Original Article

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Second Primary Malignant Tumours in Patients with Renal Cell Carcinoma

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Abstract

Objective: The primary aim of our study is to establish the frequency and clinicopathological features of seconder primary malignant tumours (SPMTs) in cases with renal cell carcinoma (RCC).

Materials and Methods: Pathology reports of 1129 RCC cases were checked retrospectively, and 70 RCC cases with SPMTs were included in the study. One patient had two and the other had three different SPMTs, so the total number of SPMTs was 73. According to occurrence times of SPMTs, the cases were classified as the antecedent, synchronous, subsequent and unknown. The first three groups were compared according to their clinicopathological features.

Results: The incidence of SPMTs with RCC in our study was 6.2% and lower than that reported by many other studies. The most common SPMTs were gastrointestinal, breast, prostate, lung, thyroid carcinomas and haematolymphoid malignancies. Sixty-two per cent of SPMTs were developed as synchronous and subsequent. There was no statistically significant difference among groups regarding age, histological subtype and RCC size. Male patients had a higher percentage in the synchronous group. In all groups, the most common RCC subtype was clear cell carcinoma. The RCC subtype in cases with multiple SPMTs was papillary. The prostatic adenocarcinoma rate was remarkable in males with papillary type RCC.

Conclusion: RCC can coexist with secondary malignancies. Therefore, when a new tumour appears in a patient with RCC in clinical follow-up, it is appropriate to evaluate that tumour histopathologically or cytopathologically regarding SPMT before accepting it as a metastatic spread.

Keywords: Renal cell carcinoma, seconder primary malignant tumour, synchronous neoplasms, metachronous neoplasms

Introduction

The number of multiple primary malignancies has increased because of improvements in early detection and specific treatment of tumours (1,2). For seconder primary malignant tumours (SPMTs), some criteria (Warren and Gates criteria) were accepted. Each tumour must arise from a different location, have distinct histology and metastasis possibility of the other must be excluded (3). They were classified as the antecedent, synchronous or subsequent in the literature. Synchronous tumours are defined as two or more primary cancers diagnosed at the same time or within six months (1,3,4). SPMTs, in cases with renal cell carcinoma (RCC), are frequent, and the reported incidence varies from 4.5% to 27.4% (5,6,7,8).

Rabbani et al. (6) found the most five common SPMTs in cases with RCC were the prostate, breast, colon, bladder carcinomas and non-Hodgkin lymphoma (NHL). In another study, it was reported that the most common other primary tumours were those of the prostate, bladder, lung, breast, colon, rectum, melanoma and NHL (7). Gastrointestinal carcinomas were the most common in Japanese people (1).

The association between histopathological RCC subtype and SPMTs was evaluated. It was reported that papillary type RCC

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(PRCC) was associated with an increased risk of developing SPMT in the prostate and bladder (6).

SPMTs contribute to the prognosis. The presence of antecedent or synchronous SPMTs is the second most significant prognostic factor, following the pathological stage of RCC (1). In addition, it was reported that RCC cases with antecedent or synchronous SPMTs had significantly poorer overall survival than those without (7).

The primary aim of our study is to establish the frequency and types of SPMTs in cases with RCC. In addition, we classified SPMTs according to occurrence times as antecedent, synchronous or subsequent and investigated the differences among these groups regarding available data.

Materials and Methods

We retrospectively checked the pathology reports of 1,129 cases diagnosed as RCC, in pathology archives of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, between January 2000 and June 2018. All were evaluated for the possibility of having SPMTs. Only the tumours, whose diagnosis were confirmed histopathologically and/or cytopathologically, were included as SPMTs in this study.

Clinicopathological parameters including age, gender; diagnostic method, histological subtype and size of RCC; location and histological type of SPMT were recorded for each case. The time of the diagnosis of RCC was considered for patients' ages. In addition, according to occurrence times of SPMTs, all RCC cases with SPMTs were classified as the antecedent, synchronous, subsequent and unknown. Synchronous tumours were defined as those diagnosed concurrently or within six months of the operation as in the literature (1,3,4). The first three groups were compared among each other regarding clinicopathological features.

