



Second Primary Malignancies in Patients with Carcinoma of the Kidney: A Hospital Based Study

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Background: Renal cancer may be associated with other second primary malignancies. Here we retrospectively evaluate the risk factors of second primary malignancies in two major types of renal cancers, namely renal cell carcinoma (RCC) and urothelial cell carcinoma (UCC). Risk factors including sex, age, tumor-node-metastasis (TNM) staging, grading, and histological subtype are examined. **Materials and methods:** We studied 393 patients who underwent nephrectomy from January 1988 to December 2005, including 228 RCC and 165 UCC. All specimens were reviewed by 2 pathologists and clinical information was obtained from patient charts and pathological reports. Significance between demographic features and renal cancer was evaluated by logistic regression. The association between histological subtypes and second primary malignancies was examined using chi-square test. **Results:** Second primary malignancies were present in 35 of 228 RCC patients (14.91%) and 39 of 165 UCC patients (23.03%). The papillary renal cell carcinoma (PRCC) showed a higher tendency to harbor second primary malignancies ($p < 0.05$) than patients with clear cell renal cell carcinoma (CCRCC). And patients with PRCC have an increased risk of subsequent head and neck cancer ($p < 0.05$) compared with CCRCC patients. Besides, patients with papillary urothelial cell carcinoma (PUCC) were at increased risk of developing subsequent gastrointestinal cancer ($p < 0.05$). **Conclusion:** After evaluation of all risk factors, histological subtypes show statistical association with second primary malignancy. Our data indicate that patients with PRCC are more likely to develop second primary cancer than patients with CCRCC which second primary head and neck cancer is statistically significant. And gastrointestinal malignancies are the most common other primary cancers in patients with PUCC. These results may have implication for patient education, follow-up evaluation and further research works.

Key words: second primary malignancies, carcinoma, kidney

INTRODUCTION

Renal cancers account for approximately 210,000 cancers and about 102,000 deaths from the disease worldwide.¹ It is also the 9th most common cancer both in the European Union and United States,² and the 11th most common one in Taiwan. The 5-year survival rate is highly dependent on the initial stage of the disease. Near-

ly half of those victims with renal cancer died within 5 years. An increased risk of second primary malignancies has been noticed in patients with renal cancer, including antecedent, concurrent or subsequent malignancies.³⁻⁶

The study of associated second primary malignancies in patients with renal cancer is essential since it may elucidate the important etiologic factors, including a common carcinogen such as tobacco use, genetic alterations, or treatment modalities. Such findings may improve the follow up of patients with renal cancer.⁷⁻⁹

It has been reported that patients diagnosed with renal cell carcinoma (RCC) are at increased risk for second primary malignancies of the bladder, prostate, rectum, lung, non-Hodgkin's lymphoma and melanoma.⁵ The second primary malignancies associated with urothelial cell carcinoma (UCC) have been associated with bladder cancer.⁷

Here we carried out a retrospective analysis of renal

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cancers, and associated second primary malignancies of an 18-year single hospital-based renal cancer cohort in Taiwan. Risk factors including sex, age, staging, grading, and histological subtypes were analyzed.

MATERIALS AND METHODS

Subject collection

Retrospective data from a total 687 patients treated at the Tri-Service General Hospital (TSGH) from January 1988 to December 2005 for pathological proven cancer were reviewed from the TSGH Cancer Registry Council. All of those patients were treated with open radical nephrectomy at TSGH. Histological diagnosis was also recorded and classified into two major subtypes: renal cell carcinomas (RCC) and urothelial cell carcinomas (UCC, i.e. transitional cell carcinomas). Clinical histories, diagnostic methods, histology, staging and clinical course were reviewed in all patients. Demographic data were collected including age, sex, diagnosis and date of the first primary, follow-up for mortality, and diagnosis and date of the second primary, if any. A primary cancer is one that originates in a primary site or tissue and is thus neither an extension, a recurrence, nor a metastasis. Tumor staging was recorded according to the 2002 American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system. Histological grading was determined according to the Fuhrman's histological grading criteria for RCC and the World Health Organization/International Society of Urologic Pathologists (WHO/ISUP) grading system for UCC. However we excluded some unsuitable subjects including (1) no follow-up information available after nephrectomy, (2) ambiguous diagnostic information such as uncertainty of primary cancer or metastatic carcinoma, (3) unusable or unavailable FFPE specimens. Until May 31, 2010, the endpoint of this retrospective study, the final study cohort include 393 renal cancer patients between 1988 and 2005 which composed of 228 RCC and 165 UCC. There are 34/228 RCC and 42/165 UCC patients who had received chemotherapy and/or radiotherapy. Subsequent analyses were carried out upon approval of informed consent according to institutional review board guidelines.

