

URINARY TRACT TUMORS IN KOLUBARA REGION

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Summary. *High incidence of the upper urothelial tumors in the endemic nephropathy regions was described in the very beginning of the disease investigations. In Kolubara region upper urothelial and bladder tumors appeared only in Lazarevac and Lajkovac municipalities, the most frequently in three villages most affected by endemic nephropathy: Petka, Šopić and Cvetovac. Urothelial tumors affected more frequently females than males (1.4:1) aged between 50 and 80 years, the most frequently persons in the seventh decade of life. Agriculture was the main or additional occupation of patients with tumors.*

Etiology of the upper urothelial tumors is still unknown. Our study on the possible risk factors for the occurrence of these tumors indicated smoking, positive family history of endemic nephropathy in second and third degree relation, presence of the affected with other malignant tumors in the first degree of relation, agriculture as occupation, urinary tract infection and some kind of food as the factors of influence.

According to our results 82% of the upper urothelial tumors were localized in the renal pelvis or ureters, while simultaneous appearance of tumors in the pelvis and ureter was less frequent (18%). The tumors appeared more frequently unilaterally than bilaterally (82% vs. 18%). Bladder tumors were registered in 18% of our patients.

Although endemic nephropathy often precedes the appearance of the upper urothelial tumors, our investigations in Lazarevac endemic foci also revealed the patients with upper urothelial tumors appearing before clinical manifestation of endemic nephropathy. Besides, upper urothelial tumors were registered in 29.8% of patients with endemic nephropathy maintained by hemodialysis in Lazarevac.

Key words: *Upper urothelial tumors, endemic nephropathy, Kolubara region*

Introduction

In spite of permanent increase in the incidence of the upper urothelial tumors, these malignancies are rare neoplasms in comparison to all other malignant tumors and urinary tract tumors (1,2). More frequent appearance of upper urothelial tumors in the regions affected by endemic nephropathy was described at the very beginning of the disease investigation (3-5). The frequency of these tumors in endemic regions was even up to 100 times higher than in non-endemic regions (6,7). Also, in the Lazarevac municipality the risk for upper urothelial tumors development was 95 times higher for inhabitants of endemic villages as compared to the inhabitants of the neighboring non-endemic villages (8). Čukuranović et al. (9) reported incidence of upper urothelial tumors of 29.7 per 100 000 inhabitants in endemic regions, 6.4 in hypoendemic regions, and 0.5 per 100 000 inhabitants in non-endemic villages and cities in the South Morava River Basin.

The frequency of upper urothelial tumors in Kolubara region

Several investigations of frequency of the upper urothelial tumors were conducted in the Kolubara region. A retrospective thirty year analysis (1952-1982) that involved 34 villages in Lazarevac municipality with 45 622 inhabitants registered 59 patients with upper urothelial tumors. The majority of them, 33 patients were from three hyperendemic villages with 4895 inhabitants, 19 from 11 villages less affected by endemic nephropathy, two patients came from the villages with questionable existence of endemic nephropathy, and only one patient came from the remaining 11 villages without endemic nephropathy (8).

Similar results were obtained in a cross-sectional study conducted in 1969/1970 which included 85% of the inhabitants of the municipality of Lazarevac. The results showed that upper urothelial tumors and bladder tumors appeared markedly frequent in three villages most affected by endemic nephropathy (Petka, Šopić and Cvetovac), where 48.8% out of total number of patients with tumors were registered (10, 11).

A field investigation conducted in 1982 in Kolubara region discovered upper urothelial tumors only in Lazarevac and Lajkovac municipalities. The incidence of these tumors per 1000 inhabitants ranged between 0.2 and 18.7 in the Lazarevac municipality and 0.3 to 7.1 in Lajkovac municipality. Endemic nephropathy was found in 84.7% of patients with the upper urothelial tumors but in patients with bladder tumors, that were found in 10 patients, endemic nephropathy was diagnosed in only one patient (11).

