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UPPER UROTHELIAL TUMORS AND BALKAN NEPHROPATHY- DOSE RESPONSIBLE DISEASES

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Summary. *In the period 1963-1998, 1033 patients were operated from upper urothelial tumors (UUT). They lived in the region of 808 settlements (1.162.225 inhabitants). Tumors were not registered at 524 villages (243, 263 inhabitants). Patients from 16 towns (182 pts./ 452,600 inhabitants) are not included in this analysis. The remaining 268 villages (851 pts. / 466,362 inhabitants) are, according to their UUT incidence rates, classified into 10 groups, numbered from 0 to 9 as shown on the enclosed map.*
The average age of UUT patients is in inverse proportion to the incidence in the villages.
The number of villages (within brackets) and the average annual incidence of UUT per 100, 000 inhabitants in various incidence groups are: (9) 44.16; (22) 19.52; (25) 11.8; (25) 8.36; (26) 6.40); (22) 5.09;(21) 4.40; (10) 3.83; (10) 3,37; (98) 1.10.
The number of patients (within brackets) and the average age in the same groups are (124) 60.64 yrs.; (159) 62.36 yrs.; (127) 63.20 yrs.; (103) 64.17 yrs.; (62) 64.97 yrs.; (62) 66.03 yrs; (47) 64.13 yrs; (13) 59.3 yrs; (12) 65.33 yrs; (142) 62.39 yrs. The difference of average age among different incidence groups tested by "one way" ANOVA are significant ($F = 2.408$; $p = 0.011$).
The correlation of incidence with the average age of patients is suggestive of a dose responsible disease.

Key words: *Upper urothelial tumors, incidence - age depandance, Balkan endemic nephropathy*

Introduction

The relationship between Balkan endemic nephropathy (BEN) and UUT has not been completely understood.

The analogies among BEN and the analgesic, mycotoxic and herb nephropathies are promissing and suggestive, because in those three diseases with the known causative agent the renal parenchyma damage preceeds the appearance of UUT.

It was noted long ago (1) that the patients suffering from BEN are about 10 years younger than those suffering from UUT. A long-lasting clinical following up of BEN patients from one village (2) showed that, in correspondence with the passage of time, an increasing number (almost one third) of them also developed UUT.

Renal failure is common (60%) in UUT patients from BEN regions, yet it is diagnosed also in 40% UUT patients outside BEN regions (1)

Recent data (3) show lesser incidence rate of renal failure in 45% UUT cases from BEN endemic regions; 35% of those from BEN suspected regions, and 25% of those from BEN nonendemic regions.

The higher incidence of UUT outside known BEN regions and the appearance of renal failure in this kind of patients suggests that the territorial distribution of BEN has not been completely defined.

Therefore, from the point of view of methodology, it does not seem completely justified to observe clinical characteristics (sex, age, renal failure) of the UUT patients using the classification based upon the presence in the same settlement of the second following disease (BEN), especially because the most precise data about territorial localisation of BEN are dated a quarter of the century ago (4).

Patients and Methods

In the lack of a valid cancer-register and with the purpose of collecting all diagnosed upper urothelial tumor cases (UUT), we analysed data of all operated and histologically proved UUT cases within 1963-1998 period, from the archives of 16 health institutions in the research region: The Urology Clinic, The Military Academy Hospital (MAH), Belgrade City Hospital, The Zemun City Hospital, The Urology Department of Belgrade Railway Hospital, the Cancer Register of the Institute of Public Helath as well as from the regional hospitals at the towns of Loznica, Šabac, Valjevo, Smederevo, Smederevska Palanka and Požarevac.

The investigated region includes 31 communities (Table 1) with the total of population 1,162,225 (census 1991). The northern borders of the region are rivers, the Sava and the Danube, the western one is the Drina, the eastern one is the river-valley of the Pek and the southern part of the region covers the territory of 50 – 70 kilometers.

Table 1. Sex and number of UUT patients in communities and population in affected villages.