Statistical Analysis

Descriptive statistics were used to describe the data. Normal distribution was tested by the Shapiro-Wilk test and graphical methods. Categorical data were compared using the chi-square test. Non-parametric groups comprising more than two groups were compared with the Kruskal-Wallis test. The confidence intervals were calculated at the 95% confidence level. Differences at $p<0.05$ were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0.

Results

SPMT was detected in 70 of 1,129 (6.2%) RCC cases; 47 (67%) of these patients were male, and 23 (33%) were female. Two patients had multiple secondary malignancies (one patient had two malignancies, and the other had three malignancies). Therefore, 73 SPMTs were included in the study. The distribution of SPMTs accompanying RCCs by gender is summarised in Figure 1. The time of the diagnosis of RCC was considered for patients' age; the median age was 60.5 (24-82) years.

In 61 of 70 cases, the diagnosis of RCC was made in the partial or radical nephrectomy material. The other nine patients were

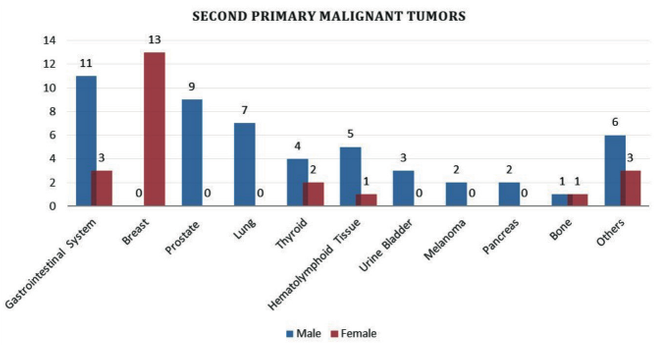

Figure 1. Distribution of SPMTs accompanying renal cell carcinomas by gender

SPMT: Sekonder primary malignant tumour

diagnosed as RCC by fine-needle aspiration (FNA) and/or core biopsy. These patients were not operated at our centre. The diagnosis of the most SPMTs was made by FNA and/or tissue (core or surgical) biopsy (TB) at our centre (FNA: 2, FNA+TB: 2, TB: 62). One SPMT was diagnosed by pleural fluid aspiration. Six cases did not have any biopsy at our centre, and the presence of SPMT was learned from clinical information.

Clear cell RCC (CCRCC) was the most common RCC subtype (in 41 cases: 58.6%), and one had sarcomatoid changes. The second and third common subtypes were PRCC (in 13 cases: 18.6%) and chromophobe (CHRCC) (in 12 cases: 17.1 %). Two cases had mucinous-tubular-spindle cell carcinoma, and two cases were unclassified RCC.

According to occurrence times, 73 SPMTs were divided into four groups: 25 in the antecedent (34.2%), 27 in synchronous (37%), 18 in subsequent (24.7%) and three in unknown (4.1%). Two SPMTs-antecedent nasopharyngeal mantle cell lymphoma and synchronous squamous cell carcinoma of the lung belonged to the same patient. In addition, another patient had three different secondary malignancies-prostate adenocarcinoma, papillary thyroid carcinoma and chronic lymphocytic leukaemia-which were in the group of unknown occurrence times.

After excluding the group of unknown occurrence times, antecedent, synchronous and subsequent groups were compared. There was no statistically significant difference between the three groups in terms of patient age ($p=0.538$, Kruskal-Wallis test). Because the median age was 60.5, age values were divided into two groups as ≤60 and >60, and the number of antecedent, synchronous and subsequent cases in each group were determined. When these parameters were compared using the chi-square test, there was no statistically significant difference between them ($p=0.742$) (Table 1).

Male patients were observed to have a higher percentage in the synchronous group than antecedent and subsequent groups (88,9%, 56%, 50%, respectively) and there was a statistically significant difference between the three groups regarding gender ($p=0.008$) (Table 1).

The most common RCC subtype in all three groups was CCRCC (56%, 66.7%, 50%, respectively), but this was not statistically significant ($p=0.298$) (Table 1).

