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MALIGNANT TUMORS OF THE UPPER UROTHELIUM AND BALKAN ENDEMIC NEPHROPATHY

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Summary. *One of the most significant features of Balkan endemic nephropathy (BEN) is its association with extremely high frequency of malignant urinary tract tumors noticed even in the first disease description. The aim of the paper is to assess the basic epidemiological characteristics of malignant upper urothelium tumors (MUUT) occurring in Jablanica region in the period of 25 years, and to determine the linear trend of malignant upper urothelium tumors' frequency in regions with BEN compared to non-endemic regions. The research period lasted from 1978 to 2002. During the analysis of the frequency of malignant upper urothelium tumors, we used the operative material of Urology Department, Health Care Center, Leskovac, and Urology Clinic, Clinical Center, Niš. Data on the total number of Jablanica region population were obtained on the basis of the Censuses from 1981 and 1991. The average annual incidence rate (AAIR) was calculated per 100,000 people. The highest AAIR of UUT was registered in endemic settlements (17.56) and the lowest one in non-endemic urban settlements (0.94). Statistically, the linear trend of MUUT in the 25-year-period shows a slow decrease ($y = -0.0054\,x + 59$; $r^2 = 0.0031$). The results show that malignant upper urothelium tumors (MUUT) in endemic settlements are 3.47 times more frequent than in hypo-endemic ones; 18.68 times more frequent than in non-endemic urban settlements; and 16.88 times more frequent in non-endemic rural settlements. The research on malignant upper urothelium tumors in Jablanica region showed a statistically significant frequency of tumors not only in certain endemic settlements with BEN (Kutles-1 tumor per 99.63 people and AAIR of 40.15) but also in certain non-endemic settlements (Brejanovac -1 tumor per 98.75 people and AAIR 40.50; Rudare 1 tumor per 139.50 people and AAIR 28.67; Bogojevče 1 tumor per 187.63 people and AARI of 21.32). High frequency of malignant upper urothelium tumors in regions with BEN in Jablanica region possibly point to the common nephropathogenic and carcinogenic etiologic factor and confirms the existence of a positive correlation between BEN and malignant tumors of the pyelon and ureter.*

Key words: *Balkan endemic nephropathy, malignant tumors of the upper urothelium, Jablanica region, type of settlement*

Introduction

One of the significant features of Balkan endemic nephropathy (BEN) is its association with an extremely high frequency of malignant urinary tract tumors noticed even in the first disease description (1).

Petković (2), in his collective series, dealing with a large number of urology centers in the former Yugoslavia, found that in the 20-year period (1953-1973) this frequency was 100 times higher in BEN regions and non-endemic areas. He also found that these tumors appeared more frequently in BEN patients (10%), as well as in the members of their families. Regarding the period analyzed, he found that one upper urothelium tumor (UUT) occurred per 135 people (Cvetovac village) or one case per 788 people (Lozovik village) in villages with BEN. During the same period, in big cities without BEN manifestations, one pyelon or ureter tumor occurred per 16,000 people (Belgrade) or per 21,000 people (Šabac).

Bulgarian authors obtained similar data. However, in Bulgaria, tumors of the pyelon and ureter appeared in 20-40% of the diseased from BEN (3). Radovanović and Krajinović (4) have proved Petković's findings and they also found a significant frequency of pyelon and ureter tumors in endemic settlements, where tumors of the urinary bladder were equally present in both regions. At the same time, only Petrinska *et al*. (5), by analyzing the material from the autopsy, found a higher frequency of urinary bladder tumors in BEN regions. Stefanović and Polenaković (6,7) confirmed a higher frequency of tumors of the pyelon, ureter and urinary bladder in patients with BEN, as well as in those living in endemic settlements.

Stojanović *et al.* (8) were the first to point to a high frequency of pyelon and ureter tumors in non-endemic villages of Jablanica region. These results require additional study in the aforementioned villages, given that the incidence of the chemodialyzed patients was high in those villages (9,10).

Tumors of the upper urothelium and urinary bladder can be mutually associated either simultaneously or successively. The association of tumors of the upper urothelium with those of the urinary bladder is present in more than one third of patients with upper urothelium tumors (11). Williams and Mitchell (12,13) found that pyelon tumor was associated with tumors of the urinary bladder in 46% and ureter tumors in 32% of the cases. From the studies of Mazeman (14) and Bukurov (15), we can see that in two thirds of the cases, tumors of the upper urothelium are solitary and in one third of the cases, they are multiple.