Histology

All available formalin-fixed paraffin embedded specimens were resected and H&E stained, and then reviewed by the primary study pathologist Y.C.L. without the information of original diagnosis and subsequent outcome. All cases suspicious for inconsistency were agreed on by

two study pathologists (C.P.Y. and Y.C.L.).

Secondary primary malignancies antecedent (six months before the nephrectomy)/ concurrent (at, before, or within six months after the nephrectomy) or subsequent (six months after the nephrectomy) to nephrectomy for those renal cancers were further recorded. There are 35 second primary malignancies in RCC patients and 39 second primary malignancies in UCC patients, respectively. And 4 RCC patients and 1 UCC patient had triple primary malignancies. Further analysis was performed based on the organ system of second primary malignancies initiated sites.

Statistical analysis

Clinicopathological features were categorized as table 1, and follow-up interval of each patient was defined in number of days from the nephrectomy to the date of second primary malignancy, date of death, date of last contact or the end of follow-up, and followed by dividing 365.25 to calculate years. The second primary malignancy risks of each clinicopathological features were estimated using logistic regression model. And distribution of different histological subtypes and second primary malignancy initiated sites were analyzed with chi-squared tests. The overall survival assay of renal cancer with/without second primary malignancies was estimated using Kaplan-Meier curves with log-rank test. All the statistical analyses were performed by using SPSS 13.0 and Excel 2003. All statistical tests and p values were two-sided and the level of significance was set at <0.05 .

RESULTS

Clinicopathological features and second primary malignancy incident risk

Clinicopathological features of this renal cancer cohort were summarized in the table 1. We evaluated the age, sex, laterality, primary renal tumor size, regional lymph node involvement, distant metastasis, staging, grade, and histological type of those renal cancers. There were 35 of 228 RCC patients and 39 of 165 UCC patients with another biopsy-verified primary malignancy in our follow up period. In these 35 RCC patients, 13 (37.1%) was antecedent, 10 (28.6%) was concurrent and 12 (34.3%) was subsequent; as well as the 39 UCC patients, 6 (15.4%) was antecedent, 22 (56.4%) was concurrent and 11 (28.2%) was subsequent. Besides, there were 4 of RCC and 1 of UCC who had two other primary malignancies. 228 RCC patients histologically composed of 189 clear cell type (CCRCC), 24 papillary type (PRCC), and

Table 1 Clinicopathological features in patients with kidney cancers

	RCC (n=228)				UCC (n=165)			
	No. (%)	No. 2 nd	RR (95%CI)	p ^a	No. (%)	No. 2 nd	RR (95%CI)	p ^a
Age								
Median (range)	62 (21-86)				67 (26-89)			
<65y/o	133 (58.3)	18	reference		69 (41.8)	12	reference	
65y/o	95 (41.7)	17	1.392 (0.676-2.868)	0.369	96 (58.2)	27	1.859 (0.865-3.995)	0.112
Sex								
Female	75 (32.9)	14	reference		68 (41.2)	19	reference	
Male	153 (67.1)	21	1.443 (0.687-3.027)	0.333	97 (58.8)	20	0.670 (0.325-1.380)	0.277
Laterality								
Right	105 (46.1)	16	reference		82 (49.7)	14	reference	
Left	123 (53.9)	19	0.984 (0.478-2.027)	0.965	83 (50.3)	23	1.902 (0.896-4.039)	0.094
Primary tumor size								
pT1	97 (42.3)	17	reference		39 (23.8)	8	reference	
pT2	45 (19.8)	8	1.833 (0.612-5.490)	0.279	44 (26.7)	7	0.708 (0.214-2.350)	0.573
pT3+pT4	86 (37.8)	10	1.765 (0.472-6.603)	0.399	82 (49.5)	14	0.783 (0.277-2.215)	0.645
Lymph node								
pNx+pN0	207 (90.9)	32	reference		152 (92.2)	27	reference	
pN1+pN2	21 (9.1)	3	1.001 (0.179-5.079)	0.990	13 (7.8)	2	0.840 (0.159-4.421)	0.836
Distant metastasis								
M0	204 (89.3)	31	reference		154 (93.3)	28	reference	
M1	24 (10.7)	4	2.924 (0.357-23.948)	0.317	11 (6.7)	1	0.411 (0.047-3.569)	0.42
Staging (AJCC TNM stage)								
I	92 (40.2)	18	reference		39 (23.8)	8	reference	
II	35 (15.2)	6	1.941 (0.479-7.861)	0.353	44 (26.7)	7	0.708 (0.214-2.350)	0.573
III	59 (25.9)	6	1.846 (0.352-9.692)	0.469	65 (39.0)	11	0.779 (0.263-2.312)	0.653
IV	42 (18.7)	5	0.960 (0.191-4.826)	0.960	17 (10.5)	3	0.797 (0.166-3.833)	0.777
Grading (Fuhrman's histological grading criteria)								
1+2	91 (39.9)	16	reference		70 (42.4)	15	reference	
3	89 (39.0)	15	2.347 (0.738-7.464)	0.149	95 (57.6) ^b	20	0.978 (0.451-2.121)	0.955
4	48 (21.1)	4	2.230 (0.696-7.144)	0.177				
Histological subtype								
CCRCC ^c		189 (82.9)	26	reference				
PRCC ^c	24 (10.5)	8	2.932 (1.149-7.482)	0.024				
ChRCC ^c	15 (6.6)	1	0.443 (0.056-3.529)	0.443				
SUCC ^d					78 (47.3)	15	reference	
PUCC ^d					87 (52.7)	24	1.600 (0.859-3.299)	0.092
Adjuvant therapy for subsequent second primary malignancies ^e								
No	194 (85.1)	11	reference		123 (74.5)	10	reference	
Yes	34 (14.9)	1	0.504 (0.063-4.037)	0.519	42 (25.5)	1	0.276 (0.034-2.220)	0.226

