ARTICLE Libri Oncol., Vol. 35 (2007), No 1-3, 7 – 15

WHAT CAN WE LEARN FROM STUDIES ABOUT MULTIPLE PRIMARIES?

IRENA NOVOSEL[1], MARIJANA TURČIĆ[2], BORISLAV SPAJIĆ[3], IVAN PRSKALO[4], ANTE RELJIĆ[3] and BOŽO KRUŠLIN[2]

[1] Department of Pathology, Dr. Ivo Pedišić General Hospital, Sisak, Croatia
[2] Ljudevit Jurak Clinical Department of Pathology , Sestre milosrdnice University Hospital, Zagreb, Croatia
[3] Clinical Department of Urology, Sestre milosrdnice University Hospital, Zagreb, Croatia
[4] Teachers Faculty, University of Zagreb, Zagreb, Croatia

Summary

Simultaneity of primary renal cell carcinoma (PRCC) and second primary malignant tumors (SPMT) of other organs is considered to be very rare.

This study was run in order to determine the incidence of SPMT in patients with PRCC.

During the period 1997-2001, 287 patients underwent surgery for PRCC. They included 196 male and 91 female patients aged 24-91 years.

SPMTs were present in 11(3.8%) out of 287 patients with PRCC and in 14 (4.9%) of tumors, respectively. The most common were SPMT of bladder (1.0%), colon (1.0%), prostate (0.7%) and skin (0.7%). Out of 14 SPMT, 8 were synchronous (57.1%), 5 subsequent (35.1%) and 1 antecedent (7.1%).

Our survey identified a patient with three simultaneous SPMTs involving the urinary bladder, the prostate and the colon.

SPMTs are not so rare in the population. Hence, the clinician should be stimulated to maintain a lifetime follow–up of patients with primary malignant disease.

KEY WORDS: *kidney, primary renal cell carcinoma, second primary malignant tumors, multiple primaries*

ŠTO MOŽEMO NAUČITI IZ ISPITIVANJA VIŠESTRUKIH PRIMARNIH TUMORA?

Sažetak

Istodobna pojavnost primarnog karcinoma bubrežnih stanica (PRCC, od engl. primary renal cell carcinoma) i drugih primarnih zloćudnih tumora (SPMT, od engl. second primary malignant tumor) drugih organa smatra se velikom rijetkošću.

Ovo se ispitivanje provodilo sa svrhom da se utvrdi stopa pojavnosti drugih primarnih zloćudnih tumora u bolesnika s primarnim karcinomom bubrežnih stanica.

Tijekom razdoblja 1997.-2001. zbog primarnog karcinoma bubrežnih stanica operirano je 287 bolesnika. Među operiranim bolesnicima bilo je 196 muškaraca i 91 žena u dobi od 24-91 godine.

Drugi primarni zloćudni tumori bili su prisutni u 11 (3,8%) od 287 bolesnika s primarnim karcinomom bubrežnih stanica te u 14 (4,9%) tumora. Najčešća sijela drugih primarnih zloćudnih tumora bila su mjehur (1,0%), debelo crijevo (1,0%), prostata (0,7%) i koža (0,7%). Od 14 drugih primarnih zloćudnih tumora 8 ih je bilo sinkrono (57,1%), 5 ih se razvilo naknadno (35,1%), a 1 je bio prisutan i prethodno (7,1%).

U našem je ispitivanju otkriven bolesnik s tri druga primarna zloćudna tumora istodobno prisutna u mokraćnom mjehuru, prostati i debelom crijevu.

Drugi primarni zloćudni tumori u populaciji nisu baš rijetkost pa liječnike treba poticati na doživotno praćenje bolesnika s primarnom zloćudnom bolešću.

KLJUČNE RIJEČI: *bubreg, primarni karcinom bubrežnih stanica, drugi primarni zloćudni tumori, višestruki primarni tumori*

INTRODUCTION

At the beginning of a new century it seems to me that we are at the beginning of knowledge, no matter how deep and thorough our search for truth may be. The change of our attitude towards established principles in science, clinical approach and treatment of patients is a sign of hope as well as of limits of our current knowledge. Somehow, I feel that the time has come to break down the ingrained rules in medicine. A global point of view, especially in tumor pathology, is no longer an exception, but a necessity. The latest breakthrough in pathology is developing together with the genetic approach which influences the pathologist's mind. We must not be afraid of new principles that give our microscopic field a depth of which we were aware before, but we could not reach it. Genes and their mutations imply a new and definite change in diagnosis as well as in the therapy of malignancies.