Our recent study confirmed that incidence of the upper urothelial tumors in the Kolubara region, as well as the incidence of endemic nephropathy are not decreasing. The retrospective study involved all patients with urinary tract tumors treated at the Institute of Endemic Nephropathy in the period 1974-2001. According to the medical records, out of 421 patients with urinary tract tumors 172 patients (40.9%) had pelvic tumors, 154 (36.7%) had ureteral tumors and 95 (22.6%) bladder tumors. The total of 182 (43.2%) patients originated from endemic villages and both diseases, endemic nephropathy and tumors, were found in 125 (26.7%) patients (12).

Demographic characteristics of patients with urothelial tumors in endemic nephropathy foci of Lazarevac

Aiming to find out the main characteristics of patients with urothelial tumors from Lazarevac endemic nephropathy foci, 73 patients with histopathologically confirmed tumors were examined. The patients were treated at the Institute of Endemic Nephropathy in Lazarevac and Institute of Urology and Nephrology, Belgrade between 1992 and 1994. The descriptive epidemiological method was used (13-15).

Sex. Females were more frequently affected by urothelial tumors than males (1.4:1) (Fig. 1). This is consistent with the results obtained in other studies conducted in the endemic regions (8,9,16,17). In non-endemic regions foreign authors found the males to be more frequently affected by the upper urothelial tumors (18,19).

Age. The majority of patients were 50-80 years old, 59% were in the seventh decade of life (Fig. 1). The mean age was 64.2 ± 6.8 years. Our results are consistent with the results obtained both in the regions with endemic nephropathy and out of them (20,21).

Occupation. In our study the number of patients with tumors from the villages known as endemic foci was 70 times higher than the number of patients who came from the city. The majority of them lived in two villages most affected by the endemic nephropathy in the Lazarevac municipality, Petka and Šopić (Fig. 1). Agriculture was the main or additional occupation of patients with tumors. Other authors from our country found also that farmers were the most affected by the upper urothelial tumors (22,23). The studies carried out in the

regions without endemic nephropathy foci provided no data on the farming as a risk factor for the development of the upper urothelial tumors (21,29).

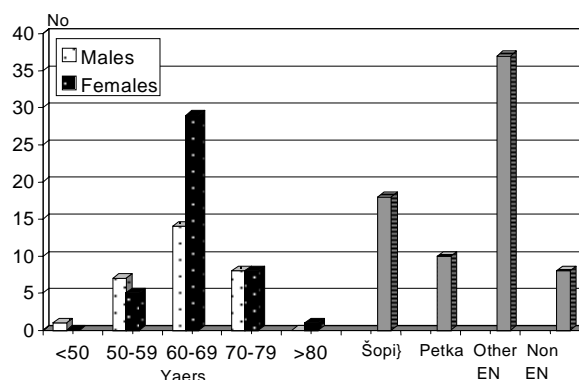


Fig. 1. Sex and age of patients with upper urothelial tumors treated at the Institute of Endemic Nephropathy in Lazarevac between 1992 and 1994 and their distribution in the settlements of Lazarevac municipality Šopić and Petka – the most affected villages with endemic nephropathy; other EN – other endemic nephropathy villages; non EN- non-endemic villages.

Familial pattern. The analysis of genealogical trees as far as the fourth degree of kinship was done for each patient examined, both for urothelial tumors and endemic nephropathy. The family agglomeration of the upper urothelial tumors and endemic nephropathy in patients with upper urothelial tumors was observed in all degrees of relation, especially in the second and third generations (Table 1).