^a Based on logistic regression analysis^b Grade 1+2 vs grade 3+4 in UCC population^c CCRCC (clear cell renal cell carcinoma), PRCC (papillary renal cell carcinoma), ChRCC (chromophobe renal cell carcinoma)^d SUCC (solid urothelial cell carcinoma), PUCC (papillary urothelial cell carcinoma)^e Only second primary malignancies analyzed, including 12 RCC and 11 UCC

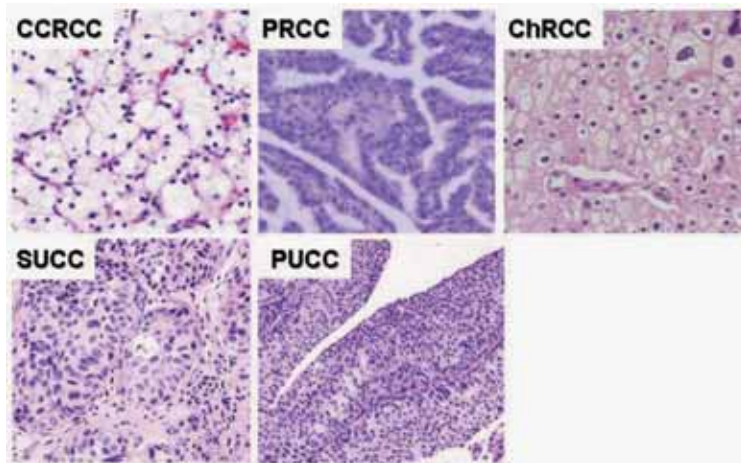


Fig. 1 Representative H&E stained profiles of major histological subtypes of RCC and UCC. Abbrev: CCRCC: clear cell renal cell carcinoma, PRCC: papillary renal cell carcinoma, ChRCC: chromophobe renal cell carcinoma, SUCC: solid urothelial cell carcinoma, PUCC: papillary urothelial cell carcinoma.

15 chromophobe type (ChRCC), and 165 UCC patients composed of 78 solid type (SUCC) and 87 papillary type (PUCC). The representative H&E staining profiles of each histological type were presented in Fig 1. Patients with PRCC had higher incidence of developing second primary malignancies than patients with CCRCC and ChRCC (Table 1, $p < 0.05$). However, adjuvant therapy (chemotherapy or radiotherapy) of renal cancer confers no significant effect on subsequential second primary malignancies.

Histological subtype and second primary malignancy initiated site

Table 2 and table 3 showed the relationship between the second primary malignancy initiated site and the histological type of RCC and UCC. Patients with PRCC were significantly more likely to have head and neck cancer (Table 2, $p = 0.04$). Patients with PUCC were significantly more likely to have gastrointestinal cancer (Table 3, $p = 0.048$). However there is no significant difference of other second primary malignancy initiated sites including genital, urinary tract and others among RCC and UCC histological subtypes.