The first serious research of multiple malignancies goes back to Warren and Gates already in 1932 (1). According to their definition of multiple malignancies each tumor must present a definite pattern of malignant disease, each must be distinct, and the possibility of one tumor being a metastasis of another must be excluded.

Correct and concurring data about the incidence of multiple primaries are extremely hard to find, partly because they are generally considered to be a curiosity. However, recent data present a different picture. Namely, according to the American Cancer Society, one out of five Americans will develop cancer. Furthermore, one out of three such patients have a chance to develop a synchronous, antecedent or subsequent tumor in his/her lifetime.

In 1968, it seemed that the Hajdu´s survey would originate an avalanche. Among 3,321 autopsy cases, Hajdu found out that 177 patients or 5.3% had multiple primaries. As many as 29% of the patients with renal carcinoma at autopsy had another primary, making primary renal cell cancer (PRCC) the most common type of malignancy associated with multiple primaries of different organs (2, 3).

Since then, studies dealing with multiple primaries have increasingly been reported for a number of reasons: daily advances of imaging technology, growing awareness of global environmental changes influencing human's health and, last but not the least, the genetic approach to tumor diseases started with the discovery of oncogenes and tumor suppressor genes. All the investigated studies emphasized the need for an extensive clinical preventive diagnostic approach to consistent lifetime follow-up of previously operated patients for malignant disease, especially if a patient with PRCC is involved.

In spite of the foregoing, for almost five decades since the first modern study about multiple primaries (2), and seven decades since the first definition of multiple primaries (1), no major etiological breakthrough has provided an answer why multiple malignancies develop at all. Perhaps, at this very moment we may be observing the dawn of a solution, because telogenomic instability could be the long expected revelation.

But still there is the question of why renal cancer is most frequently associated with another second malignancy. This may be a subject for speculation, but there is no valid explanation.

All the surveys mentioned in the following text are retrospective studies; because of that, no matter how thorough they may be, they suffer as well as ours from limited information and stochastic recognition of second primaries. The given data represent second primary malignant tumor (SPMT) incidence in PRCC patients only partially.

PATIENTS AND METHODS

During the five-year period (1997-2001), 310 patients underwent surgery for a renal neoplasm at the Clinical Department of Urology. According to the Clinical Department of Pathology computer database, 287 of these were patients with PRCC. There were 196 males and 91 female patients rang-

ing in age from 24 to 91 years. The youngest patients were two females under thirty.

This survey dealt with a consistent adult population without any patient with transplanted kidneys or in pediatric age group. In addition, the tumor disease in any of our patients, to our knowledge, cannot be described by any of the common syndromes.

The remaining 23 patients presented pathohistologically confirmed benign tumors, or lymphomas and tumors of mesenchymal origin. We focused on 287 patients with PRCC. The computer database was thoroughly studied for each PRCC patient in order to reveal the SPMT.

PRCC data as well as SPMT data were analyzed according to gender, age and simultaneity of appearance. The parameter for placing malignancy into the group of synchronous tumors was its occurrence within three months before and three months after the diagnosis of PRCC. In that way, SPMTs were additionally divided into synchronous, subsequent or antecedent tumors.

Our research data were statistically evaluated by the Microsoft Computer Program: Statistica 6.0 . The *p*-level was computed based on the t-value for the respective comparison:

$$|t|=\square[(N_1*N_2)/(N_1+N_2)]*|p_1-p_2|/\square(p*q)$$

where

$$p=(p_1*N_1+p_2*N_2)/(N_1+N_2)$$

$$q=1-p.$$

The degrees of freedom are computed as

$$N_1 + N_2 -2$$

RESULTS

We shall now pick out the salient data brought to light by this survey.

Primary renal cell carcinomas (PRCC)

Out of 287 PRCC patients, there were 196 males and 91 female patients ranging in age from 24-91 years.

Most PRCCs occurred between 60 and 69 years of age, in total population (p=0.0217), as well as in females and males. Therefore, this life period is the most interesting for PRCC detection in patients (Table 1 and Table 2a).

In addition, as many as 64.4% of PRCCs found in the total population occurred between 50 and 69 years of age. Similar incidence was present in the male and female populations (62.2% and 69.2%, respectively) of the observed age groups but with a significant difference. While the incidence of PRCC was almost the same in males in the sixth and seventh decade (p=0.8313), in the female population aged 60-70 there were twice as many PRCCs as in the 50-60 group (p=0.005) (Table 2abc).