Community	Patients	M	F	Villages	End.inhabit.	Tot. inhabit.
Aranđelovac	7	4	3	7	12,483	47,618
Barajevo	35	13	22	9	16,437	21,674
Bogatić	18	10	8	9	20,381	34,438
Golubac	13	4	9	10	7,144	12,513
Grocka	13	10	3	4	24,516	69,448
Koceljeva	3	2	1	3	5,284	17,064
Krupanj	5	2	3	4	7,580	21,879
Kučevo	48	20	28	14	14,630	25,649
Lajkovac	58	25	33	12	12,515	17,716
Lazarevac	119	62	57	13	20,260	58,882
Loznica	53	25	28	24	45,342	86,875
Ljig	8	4	4	7	6,286	15,912
M. Crnjiće	40	15	25	14	16,888	19,940
M. Zvornik	2	1	1	2	6,895	14,029
Mionica	4	3	1	3	2,863	17,368
Mladenovac	6	1	5	4	4,904	56,389
Obrenovac	12	4	8	8	20,435	70,234
Osečina	1	1	0	1	2,934	16,745
Petrovac	34	12	22	16	19,375	46,614
Požarevac	74	23	51	16	31,825	84,678
Sm, Palanka	13	6	7	5	16,052	59,822
Smederevo	29	10	19	11	26,256	15,617
Sopot	20	7	13	7	9,623	20,527
Svilajnac	15	7	8	6	11,151	33,136
Šabac	12	3	9	8	23,590	23,633
Ub	19	9	10	13	11,871	34,593
V. Gradište	13	7	6	7	7,583	27,174
Valjevo	9	5	4	9	7,625	98,226
V. Plana	86	31	55	10	32,817	51,150
Vladimirci	3	3	0	3	5,089	23,335
Žabari	79	31	48	9	15,728	19,347
Total 31	851	360	491	268	466,362	1,162,225

The patients are farmers who have been living continually in their places of birth. The city and town population who at least have spent the initial 15 years of their lives in an endemic settlement have been registered as dwellers of their birth-places. This is done because the migrant-studies have shown that moving after having spent the initial 15 years of one's life in an endemic settlement does not prevent subsequent appearance of the tumor (5,6).

Of the 808 settlements within the region, the UUT was registered in 268 villages and 16 towns. The towns are: Arandjelovac, Bogatić, Lazarevac, Loznica, Mladenovac, Obrenovac, Petrovac, Požarevac, Smederevska Palanka, Smederevo, Svilajnac, Šabac, Ub, Veliko Gradište, Valjevo and Velika Plana. In these towns there were 182 UUT cases (69 males, 113 females) in the population of 452,600 which gives 35-year average incidence of 1.15 tu / 100.000 inhabitants. The population of these towns more than doubled its increase during the last two decades of the previous century, mostly by immigrations from the surrounding villages. Because of the lack of data about the birth-place of each of the patients in these towns, and because of the knowledge that BEN does not appear in towns, while the UUT could be attributed to other factors, the further analysis of the patients in these towns was abandoned.

At the remaining 268 villages there were 851 UUT patients (out of 466,362 inhabitants) which makes up the average annual incidence (during 35 yrs. period) of 5.21 UUT / 100,000 inhabitants.

Table 1 shows the names of the analysed communities in the region, the number of the UUT patients and their sex. There are also: the number of the population exposed to risk by living in the endemic villages, and the total number of the population in the analysed region classified by communities according to the latest census, that of 1991.

Purpose

1) To survey the geographic localization of villages with different UUT incidence rates and of those at which the appearance of the tumor was not recorded (1963-1998);

2) to compare obtained geographical localisation of UUT with the known localisation of BEN;

3) to see whether the age of patients is in any way related to the incidence of UUT.

Methods

On the basis of the incidence of UUT, the villages are classified into 10 groups, numbered 0 – 9. The 0 group includes the most endemic villages during the research period, the ones in which there was less than 99 inhabitants per 1 diagnosed tumor.

