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# Balkan endemic nephropathy and associated urothelial tumors: A surgery based study from 1969 to 1998

**KEYWORDS:** Balkan Nephropathy; Bladder Neoplasms; Endemic Diseases; Neoplasm Staging

## INTRODUCTION

Balkan endemic nephropathy (BEN), interstitial noninflammatory disease of the kidney that occurs in the restricted areas of Balkan countries, was recognized about forty-five years ago, as a disease with the high concomitant appearance of UUT (1-3).

The aim of this study was to analyze the incidence of both UUT and bladder tumors as the most important associated pathology with BEN, their epidemiological and clinical characteristics in nonendemic and endemic areas in the region of south Morava river during the period from 1989 to 1998. A comparison is also made with the results of a similar study of the same region from 1969 to 1988 (2).

## MATERIAL AND METHODS

From 1989 to 1998, a total of 575 urothelial tumors were revealed from the central epidemiological database and from the clinical database from Clinic of Urology and Institute of Nephrology and Hemodialysis, which are the main centers for the treatment of BEN, UUT, and bladder tumors of patients from the south Morava river basin. Out of them, there were 93 UUT (9 from endemic, 5 from hypoendemic and 79 from nonendemic areas) and 482 bladder tumors (11 from endemic, 5 from non endemic and 466 from nonendemic areas).

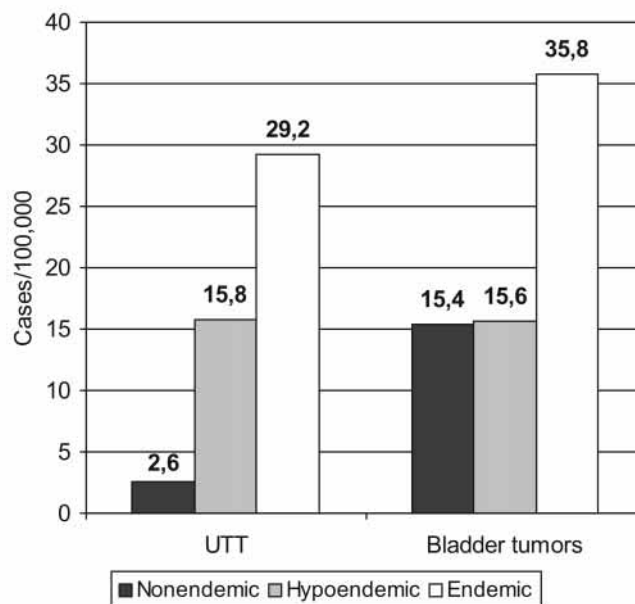
In all patients with UUT or bladder tumors appropriate surgery was performed, (ureteronephrectomy, transurethral resection of the tumor, total cystectomy or partial resection of the bladder) and diagnosis was histologically confirmed. For all patients specific incidence rates were calculated (census from 1991 was used for the statistics) in both endemic and nonendemic areas as well as female to male ratio. After the surgery, tumor grade and stage were performed in both groups of tumors. Yates corrected  $\chi^2$  test (for the small samples) was used for the statistics.

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## RESULTS AND DISCUSSION

Incidence of UUT in endemic, hypoendemic, and nonendemic areas are shown in the Figure 1. Comparison of incidence of UUT and bladder tumors in the last decade (1989-1998) with the previous two decade period (1969-1988) is shown in the Table 1. Male to female ratio in the recent decade compared to the previous two decade period is shown in the Table 2. Staging and grading of neoplasms in endemic and non endemic areas are shown in the Table 3.



**Figure 1.** Incidence of bladder and UUT in endemic, hypoendemic and nonendemic areas

**Table 1.** Frequency of UUT and bladder tumors in endemic, hypoendemic and control areas

Area	UUT		Bladder tumors	
	1969-1988*	1989-1998	1969-1988*	1989-1998
Endemic : control	57.0 : 1	11.2 : 1	11.9 : 1	2.3 : 1
Endemic : hypoendemic	4.3 : 1	1.9 : 1	2.5 : 1	2.2 : 1
Hypoendemic : control	13.3 : 1	6.0 : 1	4.8 : 1	1.0 : 1

\*Data from a previous publication [2]

**Table 2.** Male to female ratio of UUT and bladder tumors in endemic and nonendemic areas

Period	UUT	Bladder tumors
	Male : female	Male : female
Nonendemic areas, 1969-1988*	1.8:1	7.2:1
Nonendemic areas, 1989-1998	1.1:1	5.7:1
Endemic areas, 1969-1988*	1.3:1	3.2:1
Endemic areas, 1989-1998	3.5:1	2.7:1

\*Data from a previous publication [2]

**Table 3.** Tumor grade and stage in endemic and nonendemic areas

Tumor grade/stage	Bladder tumors*		UUT*	
	Endemic	non endemic	Endemic	non endemic
Low grade (grade 1-2)	7	146	7	53
High grade (grade 3-4)	4	31	2	26
Low stage ( $\leq T1$ )	9	121	1	7
High stage ( $\geq T2$ )	2	56	8	46

\*Non significant statistical difference in the number of high grade and stage neoplasms in endemic compared to non endemic areas (Yates corrected Chi2 test).

## DISCUSSION

Our results confirm the increased existence of urothelial tumors associated to BEN. During the recent years all hypothesis about these two entities suggested that they have the common etiological factor(s). The possible etiological factors could be summarized in several groups: intake of heavy metals, inges-

tion of the ochratoxin A, intake of chemicals derived from Pliocene lignites or infectious etiology (7). No one of these hypotheses is consistent, so multifactorial etiology of both diseases seems to be acceptable.

There are several reports about decreasing incidence of BEN (4,5). Since the time of the first description of BEN in 1957, incidence of UUT was confirmed as almost 100 times greater (3). During the next years and decades, the close relationship between BEN and UUT remained, but the occurrence of UUT was constantly decreasing as well as the concomitance (2, 3). Male to female ratio in our previous studies showed different male:female ratio in endemic, hypoendemic areas and general population (2). Data from the last decade confirms that male:female ratio in endemic areas became less specific in the recent time, and looks like the relationship in general population previously described in the literature on urology (1).

When the insight in the whole process is performed, BEN looks as a disappearing entity i.e. epidemiologically self-solved problem that will disappear exactly on the same way as it had grown up (6). UUT in endemic areas have the same trend, their incidence goes toward the incidence in general population, and difference in their malignancy in endemic and non endemic areas is less expressed. Habitual intake of laxatives, analgesics, smoking etc. is clearly proved as responsible for the most frequent occurrence of UUT. Importance of these facts is relatively higher when the influence of BEN is decreased. In our series we had the same incidence of recurrent tumors in the bladder and no cases with the metachronous bilateralism. Taking in account BEN in a decision making for the type of surgery does not look to be reasonable any more, especially when the survival of patients with BEN could be very long (8,9). Tumor grade and stage were not significantly different regardless the area of registration. It is hard to explain sex differences in the occurrence of UUT and bladder tumors in endemic and nonendemic areas. One possible explanation is different urothelial susceptibility in males and females to ochratoxin A or another carcinogen (7).

Finally, it looks that BEN and associated urothelial cancer, after forty years of investigation, are still full of secrets with more questions than answers but fortunately less frequent, and less important health problem. Anyway, with this trend of decreasing incidence, we have to wait at least one or two decades to follow up the problem, before closing it.

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