Comparing the above most frequent age groups and the gender cohorts, the PRCC incidence in the fifty-year-olds showed no significant difference. On the other hand, between 60 and 69 years of age there were 31.63% of men with PRCC, while there were 47.25% of women (p=0.0148) (Table 1).

Table 1.

PRCC INCIDENCE ACCORDING TO AGE GROUPS.

Age groups	Total	%	Males	%	Females	%	*p*
0-9	0	0	0	0	0	0	1.0000
10-19	0	0	0	0	0	0	1.0000
20-29	2	0.69	0	0	2	2.20	0.4898
30-39	10	3.48	7	3.57	3	3.30	0.6759
40-49	**37**	**12.89**	**30**	**15.31**	**7**	**7.69**	**0.0995**
50-59	**80**	**27.87**	**60**	**30.61**	**20**	**21.98**	**0.1158**
60-69	**105**	**36.59**	**62**	**31.63**	**43**	**47.25**	**0.0148***
70-79	47	16.38	33	16.84	14	15.38	0.6703
80-89	5	1.4	3	1.53	2	2.20	1.0000
90-99	1	0.35	1	0.51	0	0	1.0000
99+	0	0	0	0	0	0	1.0000
Results	**287**	**99.99**	**196**	**68.3%**	**91**	**31.7%**	

Table 2a.

TOTAL POPULATION P-VALUE OF PRCC INCIDENCE ACCORDING TO AGE GROUPS.

p	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
20-29								
30-39	0.0876							
40-49	0.0000	0.0000						
50-59	0.0000	0.0000	0.0000					
60-69	0.0000	0.0000	0.0000	0.0217				
70-79	0.0000	0.0000	0.3078	0.0006	0.0000			
80-89	0.3248	0.4432	0.0000	0.0000	0.0000	0.0000		
90-99	1.0000	0.0876	0.0000	0.0000	0.0000	0.0000	0.3248	

Table 2b.

MALE POPULATION P-VALUE OF PRCC INCIDENCE ACCORDING TO AGE GROUPS.

p	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
20-29								
30-39	0.0579							
40-49	0.0000	0.0002						
50-59	0.0000	0.0000	0.0002					
60-69	0.0000	0.0000	0.0001	0.8313				
70-79	0.0000	0.0000	0.5895	0.0013	0.0006			
80-89	0.4159	0.2465	0.0000	0.0000	0.0000	0.0000		
90-99	1.0000	0.0579	0.0000	0.0000	0.0000	0.0000	0.4159	

Table 2c.

FEMALE POPULATION P-VALUE OF PRCC INCIDENCE ACCORDING TO AGE GROUPS.

p	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
20-29								
30-39	0.6662							
40-49	0.0649	0.1408						
50-59	0.0001	0.0001	0.0089					
60-69	0.0000	0.0000	0.0000	0.0005				
70-79	0.0019	0.0052	0.1406	0.2256	0.0000			
80-89	1.0000	0.6662	0.0649	0.0001	0.0000	0.0019		
90-99	0.5796	0.3365	0.0239	0.0000	0.0000	0.0006	0.5796	

This result implies that male patients in their sixties and seventies run the same risk of developing PRCC, while there is a greater probability for females developing PRCC in their sixties.

The mean age for the total population was 59.9±6.9 years, with a two–year difference between the male and female groups (59.5±11.2 and 61.3±10.3, respectively) (Table 3). At first glance, one may presume that PRCC in males and females occurred in almost the same age groups and with almost the same incidence. Therefore, the dispersion of PRCC must not be overlooked (Table 1). *It provides better information to the epidemiologist as well as to the pathologist and clinician.*

Table 3.

MEAN AGE OF PRCC PATIENTS WITH AND WITHOUT SPMT.

Mean age of PRCC patients		Mean age of PRCC patients with SPMT	
		Mean age when PRCC was diagnosed	Mean age when SPMT was diagnosed
Females	61.3±10.3	59.6±6.9	59.6±6.1
Males	59.5±11.2	64.3±13.3	69.7±11.8
Total	59.9±11.1	62.2±11.1	66.1±12.1

Table 4.

ELEVEN PRCC PATIENTS WITH SPMT.