Group 1 consists of villages with 100-199 inhbs / 1 tumor case; group 2 includes the villages with the incidence of 200-299 inhbs / 1 UUT case, etc.

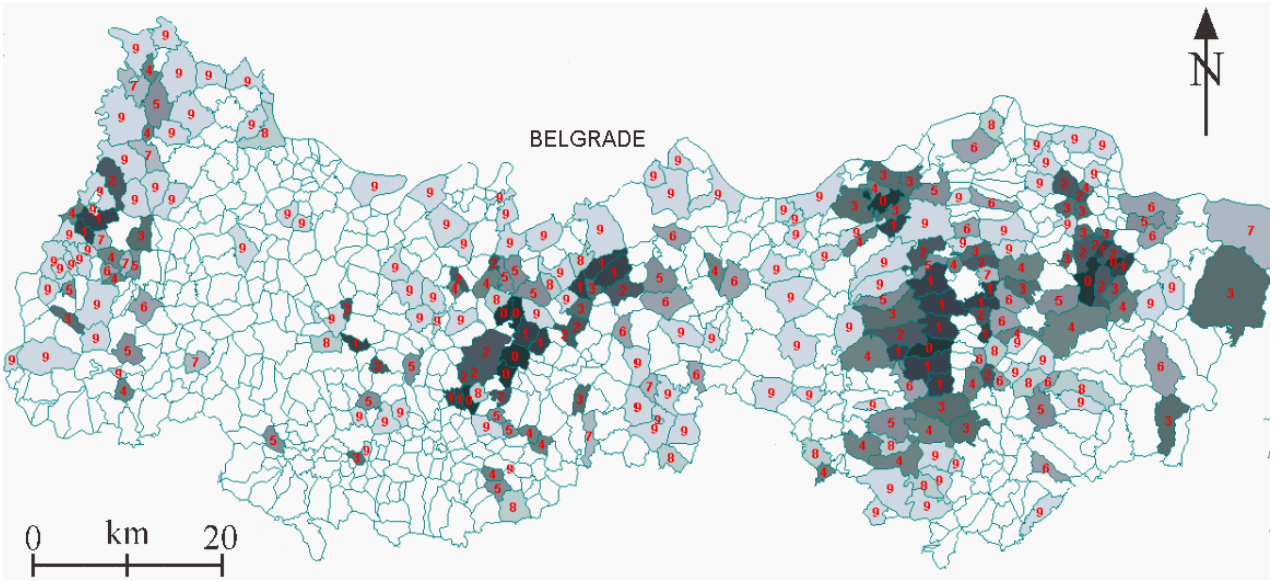
The last group, numbered 9, covers the settlements with more than 900 inhbs / UUT.

The average annual UUT incidence per 100,000 inhabitants (during 35 yrs. period) for each of those 10 endemical village groups is 44.16; 19.52; 11.08; 8.36; 6.40; 5.09; 4.40; 3.83; 3.37 and 1.10 patients respectively.

Dependence on the age in different incidence groups (0-9) was analyzed by "one way " ANOVA (analysis of variance).

We established significant difference in this model ($F = 2.408$; $p = 0.011$).

This significant difference really is generated by the difference in mean ages in first and sixth groups (60.64: 66.3) (Table 2).



Map 1. UUT settlements with their endemic numbers (0 – 9).

Table 2. Mean age in different incidence groups of villages

Descriptives AGE

Incidence group	UUT Patients	Mean Age	Std. Dev.	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
0.	124	60.64	9.73	.87	58.91	62.37	30	81
1.	159	62.36	9.36	.74	60.90	63.83	32	82
2.	127	63.20	9.66	.86	61.51	64.90	33	84
3.	103	64.17	9.50	.94	62.31	66.02	32	81
4.	62	64.97	9.64	1.22	62.52	67.42	35	79
5.	62	66.03	9.20	1.17	63.69	68.37	45	88
6.	47	64.13	9.48	1.38	61.35	66.91	25	82
7.	13	59.31	14.40	3.99	50.61	68.01	32	77
8.	12	65.33	12.96	3.74	57.10	73.57	35	83
9.	142	62.39	10.12	.85	60.71	64.07	33	83
Total	851	63.01	9.84	.34	62.35	63.67	25	88

Discussion

In the researched region there are 53.6% (45/84) certain and 53.2% (139/261) possible BEN focuses, although the analyzed region consists of only 19.4% (808/4164) of all settlements in Serbia (4).