Table 1. Prevalence of the upper urothelial tumors and endemic nephropathy among the relatives of patients with upper urothelial tumors treated at the Institute of Endemic Nephropathy in Lazarevac between 1992 and 1994

Degree of kinship	Prevalence (%)	
	Upper urothelial tumors	Endemic nephropathy
First	0.6 (5/320)	6.2 (20/320)
Second	2.1 (16/766)	6.5 (50/766)
Third	1.3 (11/845)	7.2 (61/845)
Fourth	0.5 (4/726)	3.2 (23/726)

Risk factors for occurrence of the upper urothelial tumors

The etiology of the upper urothelial tumors is still unknown. The association of two diseases, endemic nephropathy and upper urothelial tumors, led to the suggestion on a possible mutual or the same etiological factor for both diseases (6,8,9,20,24,25). Several factors were investigated as possible risk factors for the occurrence of these tumors in non-endemic regions. One of the most important is smoking indicated by many authors (26-30). They found that smoking increased relative risk for occurrence of these tumors for 4 to 7

times. It was also evidenced that consumption of black coffee increased the risk for development of urothelial tumors (27-30).

The association between transitional cell carcinoma of the renal pelvis and analgesic abuse has been known for three decades (31), and it was confirmed by a number of authors (26,30,32,33). Additionally, the influences of occupation (26, 27) and calculosis (30,34) as well as possible role of viruses (35,36) in development of renal pelvis and ureteral tumors were also studied. Numerous authors studied the role of ochratoxin A in etiopathogenesis of the endemic nephropathy and upper urothelial tumors (37,38).

Investigations of risk factors for occurrence of the upper urothelial tumors in Kolubara region

In order to contribute to the investigations of possible risk factors for the occurrence of upper urothelial tumors, a case control study was carried out in the Kolubara region in the period between 1992 and 1994. The study included 73 patients with histopathologically confirmed upper urothelial tumors and the same number of sex-age matched controls. Using epidemiological questionnaire the data on the age, sex, education, occupation, diet, habits (smoking, usage of coffee, tea, alcohol, analgesics, and artificial sweeteners) were registered. The genealogic analysis of genealogical trees as far as the fourth degree of kinship for each patient was done (13,39).

The results of the multivariate logistic regression analysis showed that risk factors for occurrence of the upper urothelial tumors were smoking, positive family history of endemic nephropathy in second and third degree relations, presence of the relatives affected by other malignant tumors in the first degree of relation (Table 2). Our patients used analgesics very rarely and in small doses and the relationship between the upper urothelial tumors and analgesics could not be found.

Agriculture was the main occupation of the patients with tumors, and length of work in the field or in the garden as permanent activity, as well as utilization of herbicides, pesticides and rodenticides was significantly higher in patients with tumors than in the controls ($p < 0.001$).

According to the results of our study, patients with the upper urothelial tumors had significantly more frequent urinary tract infections than the controls (RR = 2.7; 95% CI: 1.1–6.7; $p < 0.05$). McLaughlin and coworkers (26) reported increased risk for occurrence of renal cancer in patients with renal infections (RR = 2.8 for males and 2.2 for females).

The significant relationship was found between the use of some kinds of food and urothelial tumors appearance. Raspberry and currant as well as cheese and yogurt were found to protect against development of urothelial tumors. That could be explained by protective effect of vitamins found in these foodstuffs (fruits rich with vitamin C, milk products rich with vitamins A and B). There is no logical explanation for the use of fish and apple, and tumor appearance but this population used those foodstuffs very rarely.

Localization of tumors

It is well known that in non-endemic regions urinary bladder tumors are significantly more common than tumors of the renal pelvis and ureters, but this is not the case in endemic regions (40). Our study showed a similar frequency of tumors of the renal pelvis and ureters, and less frequent simultaneous appearance of tumors in the both localisations (Table 3). The tumors appeared more frequently unilaterally than bilaterally. Bladder tumors were registered in 13 (18%) patients with upper

Table 3. Localization of upper urothelial tumors in 73 patients treated at the Institute of Endemic Nephropathy in Lazarevac between 1992 and 1994

Localization	No of patients	%
Renal pelvis	31	42.5
Ureter	29	39.7
Renal pelvis & ureter	13	17.8
Total	73	100.0
Unilateral	60	82.2
Bilateral	13	17.8
Total	73	100.0
Bilateral synchronous	4	30.8
Bilateral successive	9	69.2
Total	13	100.0