PRCC				SPMT				
Pt.	Gender	Age	Stage	Age	Site	Pathohistology	Appearance	Follow-up
1	f	59	T1N0Mx	60	bladder	urothelial papillary carcinoma	s	
2	f	64	T2N0Mx	65	peritoneum	leiomyosarcoma	s	†1998
3	m	76	T1NxMx	76	prostate	adenocarcinoma	sy	
4	f	50	T1N1Mx	50	uterus	bilateral serous ovarian cystadenocarcinoma	sy	†2000
5	m	52	T2N0Mx	54	colon	adenocarcinoma	s	
6	f	55	T2N0Mx	53	skin	melanoma	a	
7	m	76	T2N0Mx	77	skin	baseocellular carcinoma	s	
				77	skin	baseocellualar carcinoma	s	
8	m	55	T1N0Mx	55	bladder	urothelial papillary carcinoma	sy	
9	m	47	T2N0Mx	47	colon	adenocarcinoma	sy	
10	f	70	T2N0Mx	70	urether	urothelial papillary carcinoma	sy	†2000
11*	m	80	T2NxMx	80	bladder	urothelial carcinoma	sy	
				80	prostate	adenocarcinoma	sy	
				81	colon	adenocarcinoma	sy	†2000

Legend: Pt-Patient, M-Male patient, F-Female patient, , s-subsequent, sy-synchronous, a-antecedent
* Patient with four primary malignancies (Box 1)

Second primary malignant tumors (SPMT)

Out of 287 patients with PRCC, there were 11 patients with 14 SPMT or 3.8% (Table 4).

There were 5 female and 6 male patients who had at least one SPMT with a descending order of appearance: bladder (1.05%), colon (1.05%), skin (1.05%), prostate (0.7%), ureter (0.35%), uterus (0.35%), peritoneum (0.35%) (Table 5). The bladder was the most common urologic site (3 SPMT or 1.05%), followed by the prostate with 2 SPMTs or 1.02% if only the male population is counted. In the total SPMT population, the prostate accounts for 0.7%. Colon and skin were present as the most common sites of nonurologic origin each with 3 SPMTs or 1.05%. In addition, among skin cancers there were one patient with melanoma and one patient with two basal cell cancers. There was also one ureter and peritoneum SPMT. This means that 57.1% of SPMTs was of nonurologic origin.

Table 5.

SPMT INCIDENCE ACCORDING TO LOCALISATION IN ELEVEN PRCC PATIENTS.

SITE	No. (%)
Bladder	3 (1.05%)
Colon	3 (1.05%)
Skin	3 (1.05%)
Prostate	2 (1.02% or 0.7%, respectively)
Urether	1 (0.35%)
Uterus	1 (1.16% or 0.35%, respectively)
Peritoneum	1 (0.35%)
Total	**14**

Among eleven patients, nine had only one SPMT, but there were also a patient with two and a patient with three other malignancies. The former was mentioned before (Patient No.7), but the latter (Patient No.11) is a unique case in recent literature: the patient had three synchronous malignancies: two of urologic origin (prostate and bladder), and one of the colon.

According to gender, there is no significant difference in numbers (5 female and 6 male patients), but males had almost twice as many SPMTs as females (9:5) (Table 6a and 6b). Among female patients, there were 2 synchronous, 2 subsequent and 1 antecedent SPMT, while in the male population there were 6 synchronous and 3 subsequent SPMT tumors (Table 6a). Once again, it is important to emphasize that two male patients had more than two SPMTs or, to be precise, two patients had altogether 2 PRCCs in association with 5 SPMT with as many as 3 SPMTs of nonurologic origin.

Table 6a.

ANTECEDENT, SYNCHRONOUS AND SUBSEQUENT SPMTS IN ELEVEN PRCC PATIENTS.

gender	appearance	No.	SITE						
			bladder	*colon*	*skin*	*prostate*	*urether*	*uterus*	*peritoneum*
female	antecedent	***1***			***1***				
	synchronous	***2***					***1***	***1***	
	subsequent	***2***	***1***						***1***
male	antecedent	***0***							
	synchronous	***6***	***2***	***2***		***2***			
	subsequent	***3***		***1***	***2***				
Total		***14***	***3***	***3***	***3***	***2***	***1***	***1***	***1***

Table 6b.