We could not reach the clinical stage information of the cases. Since the most reliable data available for the pathological stage was

tumour size, we found it appropriate to evaluate this parameter statistically. Tumour size was known for 66 RCC, and one of them was accompanied by two different secondary malignancies. Tumour size could not be determined for four cases, and one of them had three different secondary malignancies. So, 67 SPMTs were analysed for RCC size. There was no statistically significant result between antecedent, synchronous and subsequent groups regarding RCC size (p=0.718, Kruskal-Wallis test). Then, RCC diameters were divided into four categories: ≤4 cm, >4-7 cm, >7-≤10 cm and >10 cm. The cases with ≤4 cm in RCC size were more frequently in the antecedent (13/24, 54.2%) and synchronous (11/25, 44%) groups. In the following group, the RCC size was >4 cm in most cases (13/18, 72.3%). However, the results were not statistically significant (p=0.353, chi-square test) (Table 2).

The most common SPMTs were gastrointestinal malignancies (19.1%), breast carcinomas (17.8%) and prostate carcinomas (12.3%). The distribution of SPMTs according to locations, histological types and occurrence times are listed in Tables 3 and 4.

When we compared the common SPMTs according to occurrence times, we found that gastrointestinal system (GIS) and lung tumours were most frequent in the synchronous group (57.1% and 71.4%, respectively), and breast tumours most frequently appeared as an antecedent (61.5%).

When we compared the histopathological RCC subtypes and SPMTs, CCRCC was the most common RCC subtype that accompanied SPMTs in all the series. CCRCC percentages were higher in the GIS, breast, lung, urinary bladder and pancreas (78.6%, 69.2%, 85.7%, 66.7% and 100%, respectively). In the CCRCC group, the occurrence times of the cases were parallel to characteristics of the general group: GIS and lung tumours most frequently appeared as synchronous (54.5% and 66.7%, respectively), and breast tumours were most frequent in the antecedent group (55.5%).

The proportion of prostatic adenocarcinoma in men with PRCC was remarkable, one of which also had two more SPMTs in addition to prostatic adenocarcinoma (papillary thyroid carcinoma and chronic lymphocytic leukaemia). In nine cases, prostatic adenocarcinoma was detected as SPMT. Renal carcinoma in five (55.6%) of them was PRCC. There was no

Table 1. Classification of SPMTs based on occurrence time and comparison of each group according to clinicopathological features

		Antecedent	Synchronous	Subsequent	Total	p
		n (%)				
		Median (min-max)				
Age (years)		60 (24-82)	64 (40-81)	59.5 (44-73)	60 (24-82)	0.538
Age (years)	≤60	13 (52)	12 (44.4)	10 (55.6)	35 (50)	0.742
	>60	12 (48)	15 (55.6)	8 (44.4)	35 (50)	
Gender	Female	11 (44)	3 (11.1)	9 (50)	23 (32.86)	0.008
	Male	14 (56)	24 (88.9)	9 (50)	47 (67.14)	
Histological type of RCC	Clear cell	14 (56)	18 (66.7)	9 (50)	41 (58.6)	0.298
	Papillary	3 (12)	4 (14.8)	6 (33.3)	13 (18.6)	
	Chromophobe	5 (20)	5 (18.5)	2 (11.1)	12 (17.1)	
	Others	3 (12)	0 (0)	1 (5.6)	4 (5.7)	
TOTAL		25 (100)	27 (100)	18 (100)	70 (100)*	

*: The RCC case with three SPMTs of unknown occurrence time was not included in the statistical analysis, Min: Minimum, Max: Maximum, SPMT: Seconder primary malignant tumours, RCC: Renal cell carcinoma

Table 2. Comparison of the antecedent, synchronous and subsequent groups according to RCC size

		Antecedent	Synchronous	Subsequent	Total	p
		n (%)				
		Median (min-max)				
RCC size (cm)		4 (1.6-14)	5 (1.7-15.50)	5 (1.5-15)	4.5 (1.5-15)	0.718
RCC size (cm)	≤4	13 (54.2)	11 (44)	5 (27.7)	29 (43.3)	0.353
	>4-≤7	8 (33.3)	8 (32)	11 (61.1)	27 (40.3)	
	>7-≤10	1 (4.2)	4 (16)	1 (5.6)	6 (8.9)	
	>10	2 (8.3)	2 (8)	1 (5.6)	5 (7.5)	
TOTAL		24 (100)	25 (100)	18 (100)	67 (100)*	