Multiplicity and bilaterality of tumors of the pyelon and ureter in the regions with endemic nephropathy is significant. Simultaneous occurrence of pyelon and ureter tumor ranges between 2-5%. The biggest published series of bilateral tumors is 9%. Multiplicity of tumors goes to 30% (15).

Aim

The aim of the paper is to assess the basic epidemiological characteristics of malignant upper urothelium tumors (MUUT), such as the incidence, sex, age, geographic distribution of the diseased from Jablanica region in the 25-year period, as well as determining the linear trend of pyelon and ureter tumors' frequency in regions with BEN compared to non-endemic regions, bearing in mind those recent studies that have shown a significant decrease in the incidence of the diseased from BEN.

Patients and Methods

The research period lasted from 1978 to 2002. In the analysis of the frequency of malignant upper urothelium tumors, we used the operative material of Urology Department, Health Care Center, Leskovac, and Urology Clinic, Clinical Center, Niš. The patients were divided according to the place of residence - certain areas of Jablanica region. The data from the Institutes of Nephrology and Hemodialysis were used for the classification of the area. (A – endemic settlements for Balkan endemic nephropathy; B – hypo-endemic; C – non-endemic urban type; and D – non-endemic rural type.)

Data on the total number of Jablanica region population were obtained on the basis of the Censuses from 1981 and 1991. The incidence rate was measured per 100,000 people. Some of the investigations in the study were conducted in the way that C and D groups were presented as a unique group of non-endemic settlements.

Results

In the period from 1978 to 2002 in Jablanica region, we registered 83 malignant upper urothelium tumors, out of which 23 were ureter tumors (TU), 33 were pyelon tumors (TP) and 21 were associated tumor. Of 83 tumors registered, 40 (48.18%) occurred in males and 43 (51.81%) in females.

In Jablanica region, there are endemic, hypo-endemic and non-endemic areas with BEN. The statistics related to the diseased from malignant UUT is shown in the Table 1, depending on their residential area.

Table 1. Distribution and AAIR of malignant tumors of upper urothelium in Jablanica region in the period 1978-2002 in relation to the type of settlement

Settlement group	UUT	
	Number of patients	AARI
A	13 (15.66%)	17.56
B	8 (9.64%)	5.06
C	18 (21.69%)	0.94
D	44 (53.01%)	1.04
Jablanica region	83 (100.00%)	1.30

The highest AAIR of UUT is in endemic settlements (17.56) and the lowest one is in non-endemic urban settlements (0.94).

Table 2. Distribution of UUT in Jablanica region in the period 1978-2002 in relation to separate and associated tumors regarding the ype of settlement

Settlement group	MUUT	TuU	TuP	associated Tu
A	13	3	5	5
B	8	1	4	3
C	18	8	6	4
D	44	17	18	9
Jablanica region	83	29(34.94%)	33(39.76%)	21(25.30%)

Of the total number of malignant UUT, associated tumors appear in 25.30% of the cases.

Table 3. General characteristics of malignant upper urothelium tumors in Jablanica region in the period 1978-2002

Type of settlement's characterstics	A	B	C	D	Jablanica region
No of tumors	13	8	18	44	83
Age	65.318±8.758	64.132±7.867	61.731±9.283	62.647±8.715	63.01±8.80
Relation - sex (f/m)	7/6	3/5	9/9	21/23	40/43
No of people	2 961	6 325	76 352	169 369	255 011
Tu U(f/m)	2/1	0/1	5/3	9/8	29 (16/13)
Tu P(f/m)	2/3	2/2	2/4	10/8 **	33 (16/17)
Tu U+Tu P(f/m)	2/2	1/1	1/1	0/5 *	13 (4/9)
TuU+TuVU (f/m)	0/0	0/1	0/1	0/2	4 (0/4)
TuP+TuVU (f/m)	1/0	0/0	0/0	1/0	2 (2/0)
TuP+TuU+TuVU (f/m)	0/0	0/0	1/0	1/0	2 (2/0)
PGSI	17.56	5.06	0.94	1.04	1.30
Tu GU/no of people	227.77	790.62	4241.78	3849.30	3 072.42

Table 4. Distribution of malignant tumors of upper urothelium in Jablanica region in the period 1978-2002 according to sex and age

Age group	30-39		40-49		50-59		60-69		70-79		80+		Total	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
A	–	–	–	–	2	1	2	2	3	3	–	–	7	6
B	–	1	–	–	1	–	–	3	2	1	–	–	3	5
C and D	1	–	2	–	8	4	11	14	8	13	–	1	30	32
Jablanica region	1	1	2	–	11	5	13	19	13	17	–	1	40	43