SPMT INCIDENCE P-VALUE ACCORDING TO GENDER.

male vs female	***p***
antecedent	*0.3229*
synchronous	*0.1011*
subsequent	*0.6300*
Total	***0.1505***

DISCUSSION

The results of this study as well as those found in literature suggest the great importance of continuous and thorough follow-up of patients previously operated for PRCC because of the possible simultaneous or subsequent existence of another primary cancer originating inside and, what is more important, outside the urinary system.

If we look at SPMTs *per se* even 57.1% were of nonurologic origin. SPMTs of the bladder, colon and skin are the most frequent. The incidence of each was 21.4%. Even among the most frequent SPMTs, malignancies treated outside the urologic system prevailed with 6:3.

In terms of timing, the mean age of PRCC-SPMTs patients at the time of undergoing treatment for PRCC was 62.2±11.1 years, 59.6±6.9 females and 64.3± 13.3 males (Table 3). This is interesting because they are a subgroup of PRCC patients who develop renal cancer at a later stage (mean age 62.2±11.1) than the rest of PRCC population without SPMT (mean age 59.9±11.1). There is also a difference regarding gender: while the female population seems to develop PRCC at a *younger* mean age than the total population (59.6±6.9 vs. 61.3±10.3), males undergoing treatment for SPMT develop PRCC later in their lives than the rest of the PRCC population (64.3±13.3 vs. 59.5±11.2) (Table 3).

In the total population, the mean age for SPMT was 66.1±12.1 years, which is about four years after the PRCC occurrence (62.2±11.1). According to gender, however, the mean age of SPMT occurrence for females was 59.6±6.1 and for males it was significantly higher (69.7±11.8). This clearly shows that the mean age of PRCC patients who will develop or had already developed SPMT was 5 years higher in the male population. Unexpectedly, females showed the same age at the occurrence of PRCC and SPMT (Table 3). Perhaps this is related to better self control and the newly-introduced screening of females for cervical and breast cancer.

Of course, the clinician cannot know if the patient in front of him is a potential SPMT case. It is precisely this slight disbalance of mean ages that may be of some help. For instance, a PRCC female two years younger and a PRCC male five years older, compared to the mean age of the total PRCC population, may give cause for suspicion of SPMT.

In terms of tumor site, there are no significant differences among SPMTs, but if we consider timing, then there is a significant difference in incidence between synchronous and antecedent SPMTs (Table 6b). The patient sample is too small for a precise and categorical claim about the importance of statistically (in)significant data between the subgroups, but it could provide some warning to the clinician.

No less important is a synchronous bladder SPMT in males considering that there was no such tumor in the female group. Other data that cannot be disregarded confirm that 100% of colon SPMTs occur in male population; furthermore, one-third of them are diagnosed as subsequent tumors (Table 6a). The next question is whether a subsequent

colon SPMT existed at the moment of PRCC diagnosis. The mean ages presented in Table 3 suggest their probable, but not discovered, simultaneous existence. The case report about Patient No. 11 strongly confirms our theory.

SPMTs of the bladder and prostate were the most frequent urologic tumors, but to the author's opinion, the colon remains the most interesting site for several reasons.

Namely, as we can see in Table 5 and Table 6a, most SPMTs were of urologic origin. This could explain the urologist's concern and diagnostic approach to these organs. But it does not explain two thirds of synchronous tumors found in the colon. *This implies that the urologist could be the first clinician to raise suspicion and even detect colon SPMT with only a basic diagnostic approach.* Furthermore, it would probably help discover colon cancer at an earlier stage.

The idea of tumor division into synchronous, simultaneous and subsequent groups must be taken with a reasonable dose of caution by every vigilant clinician. The period of three months before and after PRCC diagnosis is arbitrary in order to describe clinical knowledge of tumor simultaneity, although it is meaningless for the pathologist knowing carcinogenesis and the cell immortalization.

We are aware of the inherent limitations of any retrospective studies. They deal with data that could not be expanded with additional clinical diagnostic treatments nor focused on discovering another malignancy. Therefore, the best we can do is our humble pointing that the clinician should take into consideration latent SPMT existence at the moment of PRCC diagnosis.

This is also experience of all surveys which mostly report on elderly males with clinically asymptomatic PRCC. SPMTs were discovered inadvertently on CT scans done to determine the extent of the first discovered renal carcinoma.