*Tumour size could be determined in 66 RCC cases. One had 2 SPMTs. Therefore, the statistical analysis was performed based on 67 SPMTs, RCC: Renal cell carcinoma, SPMT: Seconder primary malignant tumours, Min: Minimum, Max: Maximum

Table 3. Distribution of locations and histological types of SPMTs			
SPMTs	**Histological Type of SPMT**	**n**	**%**
Gastrointestinal system		14	19.1
Colorectum	Adenocarcinoma	11	
Stomach	Adenocarcinoma	1	
Stomach	Gastrointestinal stromal tumour	1	
Small Intestine	Neuroendocrine carcinoma	1	
Breast		13	17.8
	IDC*	6	
	Mixed IDC + mucinous carcinoma	2	
	Mixed IDC + lobular carcinoma	1	
	Mixed IDC + micropapillary carcinoma	1	
	Mucinous carcinoma	1	
	In-situ ductal carcinoma	1	
	Unknown**	1	
Prostate	Prostatic adenocarcinoma	9	12.3
Lung		7	9.6
	Small cell carcinoma	3	
	Adenocarcinomas	2	
	Squamous cell carcinoma	2	
Thyroid		6	8.2
	Papillary thyroid carcinoma	5	
	Hurthle (oncocytic) variant of follicular carcinoma	1	
Haematolymphoid tissue		6	8.2
	Chronic lymphocytic leukaemia	3	
	Mantle cell lymphoma (1 of them is nasopharyngeal)	2	
	Large B cell lymphoma of the skin	1	
Urinary bladder	Urothelial carcinoma	3	4.1
Melanoma		2	2.7
	Uveal melanoma	1	
	Skin melanoma	1	
Pancreas		2	2.7
	Ductal adenocarcinoma	1	
	Low-grade neuroendocrine tumour	1	
Bone		2	2.7
	Chondrosarcoma	1	
	Ewing sarcoma	1	
Lip	Squamous cell carcinoma	1	1.4
Larynx	Unknown**	1	1.4
Liver	Adenocarcinoma	1	1.4
Cervix	Squamous cell carcinoma	1	1.4
Ovary	Endometrioid adenocarcinoma	1	1.4
Testis	Germ cell tumour	1	1.4
Abdominal wall	Synovial sarcoma	1	1.4
Skin	Basal cell carcinoma	1	1.4
Metastasis in pleural fluid	Signet ring cell carcinoma of unknown primary origin	1	1.4
Total		73	100

*: IDC: Invasive ductal carcinoma (invasive carcinoma of no special type).
**: These cases were diagnosed at another hospital, and pathology reports could not be reached, SPMT: Seconder primary malignant tumour

significant difference regarding occurrence time in all prostatic adenocarcinomas developing as SPMT. However, the time of occurrence of four prostate adenocarcinomas associated with PRCC was known, and half of them occurred subsequently. Also,

Table 4. Distribution of SPMTs according to occurrence times						
SPMTs	**antecedent**	**synchronous**	**subsequent**	**unknown**	**n**	**%**
Gastrointestinal system	4	8	2	-	14	19.1
Colorectal	3	6	2	-	11	15.0
Stomach	-	2	-	-	2	2.7
Small Intestine	1	-	-	-	1	1.4
Breast	8	1	4	-	13	17.8
Prostate	3	2	3	1*	9	12.3
Lung	1	5**	1	-	7	9.6
Thyroid	-	1	4	1*	6	8.2
Haematolymphoid tissue	2**	2	1	1*	6	8.2
Urinary bladder	1	2	-	-	3	4.1
Melanoma	1	1	-	-	2	2.7
Pancreas	-	2	-	-	2	2.7
Bone	2	-	-	-	2	2.7
Lip	1	-	-	-	1	1.4
Larynx	1	-	-	-	1	1.4
Liver	-	-	1	-	1	1.4
Cervix	-	-	1	-	1	1.4
Ovary	-	1	-	-	1	1.4
Testis	1	-	-	-	1	1.4
Abdominal wall	-	1	-	-	1	1.4
Skin (BCC)***	-	1	-	-	1	1.4
Metastasis in pleural fluid****	-	-	1	-	1	1.4
Total	**25**	**27**	**18**	**3***	**73**	**100**