Table 5. Distribution of UUT in characterstic places in Jablanica region in the period 1978-2002

Settlement group	Settlement	No of people	UUT	Tumor per person	AAIR
Endemic	Brestovac	2 164	5	432.80	9.24
	Kutleš	797	8	99.63	40.15
Hypo-endemic	Sarlinac	945	2	472.50	8.46
	Lapotince	690	1	690.00	5.79
Non-endemic	Brejanovac	395	4	98.75	40.50
	Rudare	558	4	139.50	28.67
	Bogojevac	1 501	8	187.63	21.32
	Leskovac	61 963	14	4 425.90	0.90
	Vlasotince	14 389	4	3 597.25	1.11
Jablanica region		255 011	83	3 072.42	1.30

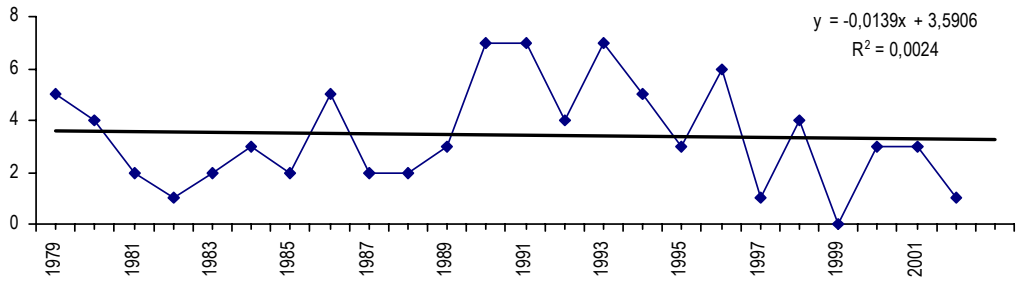
Table 3 shows basic upper urothelium tumors' characteristics. One UUT in Jablanica region occurs per 3,072 people for the observed period of 25 years. Usually, it appears in endemic settlements (1 tumor per 227 people).

Of 83 tumors of the upper urothelium, 40 occurred in males and 43 in females.

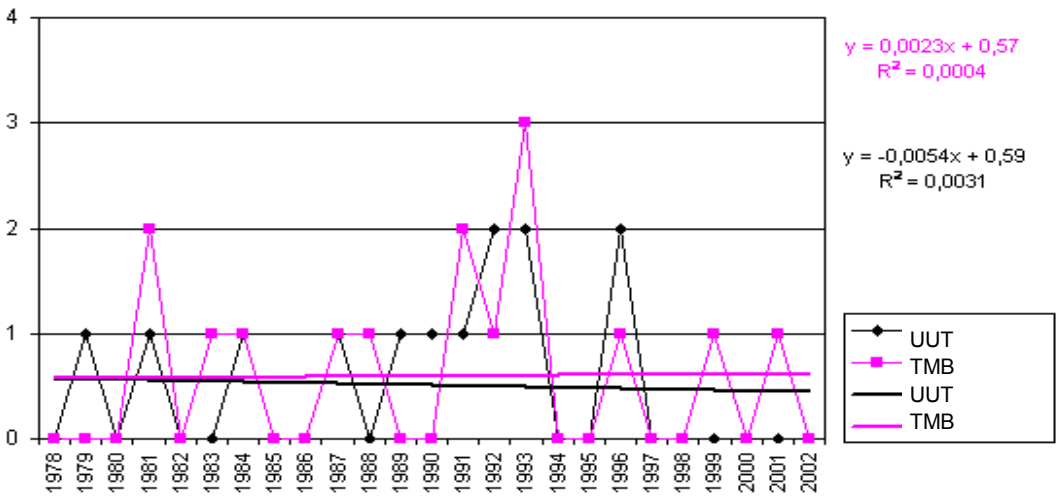
Of all endemic settlements, Kutleš has the highest rate (40.15), while Brejanovac exhibits the highest rate among non-endemic areas (40.50).

Discussion

A higher incidence of tumors of the pyelon and ureter in settlements with endemic nephropathy, which has so far been described by numerous authors of the former Yugoslavia and Bulgaria, has also been confirmed in our study.



Graph 1. Linear trend of UUT of Jablanica region in the period from 1978 to 2002.