At 5 certain BEN focuses and 75 possible ones there was not any case of UUT diagnosed during the observed period (1963-1998).

Table 3 shows that 40 villages with 301 UUT patients are well-known BEN settlements, while other 64 villages (233 pts.) have been registered (4) as possibly endemic ones.

The incidence of UUT (35 yrs. average) calculated per 100,000 inhabitants is in BEN endemic settlemets 11.74; in the possibly endemic ones 5.08, and in nonendemic ones 3.45 patients.

Table 3. Frequency of UUT patients in endemic, possible endemic and non endemic settlements

Region	Villages	Inhabitants	Patients	M : F	Pts/village	Inhab/UUT	Incidence
Endemic	40	73.224	301	141:160	7,52	243,3	11,74
Possible Endemic	64	130.918	233	77:156	3,64	561,9	5,08
Non Endemic	164	262.220	317	142:175	1,93	827,2	3,45
Total	268	466.362	851	360:491	3,17	548,0	5,21

Territorial distribution of UUT is much larger than the known distribution of BEN, because 164 out of 268 villages with UUT patients have not been registered as BEN endemic or possibly endemic ones.

Villages with low UUT incidence (though a few times higher than expected) have not been recognized as endemic, and in the analyses by other authors (1,3,7) have been classified within nonendemic regions, because they were not included in the list of BEN settlements.

Map 1 shows UUT settlements with their endemic numbers (0–9).

In the analyzed region, the territorial distribution of villages with varying UUT incidence has a concentric, rather than a mosaic pattern.

Table 4. Incidence and mean age of UUT patients in diffrent village incidence groups

End. group	0	1	2	3	4	5	6	7	8	9	Total
Villages	9	22	25	25	26	22	21	10	10	98	268
Patients	124	159	127	103	62	62	47	13	12	142	851
M : F	63:61	60:99	51:76	47:56	15:47	23:39	22:25	8:5	5:7	65:77	360:491
Pts/village	13.78	7.23	5.08	4.12	2.38	2.82	2.24	1.30	1.20	1.45	3.17
Incidence	44.16	19.52	11.08	8.36	6.40	5.09	4.40	3.83	3.37	1.10	5.18

The most endemic of the settlements (endemic numbers 0, 1, 2) are in the central part of the river-valleys; the less endemic ones (end. nos. 3, 4, 5) are situated in their surrounding, and the villages with low tumor incidence (end. nos. 6, 7, 8, 9) are even more remote from the most endemic settlements. The villages with low incidence are also situated at a higher altitude (8,9).

Are the villages with the minimal UUT incidence of any epidemiological importance? The appearance of one or two UUT patients in a village of 700 to 1,500 inhabitants within the 35 year period, though often higher than the incidence expected, is of no importance, because UUT can appear also for nonendemic reasons, as they do in other parts of the world. Yet, for the purpose of this investigation even the villages with the minimal UUT incidence are important because:

1) their number is high, much higher than expected;

2) their distribution among 524 villages without a single UUT case is not haphazard, but rather shows the tendency of grouping (e.g. the villages in the communities of Arandjelovac, Golubac, Petrovac). Moreover, the greatest majority of such villages are situated in the vicinity of the hypoendemic territories, those on the more remote periphery of endemic focuses. The same phenomenon is noticeable in the main river-basins of the analyzed region (those of the Drina, the Kolubara, the Velika Morava, the Mlava and the Pek);

3) female patients in those villages are more numerous than the male ones (table 4). Outside the Balkans, as well as in the Serbian towns free from BEN, the male population is 2 to 3 times more affected by UUT than the female one;

4) renal failure is also noted in these patients in 25% of cases (3), which is 2 times lower than in the BEN endemic territories, yet sufficient to prove that the greatest number of UUT cases at low-incidence villages makes part of its general endemic appearance caused by the same agents.