Table 2. Variables associated with higher risk for occurrence of the upper urothelial tumors in Kolubara endemic nephropathy region (multivariate logistic regression)

Variables	B	SE	RR	p	95% CI
Smoking	1.147	0.329	3.15	0.000	1.65 – 6.00
Fish in diet	1.600	0.491	4.95	0.001	1.89 – 12.97
Apple in diet	0.445	0.148	1.56	0.002	1.17 – 2.08
No of EN patients in 2 nd degree relation	3.731	1.328	41.71	0.005	1.13 – 563.22
No of patients with other tumors in 1st degree relation	2.531	0.931	12.56	0.006	2.02 – 77.96
Raspberry & currant in diet	-0.380	0.140	0.68	0.007	0.52 – 0.90
No of EN patients in 3 rd degree relation	3.311	1.296	27.41	0.011	2.16 – 347.36
Cheese & yogurt in diet	-0.593	0.246	0.55	0.016	0.34 – 0.89
Constant	-1.745	0.879		0.047	

B- coefficient of logistic regression; RR-risk ratio, CI- confidence interval; EN-endemic nephropathy

urothelial tumors. Our results on the localization of urothelial tumors are in accordance with those obtained in the studies carried out in endemic regions (16,20,40). The synchronous occurrence of multiple tumors was registered in 18 (25%) patients and association of multiple and bilateral tumors was found in 31 (43%) patients. Petković (6) noticed the multiplicity of tumors in 30-40% of patients and similar percentage was reported later from the same clinic (16,25). Petronić suggested that multiple and bilateral occurrence of the upper urothelial tumors and their association with urinary bladder tumors indicated that these tumors primarily developed as the multicentric ones (40).

Urinary tract tumors in endemic nephropathy and renal failure

Early studies suggested that endemic nephropathy preceded the appearance of upper urothelial tumors (6,41). Petković and coworkers found renal failure in 63% of the patients with pelvic and ureteral tumors and suggested that these tumors appeared 10–20 years after the outset of endemic nephropathy (6). Our recent study also showed renal failure in 57% of patients with the upper urothelial tumors and 35.7% of them were on maintenance hemodialysis, which is consistent with the recent results of the other authors (42). However, our investigations in Lazarevac endemic foci, also, revealed patients with upper urothelial tumors appearing before clinical manifested endemic nephropathy and several years, even decades before development of chronic renal failure (43). According to our clinical experience it was not infrequent that patients were treated in our institute due to hematuria caused by urothelial tumors without any signs of endemic nephropathy. The diagnosis of endemic nephropathy was established in these patients after diagnosis of tumors and many of them remained in the early phase of the disease for decades. More detailed investigations of this group of patients will be required.

In order to find out the frequency of the upper urothelial tumors in patients with endemic nephropathy maintained with hemodialysis, 161 endemic nephropathy patients who started dialysis at the Institute for endemic nephropathy in the period between 1979 and 1993 were analyzed. There were 79 males and 82 females aged from 40 to 74 years. Out of 79 males 26 (32.9%) were diagnosed with the urothelial tumors: 19 (73%) patients had upper urothelial tumors, 4 (15.4%) patients had bladder tumors and three had upper urothelial tumors associated with bladder tumor (Fig. 2). The successive, bilateral appearance of the upper urothelial tumors was registered in 5 (19.2%) patients after they started hemodialysis, 65.2 months after discovery of the first one, at the average. Relapse of the ureteral tumor

was registered in one patient two years after surgical ablation. In 13 patients (59.1%), tumors were diagnosed before starting dialysis. The pre-dialysis period starting with tumor diagnosis lasted 61.9 months, at average. In the remaining 9 (40.9%) patients tumors were diagnosed after hemodialysis onset, 45 months at the average. Out of 82 female patients examined, 22 (26.8) had tumors of the urinary tract, and out of them 18 patients (81.8%) had tumors of the upper urothelium. In four females bladder tumors were detected and in three of them they were associated with the upper urothelial tumors (Fig. 2). The successive, bilateral appearance of upper urothelial tract tumors was registered in eight (36.4%) patients 107 months after the first tumor appearance. Eighteen (81.8%) patients were operated. Tumors were diagnosed before starting of hemodialysis treatment in 16 (72.7%) patients. The pre-dialysis period starting with tumors diagnosing was 84 months, at the average. Six (27.3%) patients developed tumors after starting hemodialysis, after 69.2 months, averagely. The average survival was 37.4 months.