Recent studies make us conclude that the incidence of simultaneously present primary tumors is not as rare as it can be expected according to traditional literature, especially if PRCC patient is involved. Namely, Rabbani et al. (4, 5) found at least one SPMT in 27.4% patients with PRCC. Furthermore, their survey confirmed tumors being synchronous with renal cell carcinoma in 39.2%, but antecedent in even 44.5% and subsequent in 16.2% of patients. Although our study revealed 57.1% of synchronous, 35.1 of subsequent and only 7.1% of antecedent SPMTs, the absolute incidence is far from that of Rabbani (4). Namely, with 3.8% of SPMTs, the result of our survey is more similar to the studies of Onishi (6), Wegner (7) or Myldo (8, 9). It is almost equally precise or it obviously suffers from almost the same deficiencies as those of our colleagues. Other authors investigated SPMTs associated with primary tumors of the urological system with even higher results (10-13).

Highlighting the *simultaneity of colorectal and renal carcinoma* deals with great difference in incidence reported in literature. Our research showed 1.05% of colon SPMT. Recent studies of O'Boyle (14) and Halak (15) confirmed an incidence of 0.5% and 4.85 %. A significantly increased risk of rectal cancer in PRCC patients was observed over a long-term period (13, 16). On the other hand, Greenberg (17) and Jacqmin (18) point prostate SPMT and renal SPMT as more important findings. But Hajdu and Hajdu confirmed again that colon and renal primaries occur with a higher-than-expected incidence (0.1%) (3). In their studies, Polk (19), Mider (20) and Lee (21) detected the co-incidence of renal and colorectal carcinoma of 0.046%, 0.33% and 0.9%. Perhaps the most important study is the one by Hajdu and Thomas; they reported 100 cases of PRCC among 15 370 necropsy records, 30% associated with SPMT. Among them, the most common SPMT was colorectal tumor (4%) (4). Mershmeier found a similarly high association of 7.4% (22).

Reports about the significant appearance of non-Hodgkin's lymphoma in patients with PRCC are still controversial, although a significant co-occurrence was detected in previous studies (23). Our research showed no NHL-patient.

It can reasonably be assumed that higher-than-expected occurrence of co-existent urological neoplasms is the consequence of specialist's attention on a particular system. Primary malignancies outside the system can latently exist unless they have been inadvertently unmasked during the preoperative treatment. The authors are aware that this study is too small for changing the protocol, but they challenge the urologist or abdominal surgeon to think in advance about possible SPMT occurrence.

Finally, our case report of an 80-year-old patient, non-smoker, without positive hereditary history of any carcinoma, cannot be excluded from

SPMT analysis. On the contrary, this case shows very explicitly the consequences of a slow growing PRCC. The trigger, whatever it may be, but of genetic origin for sure, can influence the development not only of one but of more growths if there is enough time (26). We can doubt this theory, but the fact is that this patient should probably have lived longer if the clinician had suspected colon cancer at the moment of PRCC diagnosis. A year after urologic surgery, colon cancer was operated and described in pathohistologic analysis as Dukes-C, Astler-Coller-C2.

The intriguing incidence of SPMT in PRCC could be associated with the slow and silent growth of renal cell carcinoma due to the most often polaric tumor localizations. The case report of Gacci et al. involved a patient who refused an operation for PRCC when it had 3.0 cm in diameter. Over a nine-year period, renal cancer grew for 2.4 mm a year before provoking symptoms (27).

Bearing all these facts in mind, we propose a thorough diagnostic approach to the urinary and gastrointestinal systems for patients primarily operated for PRCC. The false-low SPMT incidence in patients with PRCC should not prevent from sustaining additional diagnostic treatments as part of standard procedures, especially colonoscopy. For instance, if colonoscopy had been carried out in our patient No.11, sigmoid carcinoma would have been discovered at an earlier stage and the survival rate of the patient would have been improved.

By way of conclusion, this survey was intended to arouse awareness of the necessity for long-term high-tech follow-up of PRCC patients with colonoscopy being the obligatory procedure. The authors would like to suggest that a better survival rate of PRCC/SPMT patients is a *conditio sine qua non* for an introduction of genetic background of these tumors (30).

Disregard of the possible SPMT existence implies the lack of effectiveness in their management.