Survival assay of the second primary malignancy of renal cancer

Of the 393 patients included 153 (67.1%) males and 75 (32.9%) female in RCC, and 97 (58.8%) male and 68 (41.2%) female in UCC; the median age was 62 years

Table 2 Second primary malignancies by RCC histological subtypes

	CCRCC ^b	PRCC ^b	ChRCC ^b	p ^c
All types of RCC	188	25	15	
All types of SNRCC ^a	26	8	1	0.194
1 Head and Neck	2	2	0	0.040
Nasopharynx	2	1	0	
Parotid	0	1	0	
2. Gastrointestinal	12	3	0	0.322
Esophagus	1	0	0	
Stomach	1	1	0	
Pancreas	2	0	0	
Liver	2	2	0	
Colon	5	0	0	
Anorectum	1	0	0	
3. Genital tract	5	1	1	0.221
Female genital tract				
Ovary	1	0	0	
Cervix	3	1	0	
Male genital tract				
Prostate	1	0	1	
4. Urinary tract	1	1	0	0.202
Bladder	1	0	0	
Ureter	0	1	0	
5. Others	2	1	0	0.432
Lung	1	1	0	
Thymus	1	0	0	
Multiple malignancies	4	0	0	0.648

^a SNRCC: second non-renal carcinoma

^b CCRCC (clear cell renal cell carcinoma), PRCC (papillary renal cell carcinoma), ChRCC (chromophobe renal cell carcinoma)

^c Based on chi-square test.

and 67 years, respectively; and the median observation time for surviving patients on 31 May 2010 was 10.23 years in RCC and 10.11 years in UCC.

In detail, the mean follow-up time of RCC patients without second primary malignancy was 7.78 ± 5.48 years, RCC patients with second primary malignancy was 6.09 ± 4.74 years, UCC patients without second primary malignancy was 6.55 ± 5.85 years, and UCC patients with second primary malignancy was 5.49 ± 4.54 years. UCC patients with second primary malignancy had significantly lower overall survival rate (p of log-rank test = 0.043) but without statistical significance between antecedent/concurrent or subsequent second primary malignancy.

DISCUSSION

Renal cell carcinoma is generally a tumor of adults (the average age at diagnosis is about 60 years) and the male-to-female ratio is about 2:1.¹ In the analysis of our

Table 3 Second primary malignancies by UCC histological subtypes

	SUCC	PUCC	p ^b
All types of UCC	78	87	
All types of SNUCC ^a	15	24	0.207
1. Gastrointestinal	0	4	0.048
Stomach	0	2	
Colon	0	1	
Pancreas	0	1	
2. Genital tract	0	2	0.178
Cervix	0	1	
Prostate	0	1	
3. Urinary tract	12	16	0.608
Bladder	11	14	
Ureter	1	2	
4. Other	3	2	0.261
Breast	0	1	
Lung	2	0	
Skin	0	1	
Unknown	1	0	
Multiple malignancies	0	1	0.342

^a SNUCC: second non-urothelial cell carcinoma^b Based on chi-square test

patients, the age, sex, and laterality of the renal tumor seemed to have no impact on the incidence of a second primary malignancy. According to the study of Rabbini et al.,³ there was no significant relationship between the AJCC TNM stage and a second primary malignancy in RCC patients. Therefore, we further investigated the influence of the tumor grade on the incidence of a second primary malignancy in patients with RCC or UCC, but there was no statistically significant association. Christian et al.¹⁰ reported that patients with localized RCC (T1–2) and other coexistent cancers had a poorer prognosis for overall survival than those patients with only localized RCC (T1–2). Among the patients at our institution, the mortality rate of patients with localized renal cancer (T1–2) and another coexistent cancer was higher (1.42-fold, $P = 0.612$) than that of patients with only localized renal cancer (T1–2). On the basis of previous studies, it is suggested that the treatment of renal cancer patients with second primary malignancies should be based not only on the stage and operability of the kidney tumor but also on an evaluation of their status regarding a second malignant disease.

