases with extensive invasion of the renal parenchyma. All were in pathological stage pT3 or pT4 and had an unfavorable prognosis (25). As previously reported, all the cases were associated to calculi, chronic infection and squamous metaplasia of the neighboring epithelium (4).

In 64% of the cases, muscle-invasive disease was found, confirming the fact that unlike urothelial carcinomas of the bladder, UUTT should therefore be regarded as an aggressive, high-grade cancer, unless proven otherwise (3,26). In the reported cases however, muscle-invasive disease was more frequent than observed in other large series, with pT2 stage or higher occurring in 42-49% of the UUTT (3,8,18,19).

In our study, 13 patients (39%) had multifocal disease at presentation. Of these, one had bilateral ureteral tumor, 5 had both pelvic and ureteral tumor, 3 had pelvic and bladder tumor, 3 had ureteral and bladder tumor and 1 had carcinoma in the pelvis, ureter and bladder. The multicentric characteristic of urothelial carcinomas may be explained by several theories, but the better accepted is the so-called field effect, suggesting that the entire urothelial surface has undergone a neoplastic change (2).

Mean time from the beginning of symptoms to diagnosis was 7 months, being hematuria the most common symptom. Even though good screening programs are not available for such tumors, adequate widespread information could lower the stage at diagnosis. In the present study, a close association was found between UUTT and bladder urothelial cell carcinoma. Diagnosis and follow up of these bladder tumors allowed an earlier diagnosis of 10% of upper tract carcinomas.

Long-term phenacetin abuse is a commonly reported risk factor for UUTT (12). However, in the present study it was not found to be a significant risk factor. Maybe the greater popularity of dipirone instead of phenacetin among Brazilians may explain this finding (27). Concerning risk factors, tobacco smoking, renal calculi and chronic infection were mostly observed.

Currently UUTT have been managed conservatively under certain circumstances, provided they are superficial tumors, with low grade of differentiation and completely removed endoscopically (28). The patient must also be strictly and regularly fol-

lowed (28). However, in patients studied, such criteria have not been fulfilled in any of the cases. In most of them, there were bulky high stage and high-grade lesions.

Overall 5-year disease-specific survival was 40%, much lower than most of the reported series, which varies from 67% to 75% (15,29,30). As stated previously, a high prevalence of muscle-invasive disease and a high stage at diagnosis was observed in these patients. As pathological stage is one of the most important prognosis predictor, a poorer survival would in fact be expected for the studied population (9,18).

When analyzing disease-specific survival, neither tumor grade nor stage was significant risk factors in the present series. However, the poor follow-up of these patients, associated to the limited number of patients could explain this observation.

In conclusion, the studied population showed prevalence of UUTT related to other urothelial and renal neoplasms similar to the ones observed in other studies. UUTT was mostly diagnosed in men in the seventh decade of life, and tobacco consumption has been the major risk factor for UUTT in the present population. UUTT was associated to a high overall and cancer-related mortality rate.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors report a study of the initial presentation of upper urinary tract urothelial tumors. The findings of the present study are coincident with the ones found in literature where those tumors are infrequent, representing less than 5% of urothelial tumors. It is highlighted that the main risk factors were tobacco smoking (66%) and recurrent infections (33%). The other risk factors described in literature (phen-

acetin, nephropathy by Chinese herbs, occupational factors, nephropathy of the Balkans) were not observed here due to population differences.

It is also mentioned that the presence of a squamous component confers more aggressiveness and worsens the patient's prognostic.

It is important to highlight the high incidence of bladder neoplasia associated to upper tract tumors, requiring close watch to it during the patient's follow-up period.

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EDITORIAL COMMENT

The authors report basic data and outcome for 33 patients with upper urinary tract tumors treated in a hospital in Brazil. Most patients had high-grade tumors and 21 out of 33 had invasive tumors. The disease-specific survival rate was 40%. The data are consistent with other reports from Europe and North America. Patients with organ-confined tumors (stages Ta/T1/T2) have a good prognosis, patients with non-organ-confined disease (stage T3/T4) have a very poor prognosis, and this has not changed much during the last 30 years.

So what is new in the treatment of upper tract tumors? Laparoscopic nephroureterectomy is a technically difficult procedure and may result in a faster recovery but will not influence the long-term prognosis. Endoscopic surgery (ureteroscopy or percutaneous surgery) may of course be excellent for patients who have small-sized low-grade tumors. Such tumors are, however, rare and have a disease-specific survival close to 100% when treated with open surgery.

The low number of patients with renal pelvic and ureteral carcinoma treated at each center is one obstacle to improvement of the prognosis but with cooperation, prospective randomized studies are still possible. It would be of interest to evaluate whether preoperative chemotherapy can improve the poor prognosis among patients with stage pT3 renal pelvic carcinoma.

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EDITORIAL COMMENT

Korkes and associates describe their retrospective, single institution study on upper tract urothelial tumors (UUTT) in 33 contemporary patients. The authors report that in long-term follow-up the disease-specific was only 40%, which highlights the aggressive nature of UUTT. Not unsurprisingly, 66% of the patients in the study were tobacco users.

Most importantly, the authors note that the average duration of symptoms prior to diagnosis was 7 months. It is during this extended period of time that curable disease may be advancing. Other studies

have also demonstrated a delay in diagnosing bladder cancer (1,2). While this study was conducted in Brazil, other studies have demonstrated that Americans' overall cancer awareness is low (3). We have also recently demonstrated that basic knowledge and public education regarding bladder cancer is low (4).

So how are we to make an impact in the overall survival of patients with UUTT and bladder cancer? The authors appropriately stress that "widespread information could lower the stage at diagnosis." The risk factors for UUTT and bladder cancer need to be publicized; patients and primary care physicians need to be educated regarding the timely evaluation of hematuria; and ultimately, screening programs for those at high-risk need to be implemented.

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