Graph 2.Linear trend UUT of Jablanica region in the period from 1978 to 2002 in endemic settlements

In our research, we showed that the frequency of pyelon and ureter tumors in Jablanica region was the highest in settlements with endemic nephropathy. The results show that, for the observed 25-year period, MUUT in endemic settlements was 3.47 times more frequent than in hypo-endemic ones; 18.68 more frequent than in non-endemic urban settlements; and 16.88 times more frequent in non-endemic rural settlements. MUUT in hypo-endemic settlements was 4.86 times more frequent than in non-endemic rural settlements and 5.38 times than in non-endemic urban settlements.

Čukuranović *et al.* (16) point out that MUUT in endemic settlements of the confluence area of the Južna Morava River is 57 times more frequent than in the surrounding rural non-endemic settlements, and 62 times more frequent compared to the surrounding urban non-endemic settlements in the period from 1969 to 1988.

Marković, following Čukuranović's research (17, 18), found that MUUT in endemic settlements of the Južna Morava River confluence in the period from 1989 to1998 is 11.2 times more frequent than in the surrounding non-endemic settlements. At the same time, he found that the incidence of these tumors in hypo-endemic settlements was 6 times higher than in non-endemic settlements.

Nikolić (19), in his 35-year-long research (1963-1998) on the operative findings at the territory with 1,162,225 people, found 1,033 cases with upper urothelium tumors, out of which 51 were registered in rural settlements and 182 in 16 urban settlements. AAIR was 11.74 in endemic settlements, 5.08 in likely endemic settlements, and 3.45 in non-endemic rural settlements. Compared to our results, he found a minor association between UUT in endemic and likely endemic settlements (2.3:1) and non-endemic (3.40:1). In the analyzed period, there were 11 patients with UUT in the hyper-endemic village Cvetovac with 276 people. AAIR was 113.9, which was more significant compared to Kutleš, the hyper-endemic village of Jablanica region, with 797 people and 8 UUT and AAIR of 40.15 tumors per 25 years.

Investigating urethra tumors, Blum *et al.* (20) found that men are susceptible to the disease three times more frequently, and Grabstald (21) found that tumors of the pyelon were two times more frequent in men. Petković *et al.* (22) did not find any difference in patients with upper urothelium tumors with respect to sex and regional distribution of endemic nephropathy.

In our study, sex distribution of patients with upper urothelium tumors in the settlements of Jablanica region, showed a somewhat higher frequency in females (1.075:1). In endemic settlements, the frequency of these tumors is somewhat higher in males (1.17:1), while in hypo-endemic and non-endemic settlements the frequency was higher in females (1.67:1 and 1.07:1, respectively). The research conducted by Nikolić (2002) included 1,033 UUT, which were more frequent in females (1.41:1), while this relation was less pronounced in endemic settlements (1.13:1).

According to Batata (23) and Petković, upper urothelium tumors most frequently appear in the 6th and 7th life decade (2). Bukurov *et al.* (15) found that these tumors usually appear in the 6th life decade in BEN regions, and in the 7th life decade in hypo-endemic and non-endemic settlements. Recent results have shown that tumor frequency in endemic nephropathy regions is the highest between 60 and 70 years of age (24). In our study, we find almost the same age participation in the 7th (38.55%) and 8th (36.14%) life decade. In relation to the type of settlement, the tumors usually appear in the 8th life decade (46.15%) in endemic settlements, and in the 7th life decade (40.32%) in non-endemic settlements.

As for the ratio of pyelon to ureter tumors, Petković (22), in his collective series of 617 cases, concluded that the frequency of pyelon tumors was almost twice higher when compared to the frequency of ureter tumors. At the Urology Clinic in Niš, the frequency of pyelon tumors was 2.6 times higher than the frequency of ureter tumors in regions with BEN. Outside these regions, pyelon tumor was 3.4 times more frequent. Regarding separate tumors, pyelon tumors were found to be more frequent than ureter tumor (1.14:1). In associated tumors, UUT with urinary bladder tumors was 9.64%, which is significantly less when compared to the results of other authors (11,12,13). In total, bilaterality was 2.41% (3.83). The association between all tumors of ureter and urinary bladder was 12.5%, while in all pyelon and urinary bladder tumors it was 8%. Contrary to the results of many authors (14,15), our material points to 25.30% of the associated tumors of the upper urothelium.

Statistically, the linear trend of MUUT in endemic settlements in Jablanica region during the 25-year period shows a slow decrease ($y = -0.0054\ x + 59$; $r^2 = 0.0031$), which corresponds to the results of 10-year long research by Marković (17).