*: One case had three different secondary malignancies including prostatic adenocarcinoma, papillary thyroid carcinoma and chronic lymphocytic leukaemia. Occurrence times of SPMTs were unknown.
**: One case had two different secondary malignancies, including antecedent nasopharyngeal mantle cell lymphoma and synchronous squamous cell carcinoma of the lung.
***: BCC: Basal cell carcinoma.
****: Signet ring carcinoma metastasis of unknown primary origin in pleural fluid, SPMT: Seconder primary malignant tumour

Table 5. Distribution of histopathological RCC subtypes in SPMTs groups										
SPMTs	**Clear cell RCC**		**Papillary RCC**		**Chromophobe RCC**		**Others**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Gastrointestinal system	11	78.6	1	7.1	2	14.3	0	0.0	14	100.0
Breast	9	69.2	1	7.7	1	7.7	2	15.4	13	100.0
Prostate	1	11.1	5	55.6	3	33.3	0	0.0	9	100.0
Lung	6	85.7	1	14.3	0	0.0	0	0.0	7	100.0
Thyroid	2	33.3	2	33.3	1	16.7	1	16.7	6	100.0
Haematolymphoid tissue	2	33.3	4	66.7	0	0.0	0	0.0	6	100.0
Urinary bladder	2	66.7	1	33.3	0	0.0	0	0.0	3	100.0
Melanoma	1	50.0	0	0.0	1	50.0	0	0.0	2	100.0
Pancreas	2	100.0	0	0.0	0	0.0	0	0.0	2	100.0
Bone	1	50.0	0	0.0	1	50.0	0	0.0	2	100.0

RCC: Renal cell carcinoma, SPMT: Seconder primary malignant tumour

RCCs in two patients with multiple secondary malignancies were PRCC. The distribution of histological subtypes of RCC in the SPMT groups that have many cases is shown in Table 5.

Discussion

The incidence of SPMTs in cases of RCC varies from 4.5% to 27.4% (5,6,7,8). It was found as 12% in Japanese patients. These differences in frequency might be because of the nature of the institutions and the pattern of the studies (1). Genetic and environmental differences can contribute to a higher or lower risk of SPMT in a given population (8). The incidence of second cancers among patients with RCC in our study was 70/1129 (6.2%) and lower than that reported by many other studies. This may be due to our data being limited to pathology reports.

Beisland et al. (7) reported that the most common other primary tumours were those of prostate, bladder, lung, breast and colon. Sato et al. (1) showed that gastrointestinal carcinomas were the most common SPMTs accompanying RCC. In another study, it was found that the largest number of SPMT arose in male genital (particularly the prostate gland), digestive and respiratory systems (8). In a population-based study, the incidence of RCC was found higher among men with many kinds of carcinomas, whereas the incidence of prostate cancer was increased only in men who had RCC (9). In our study, the most common SPMTs were respectively gastrointestinal cancer (mostly colorectal adenocarcinoma), breast carcinoma (mostly invasive ductal carcinoma/invasive carcinoma of no special type), prostatic adenocarcinoma, lung carcinomas (mostly small cell carcinoma), thyroid carcinoma (mostly papillary type) and haematolymphoid malignancies (mostly chronic lymphocytic leukaemia).

In the literature, it was reported that the small intestine was the most common location for gastrointestinal stromal tumor (GIST) that accompanied a second primary neoplasm (10,11). However, in our series, there was only one patient with GIST as SPMT, and it was localised in the stomach. Mendonca et al. (11) found nine RCC cases with GIST as SPMT that had a high frequency of CCRCC (4/9) and PRCC (4/9) subtypes. In our case, renal carcinoma was also CCRCC.