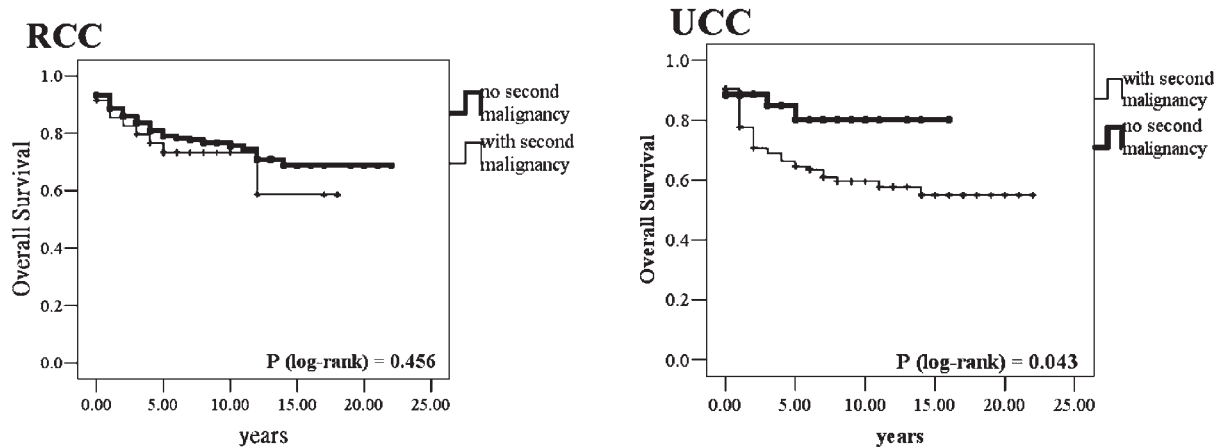
The presence of one malignant tumor does not produce immunity against the development of a second primary malignancy in the same patient. The improved survival rates for patients with malignant disease, which result predominantly from an early diagnosis, allow more patients to survive long enough to develop a second primary malignancy. Therefore, it is not uncommon for

patients diagnosed with one malignancy to inquire about the risk of additional primary cancers. In most patients, the inherent risk is equal to that in the general population. However, it is well documented that neoplastic transformation in multiple different organs can be stimulated by numerous factors, including genetic changes, environmental carcinogens, etc.^{4,6,8} The incidence of second primary malignancies has been studied using reviews of cancer registries in several countries and ranges from 0.7% to 16%.^{10–16} In the SEER Program in the United States¹¹ and a national population-based cohort study in Norway,¹⁰ patients with renal cancer had an elevated risk of second primary cancers. Renal cell carcinoma has been reported to be associated with other primary malignancies, including bladder,^{4,5,17} prostate,^{17,18} rectal,⁷ and lung cancer,¹⁷ non-Hodgkin's lymphoma,^{18,19} and melanoma.¹⁹

In the current study, we report the associated malignancies in patients with RCC and UCC with uniform pathological reviews of all specimens. Compared with the studies of Christian and Rabbani, who reported that breast, prostate, colorectal, and bladder cancer, and non-Hodgkin's lymphoma were the most common second primary malignancies in patients with RCC,^{9,10} our study did not identify breast cancer or non-Hodgkin's lymphoma in patients with RCC. Furthermore, the histological type of RCC has played an important role in the second primary malignancies associated with RCC.³ Among the cases in our study, patients with PRCC had a higher incidence of second primary malignancies than did patients with CCRCC. We have also presented previously unreported evidence that patients with PRCC at our institution were more likely to have a second head and neck cancer ($P = 0.04$; Table 2) than were patients with CCRCC or ChRCC. In previous studies, Thompson³ demonstrated that patients with PRCC were more likely to have a second colon cancer or prostate cancer than were patients with CCRCC, and Rabbani⁴ reported an increased risk of subsequent bladder or prostate cancer in patients with PRCC. Although the cause of this association remains to be clarified, knowledge of associated malignancies is essential for patient education and follow-up evaluation, and further genetic research.

Both chemo- and radiotherapy have been shown to be carcinogenic in several studies.^{11,21} In our study, 34 (14.9%) RCC and 42 (25.5%) UCC patients had received adjuvant therapy (chemo- or radiotherapy; Table 1), and we analyzed those patients with second primary malignancies, but no statistically significant association was observed. Masaki²² assumed that radiation therapy plays

(Fig 2a)



(Fig 2b)