The results of 25-year long research on MUUT in Jablanica region show that in endemic settlements (groups A and B), tumors occur at 25.30% rate, while in non-endemic settlements (groups C and D) they occur at 74.70% rate. These findings significantly differ in Lazarevac region, where the frequency of MUUT in endemic settlements was 89.04% (24,25). A relatively low percentage of MTGU in Jablanica region in endemic settlements (groups A and B) compared to Lazarevac area is explained by a high incidence in certain rural non-endemic settlements (9).

Investigations of upper urothelium tumors in Jablanica region showed a statistically significant frequency of tumors only in certain endemic settlements with BEN (Kutleš: 1 tumor per 99.63 people with AAIR of 40.15). However, this frequency in certain non-endemic settlements was very high (Brejanovac: 1 tumor per 98.75 people with AAIR of 40.50; Rudare: 1 tumor per 139.50 people and AAIR of 28.67; Bogojevče: 1 tumor per 187.63 people and AAIR of 21.32). These results require additional research in the aforementioned non-endemic rural settlements, given the fact that the incidence of chemodialyzed patients is high.

Conclusion

The high frequency of upper urothelium malignant tumors in the regions with BEN in Jablanica region possibly point to the common nephropathogenic and carcinogenic etiologic factor and confirms the existence of a positive correlation between BEN and malignant tumors of the pyelon and ureter. It is necessary that additional investigations be carried out in certain non-endemic settlements in which the frequency of UUT and chemodialyzed patients is still high.

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MALIGNI TUMORI GORNJEG UROTELIJUMA I BALKANSKA ENDEMSKA NEFROPATIJA

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Kratak sadržaj. *Jedna od značajnih osobenosti Balkanske endemske nefropatije (BEN) je činjenica, da je ova bolest udružena sa izrazito visokom učestalošću malignih tumora gornjeg urotelijuma (TuGU) koja je zapažena još u prvom opisu oboljenja. Cilj rada je sagledavanje osnovnih epidemioloških karakteristika tumora gornjeg urotelijuma (Tu*

GU) Jablaničkog okruga, u periodu od 25 godina i kakav je linearni trend učestalosti malignih TuGU u regionima sa BEN u odnosu na neendemske regione. Posmatrani period istraživanja je od 1978. god. do 2002. god. Pri proučavanju učestalosti malignih TuGU korišćen je operativni materijal urološkog odeljenja Zdravstvenog centra Leskovac i urološke klinike Kliničkog centra Niš. Podaci o ukupnom broju stanovnika Jablaničckog okruga dobijeni su na osnovu zvaničnih podataka obavljenog popisa stanovništva u 1981. i 1991. god. Prosečna godišnja stopa incidencije (PGSI) je računata na 100 000 stanovnika. Najveća PGSI TuGU je u endemskim naseljima (17,56) a najmanja u neendemskim gradskim naseljima (0,94). Od ukupnog broja malignih TuGU udruženi tumori se javljaju u 25,30% slučajeva. Od endemskih naselja najveću stopu ima Kutleš (40,15) a od neendemskih Brejanovac (40,50). Linearni trend malignih TuGU za 25-godišnji period je u statistički slabom padu ($y = -0,0054x + 0,59$; $r^2 = 0,0031$). Podaci pokazuju u posmatranom 25-godišnjem periodu, da su maligni TuGU u endemskim naseljima 3,47 češći nego u hipoendemskim; 18,68 češci nego u neendemskim gradskim i 16,88 u neendemskim seoskim naseljima. Istraživanje malignih TuGU Jablaničkog okruga je pokazalo značajnu statističku učestalost tumora samo u nekim endemskim naseljima za BEN (Kutleš - 1 tumor na 99,63 i PGSI 40,15), ali je i učestalost u pojedinim neendemskim naseljima bila vrlo visoka (Brejanovac-1 tumor na 98,75 stanovnika i PGSI 40,50; Rudare- 1 tumor na 139,50 a PGSI 28,67; Bogojevce-1 tumor na 187,63 a PGSI 21,32). Visoka učestalost malignih tumora gornjeg urotelijuma u regionima sa BEN Jablaničkog okruga, možda ukazuje na zajednički nefropatogeni i kancerogeni etiološki faktor i potvrdjuje postojanje pozitivne korelacije izmedu BEN i malignih tumora pijelona i uretera.

Ključne reči: *Balkanska endemska nefropatija, maligni tumori gornjeg urotelijuma, Jablanički region, tip naselja*