In a study, the association between NHL and RCC was evaluated. Race and gender were found significantly associated with an increased cumulative incidence of RCC after NHL. White males with NHL are at increased risk for RCC (12). In our small series, six cases had haematolymphoid malignancy as SPMT, and five were male.

The association between the histological subtype of RCC and SPMTs was investigated by some authors. Abdel-Rahman (13) found that PRCC had the highest standardised incidence ratios for subsequent kidney cancers. Rabbani et al. (6) reported that the PRCC is associated with an increased risk of developing SPMT in the prostate and bladder. Thampson et al. (14) found that cases with PRCC were significantly more likely to have colon and prostate cancer or any second malignancy compared with CCRCC. Cases with CHRCC were significantly more likely to have colon cancer than CCRCC. Cases with PRCC were more likely to have bladder cancer, but this result was not significant compared with CCRCC and CHRCC.

In our series, CCRCC was the most common RCC subtype that accompanied SPMTs. CCRCC percentages were higher in the GIS, breast, lung, urinary bladder and pancreas. We found a close relationship between PRCC and prostatic adenocarcinoma in our study: 55.6% of prostatic adenocarcinoma cases had PRCC. There were two cases with multiple secondary malignancies in our study, and one of these cases had prostatic adenocarcinoma. The kidney carcinoma of both cases with multiple secondary malignancies was PRCC.

SPMTs contributes to the prognosis of RCC cases. Sato et al. (1) found that the presence of antecedent or synchronous malignancies was the second most significant prognostic factor, following the pathological stage of RCC. Beisland et al. (7) reported that RCC cases with an antecedent or synchronous other cancer had significantly poorer overall survival than those without. Among the clinicopathological data we could obtain in our study, we compared the time of occurrence of SPMTs and the tumour size, since the tumour size was the most valuable prognostic parameter. The cases with ≤4 cm in RCC size were usually in the antecedent and synchronous groups, whereas tumours >4 cm in most cases were in the subsequent group. However, there was no statistically significant result between the occurrence time of SPMT and RCC size.

In our study, when the antecedent, synchronous and subsequent SPMT groups were compared with each other regarding clinicopathological parameters, no significant difference was found between the groups, except for the gender parameter. We thought that this was related to the limited number of cases and the clinicopathological parameters that could be reached. More comprehensive studies are required to determine the clinical and pathological characteristics of SPMTs with RCCs.

Study Limitations

Since the clinical information we obtained was limited, we could not comment on some topics, such as etiological factors, stage and survival.

Conclusion

In this study, the incidence of SMPTs with RCC was 6.2% and lower than that reported by many other studies. The most common locations for SPMTs were the GIS, breast and prostate. When SPMTs were categorised according to occurrence times, there were no statistically significant differences among antecedent, synchronous and subsequent groups regarding patient age, histological RCC subtype and RCC size. Male patients had a higher percentage in the synchronous group than antecedent and subsequent groups. CCRCC was the most common RCC subtype that was accompanying SPMTs in all our series. The proportion of prostatic adenocarcinoma in men with PRCC was remarkable. Two patients' RCCs with multiple secondary malignancies were PRCC. RCC can coexist with secondary malignancies. Our findings indicate that more comprehensive studies are required to determine the clinical and pathological characteristics of SPMTs with RCCs. However, for our practical application, we can say that: When a new tumour appears in a patient with RCC who is in clinical follow-up, it is appropriate to evaluate that tumour histopathologically or cytopathologically regarding SPMT before accepting it as a metastatic spread.

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Contribution: A valuable contribution has been made by Canser Çakalır, retired professor.

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Ethics

Ethics Committee Approval: The study protocol was accepted by Amasya University Clinical Research Ethics Committee (decision no: 2020/1-01)

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.U., Design: N.U., H.D., Data Collection or Processing: Ö.Y., E.O., D.N.D., Ç.D., H.D., İ.G., Analysis or Interpretation: H.D., Ö.Y., B.T.G., Literature Search: H.D., Ö.Y., E.O., Writing: H.D.

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