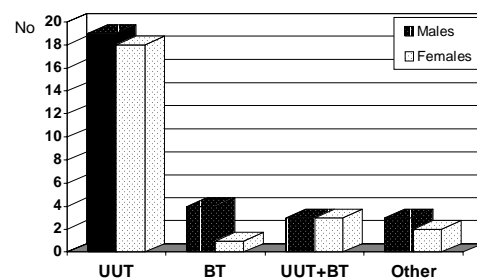


Fig. 2. Localization of tumors diagnosed in 54 out of 161 patients with endemic nephropathy maintained with hemodialysis at the Institute of Endemic Nephropathy in Lazarevac in the period from 1979 to 1993
UUT - upper urothelial tumors; BT- bladder tumors; other- other malignant tumors

Our results showed that upper urothelial tumors were registered in 29.8% of patients with endemic nephropathy maintained by hemodialysis in Lazarevac. The tumors developed more frequently (67.4% patients) before hemodialysis outset, 5 years at the average, that was not described in non-endemic patients (44,45). Other malignant tumors were discovered in 5 (6.3%) of our hemodialysis patients and the finding was less frequent in comparison to others (44,46). The average survival of hemodialysis patients with upper urothelial tumors was 46.1 months and it was not statistically significantly different as compared to the patients without upper urothelial tumors (46.8 months; $p > 0,05$). These results are in accordance with our previous investigations indicating the importance of early diagnosis and treatment of tumors.

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TUMORI MOKRAĆNIH PUTEVA U PODRUČJU KOLUBARE

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Kratak sadržaj: *Visoka incidencija tumora gornjeg urotelijuma u žarištima endemske nefropatije opisana je već posle prvih istraživanja ove bolesti. U području Kolubare tumori gornjeg urotelijuma i mokraćne bešike registrovani su u opštinama Lazarevac i Lajkovac, a najčešće u selima Petka, Šopić i Cvetovac koja su najugroženija endemskom nefropatijom. Tumori urotelijuma se u ovom području češće javljaju kod žena nego kod muškaraca (1,4:1) starosti od 50 do 80 godina, a najčešće i sedmoj deceniji života. Zemljoradnja je glavno ili dodatno zanimanje bolesnika sa tumorima.*

Etiologija tumora gornjeg urotelijuma je još uvek nepoznata. Naša istraživanja faktora rizika za nastanak tumora urotelijuma su pokazala da su od značaja pušenje, pozitivna porodična anamneza o endemskoj nefropatiju u drugom ili trećem kolenu, zemljoradnja kao zanimanje, infekcije mokraćnih puteva i neke vrste hrane.

Prema našim rezultatima 82% tumora gornjeg urotelijuma je lokalizovano u pijelonu i ureterima, istovremena pojava tumora u pijelonu i ureteru je zabeležena kod 18% bolesnika, a tumori se češće javljaju unilateralno nego bilateralno (82% vs. 18%). Tumori mokraćne bešike registrovani su kod 18% bolesnika.

Iako endemska nefropatija često prethodi pojavi tumora gornjeg urotelijuma, u žarištima endemske nefropatije oko Lazarevca otkriveni su često i bolesnici kod kojih su se tumori pojavili pre klinički manifestne endemske nefropatije. Kod bolesnika sa endemskom nefropatijom lečenih redovnim hemodijalizama u Lazarevcu tumori gornjeg urotelijuma zabeleženi su kod 29,8%.

Ključne reči: *Tumori gornjeg urotelijuma, endemska nefropatija, Kolubara*