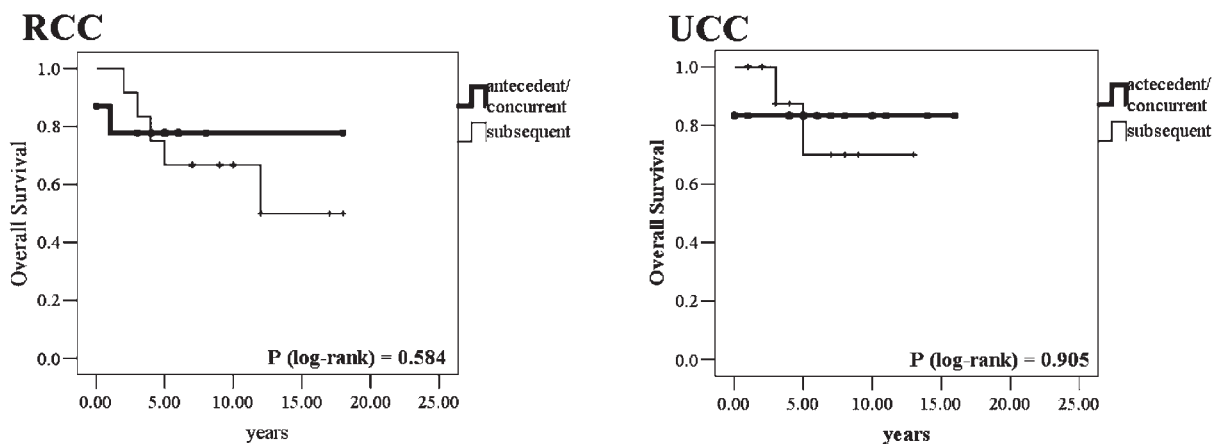


Fig. 2 Overall survival assay of RCC and UCC compared between (Fig. 2a) with or without second primary malignancy, (Fig. 2b) antecedent/concurrent or subsequent secondary primary malignancy

an important role in head and neck cancer associated second primary malignancies. However, at our institution, no RCC patient with a second primary head and neck cancer had received radiotherapy.

In a population-based survey (Connecticut, USA) of the risk of second malignancies after renal cancer, performed by Kantor,¹⁷ renal UCC showed a significantly elevated relative risk. To the best of our knowledge, no previous reports have analyzed the histological subtype of renal UCC. Our data show that the patients with papillary type of UCC had a higher risk (1.60-fold) of second primary malignancies than did patients with solid-type UCC. In a further analysis based on the different organ systems affected by second primary malignancies,

patients with PUCC were found to be more likely to develop second primary gastrointestinal cancers than were patients with SUCC.

It has been reported that patients with PRCC are significantly more likely to have multiple malignancies (≥ 3) than are patients with CCRCC.³ However, our data do not support this and all the patients with multiple malignancies (Table 2) were the CCRCC subtype. Because the power of the study was low, this was not statistically significant ($P = 0.648$). Four patients had multiple malignancies secondary to CCRCC: (1) uterine adenocarcinoma/rectal adenocarcinoma; (2) urothelial cell carcinoma of the bladder/gastric adenocarcinoma; (3) hepatocellular carcinoma/cholangiocarcinoma of the bile duct; and (4)

hepatocellular carcinoma/pancreatic adenocarcinoma. These multiple secondary malignancies seem to have been associated with the epithelial component, such as adenocarcinoma, rather than with the lymphoid system or soft tissue component, in this retrospective study.

It is well documented that cancer therapy can result in other primary cancers,^{23,24} but these usually appear after 10 years. It has also been noted that patients with RCC have a greater risk of second primary cancers, indicating that patients with RCC should be followed up more aggressively. Second primary malignancies also significantly reduce the overall survival rate in UCC patients but not in RCC patients. However, the mean follow-up time for RCC patients is significantly shorter (7.78 ± 5.48 years without second primary malignancies vs 6.09 ± 4.74 years with second primary malignancies, $P = 0.049$ by t test). These data also imply that RCC patients with second primary malignancies should be followed up more carefully and intensively.

It is fundamental that patients who have been treated for cancer require careful follow-up studies. When the symptoms and signs of a tumor recur in a patient who has been treated for an initial primary cancer, it is inappropriate to regard the condition as metastasis. The possibility of a second primary malignancy should also be considered and evaluated. The early diagnosis of these second lesions will substantially increase the survival of these patients. In conclusion, we have shown that patients with the papillary type of both RCC and UCC are more likely to have a second primary malignancy than are patients with clear-cell-type RCC or UCC. PRCC patients also have a higher risk of a second primary head and neck cancer than do CCRCC patients. PUCC patients are also at increased risk of developing a second primary gastrointestinal cancer than are SUCC patients. These data may have important implications for patients' clinical work-ups and follow-up evaluations, and for future laboratory studies designed to clarify the mechanism underlying this phenomenon.

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