Therefore, it is possible to conclude that the greatest number of villages with low UUT incidence are also the markers of the bordering lines of the endemic region. They have been situated along the borders of the endemic regions, and are situated at a higher altitude. The average age of patients from those settlements is the highest one (table 3), and the percentage of renal failure following the main disease is the smallest.

Table 4 shows the average age of the UUT patients in 10 different incidence groups. The youngest patients are in 9 villages (0 group) with the highest incidence rate (44.16 pts / 100,000 inhb. / year). The average age of 224 patients was 60.64 years. In the groups with lower UUT incidence patients are older and differences in the average age among different incidence groups are significant, tested by "one way" ANOVA ($F = 2.408$; $p = 0.011$).

If from the first group consisting of nine most endemic villages we separate the first three of them, those with the highest UUT incidence (Cvetovac, Petka and Mali Borak), we shall see that the average age of 51 patients is 59.63 years. In the most endemic of the three villages, as well as in the whole region (that of Cvetovac), 11 UUT cases per 276 inhabitants were recorded which, within the observed period, gives the average annual incidence of 113,9 pts / 100,000 inhb. and the youngest average age 54.37 yrs.

Depending on the incidence rate, the average age of patients (starting with the highest and ending with the lowest incidence rate per village) varies within the scope of almost 10 years.

This confirms the earlier statements (1) that in BEN regions UUT most commonly affects the patients between 51 and 60 years of age, while in the regions suspected of BEN, and in those where it does not exist, it tends to appear later, affecting people who are between 61 and 70 years of age.

Our opinion is that regions suspected of BEN and those without BEN are in fact regions with very low and until then unrecognised BEN incidence.

The relationship found between the incidence of UUT and the average age of patients suggests that UUT and BEN are dose responsible diseases.

The intake of a very high dose of the agent causes the early appearance of renal failure (BEN) during the third and the fourth decade of patients' lives. The progress of renal failure is a rapid one, and the patients of this kind, before the chemodialysis was discovered, normally survived only a few years after their disease had been diagnosed. Because of the rapid progress of the disease, most of them died before the actual appearance of UUT, or UUT were found at autopsises (12).

The intake of a high dose results in the appearance of UUT (and BEN) in the younger patients and it also results in an increase of incidence in the given region. It is possible that map 1, showing the incidence distribution of UUT simultaneously shows the distribution of doses of an unknown causative agent in the relevant environment.

The intake of a low dose of the unknown causative agent results in a lesser, or less recognizable, damage of renal parenchyma and in the appearance of UUT in the elder patients' group. At the same time, the low incidence of UUT in such settlements is possibly caused by the fact that a small number of people can consume from the environment the dose which is necessary for the UUT (or BEN) to show up.

The intake of a very low dose seems particularly interesting. The renal parenchyma damage can be subclinical, so that most of the patients (75%) in the settlements with low UUT incidence (3) show no symptoms of renal failure at the time of the nephrectomy or later in the eighth decade of their lives.

In case the disease is really a dose responsible one, this implies that the causative agent must reach a certain cumulative threshold for its nephropatogenous and/or cancerogenous effect to show up. This allows for the assumption that the spread of the agent is far larger than shown by the map, only its concentration in the environment is not sufficient to be consumed in the necessary

dose during a normal human life-span.

Smaller consumed doses due to the better social and economic conditions rather than to the changes of the environment can be an explanation of the noticed increase in age (5) and decrease in the incidence (13,14,15) of UUT with the passage of time.

All this suggests that the postulate of an ice-berg phenomenon is valid, and that there is still a considerable number of patients with slight renal damages who have remained unknown, as well as the regions they come from. So far as UUT is concerned, we believe that the relevant material is almost complete and that it is UUT that might be the marker in the process of following the epidemic picture of both BEN and UUT diseases.

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