REFERENCES

1. Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and a statistical study. Am J Cancer 1933; 16: 1358-414.
2. Hajdu SI, Hajdu EO. Multiple primary malignant tumors. J Am Geriatr Soc 1968; 16: 16-25.
3. Hajdu SI , Thomas AG. Renal cell carcinoma of autopsy. J Urol 1968; 97: 978-82.
4. Rabbani F, Reuter VE, Katz J, et al. Second primary malignancies associated with renal cell carcinoma: influence of histologic type. Urology 2000; 56: 399-403.
5. Rabbani F, Grimaldi G, Russo P. Multiple primary malignancies in renal cell carcinoma. J Urol 1968; 160: 1255-9.
6. Onishi T, Ohishi Y, Suzuki H, et al. Study on the clinical characteristics of double cancers associated with renal cell carcinoma. Jpn J Urol 1998; 89: 808-9.
7. Wegner HE. Multiple primary cancers in urologic patients: audit of 19-year experience in Berlin and review of the literature. Urology 1992; 39: 231-4.
8. Mydlo JH, Agins JA, Donohoe J. A review of urologic cancer patients with multiple primary malignancies. Worl J Urol 2001; 19: 240-3.
9. Mydlo JH, Gerstein M. Patients with urologic cancer and other nonurologic malignancies: analysis of a sample and review of the literature. Urology 2001; 58: 864-9.
10. Sugiyama T, Park YC, Oguchi M. Double cancer in urology. Acta Urol Jap 1984; 30: 1427-30.
11. Nogueras Gimeno MA, Espuela Orgaz R, Abad Menor F. Incidence and characteristics of multiple neoplasms in urologic patients. Acta Urol Esp 2000; 16: 316-9.
12. Mikata N, Kinoshita K. Primary multiple cancers related to urological malignancies. Jpn J Cancer Clin 1983; 29: 183-7.
13. Kantor AF, McLaughlin JK. Second cancer following cancer of the urinary system in Connencticut, 1935-82. Natl Cancer Inst Monogr 1985; 68: 149-59.
14. Boyle KP, Kemeny N. Synchronous colon and renal cancers: six cases of clinical entity. Am J Med 1989; 87: 691-3.
15. Halak M, Hazzan D, Kovacs Z, et al. Synchronous colorectal and renal carcinomas: a noteworthy clinical entity. Report of five cases. Dis Colon Rectum 2000; 43: 1314-5.
16. Begg CB, Zhang ZF, Sun M, et al. Methodology for evaluating the incidence of second primary cancers with application to smoking-related cancers from the Surveillance, Epidemiology and End Results (SEER) program. Am J Epidemiol 1995; 142: 653-65.
17. Greenberg RS, Rustin ED, Clark WS. Risk of genitourinary malignancies after cancer of the prostate. Cancer 1988; 61: 396-401.
18. Jacqmin D, Saussine C, Roca D, et al. Multiple tumors in the same kidney: incidence and therapeutic implications. Eur Urol 1992; 21: 32-4.
19. Polk HC, Spratt JS, Butcher HR. Frequency of multiple primary malignant neoplasms associated with colorectal carcinoma. Am J Surg 1965; 109: 71-5.
20. Mider GB, Schilling JA, Donovan JC, et al. Multiple cancer: a study of other cancers arising in patients with primary malignant neoplasms of the stomach,

uterus, breast, large intestine or hematopoeitic system. Cancer 1952; 6: 1104-9.
21. Lee TK, Barringer M, Myers R, et al. Multiple primary carcinomas of the colon and associated extracolonic primary malignant tumors. Ann Surg 1952; 195: 501-7
22. Mersheimer WL, Ringel A, Eisenberg H. Some characteristics of multiple primary cancers. Ann NY Acad Sci, 1964; 114: 896-921.
23. Anderson CM, Pusztai L, Palmer JL, et al. Coincident renal cell carcinoma and non-Hodgkin´s lymphoma: the M.D. Anderson experience and review of the literature. J Urol 1998; 159: 714-7.
24. Spajić B, Gall-Trošelj K, Novosel I, et al. The p53 loss of heterozigosity in multiple primary carcinomas of the kidney, bladder, prostate and colon. Acta Clin Croat, 2005; 4: 379-83.
25. Gacci M, Natali A, Bartoletti R, Rizzo M. Natural history of renal cell carcinoma. J Urol 2001; 165: 517-8.

Author's address: Irena Novosel, M.D., Department of Pathology, Dr Ivo Pedišić General Hospital, Sisak, Croatia; Phone: 385 44 553 174; Mob: 385 98 733 282; E-mail: irena.novosel@zg.t-com.hr

Note: This study was presented in part at IAP 2002 (Novosel et al. Histopathology, 2002 Vol.41, Suppl)