Original Article

A nomogram for overall survival of second primary cancers following upper-tract urothelial carcinoma: a SEER population-based study

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Background: With improving prognosis in upper-tract urothelial carcinoma (UTUC), an increasing number of second primary malignancies (SPMs) are being identified. However, there is limited research on SPMs following UTUC. This study aims to evaluate the risk of SPMs in UTUC patients and create a nomogram to predict their survival rates.

Methods: Utilizing data from the Surveillance, Epidemiology, and End Results (SEER) database, we assessed the risk of SPMs among UTUC patients. Additionally, we developed and validated an overall survival (OS) nomogram for SPM patients post-UTUC diagnosis.

Results: The prevalence of SPMs among UTUC patients was 30.23%, with solid tumors being the most prevalent type of second malignancy, constituting 95.30% of all SPMs. The overall risk of SPMs was significantly elevated across all subgroups. Univariate and multivariate Cox regression analyses identified age, race, gender, UTUC SEER historic stage, surgery, SPM site, histologic type, grade, and SEER historic stage as independent prognostic factors for SPM OS. Subsequently, we developed a nomogram for predicting SPM OS. The C-index for the training and validation sets were 0.72 [95% confidence interval (CI): 0.70–0.74] and 0.71 (95% CI: 0.67–0.75), respectively. The area under the curve (AUC) demonstrated good performance of our model in predicting the 3-year (0.73 and 0.737) and 5-year (0.723 and 0.733) OS of SPMs in both sets.

Conclusions: This study represents the first comprehensive analysis of SPM incidence in UTUC patients and introduces a nomogram for predicting SPM prognosis.

Keywords: Upper-tract urothelial carcinoma (UTUC); Surveillance, Epidemiology, and End Results (SEER); second primary; prognosis; nomogram

Submitted Mar 28, 2024. Accepted for publication Jul 07, 2024. Published online Aug 12, 2024.
doi: 10.21037/tcr-24-515
View this article at: https://dx.doi.org/10.21037/tcr-24-515

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Introduction

Upper-tract urothelial carcinoma (UTUC), encompassing tumors in the renal pelvis and ureter, represents a rare genitourinary malignancy, accounting for nearly 5% of all urothelial cancers (1). Over the past five decades, advancements in diagnostic methods and enhancements in overall survival (OS) rates have led to a rising incidence of UTUC cases (1-3).

With the improved prognosis of first primary malignancies (FPMs), an increasing number of second primary malignancies (SPMs) are being identified (4-6). While studies have explored SPMs in the urinary system such as prostate cancer (PCa) and kidney cancer (KCa), research on the incidence of SPMs following UTUC remains scarce in current literature. Previous studies have reported varying incidence rates of SPMs after PCa (3.69% to 22.5%) (7-9) and KCa (10% to 47%) (10-13).

Furthermore, recent research has demonstrated that patients with SPMs experience poorer survival outcomes (14). Nomograms have emerged as valuable tools for predicting patient mortality and have shown efficacy in genitourinary malignancies like bladder cancer and UTUC (15-18). Recognizing the importance of understanding the occurrence and prognosis of SPMs post-UTUC, this study aims to assess the risk of SPMs in UTUC patients and develop a nomogram for predicting the 3- and 5-year survival rates of SPMs. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-515/rc).

Highlight box

Key findings

- This study established a nomogram for predicting 3- and 5-year overall survival (OS) in second primary malignancies (SPMs) following upper-tract urothelial carcinoma (UTUC) patients. The robustness of our prediction model was confirmed through validation, demonstrating good accuracy.

What is known and what is new?

- Over the past five decades, the incidence of UTUC has risen, while few studies have explored SPMs in the urinary system.
- This study represents the first comprehensive analysis of SPM incidence in UTUC patients and introduces a nomogram for predicting SPM prognosis.

What is the implication, and what should change now?

- By using our nomogram, it is possible to identify the risk of SPM in UTUC patients and access their OS, optimizing individualized treatment and care.

Methods

Data source

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data for this study were sourced from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Specifically, the Multiple Primary-Standardized Incidence Ratio (MP-SIR) data were extracted from SEER Research Data {9 registries, November 2019 submission [1975–2017]}, while de-identified information on individual patients was obtained from the SEER database {18 registries excluding AK (Alaska) Custom Data with additional treatment fields [2000–2016]}.

To be included in the analysis, patients had to meet the following criteria: (I) UTUC was the first of two or more cancers, identified by site recodes [International Classification of Diseases for Oncology - Third Edition (ICD-O-3)] C65.9 (renal pelvis) and C66.9 (ureter) and morphology codes (ICD-O-3) 8120, 8122, 8130, 8131 (urothelial carcinoma/transitional cell carcinoma); (II) each individual case provided information on age, race, gender, marital status, UTUC-specific details (including laterality, SEER historic stage, grade, and therapy information), SPM details (including grade, SEER historic stage, and therapy information), months since index diagnosis, vital status, and survival months. Patients were excluded if they met any of the following criteria: (I) missing basic information; (II) lacking UTUC-related information; (III) diagnosis not consistent with transitional cell carcinoma; or (IV) missing SPM-related information. For a detailed overview of the selection process, please refer to *Figure 1*.

Statistical analyses

The risk of a SPM was assessed by calculating the standardized incidence ratio (SIR), defined as the ratio of observed cases (O) of subsequent primary cancers at a specific site to the expected (E) number of subsequent cancers at the same site. Patients were randomly allocated to either the training or validation cohort at a ratio of 7 to 3. Descriptive statistics were utilized to summarize the clinical characteristics of patients, with continuous variables presented as mean ± standard deviation (SD) and compared using Student's *t*-test. Categorical parameters

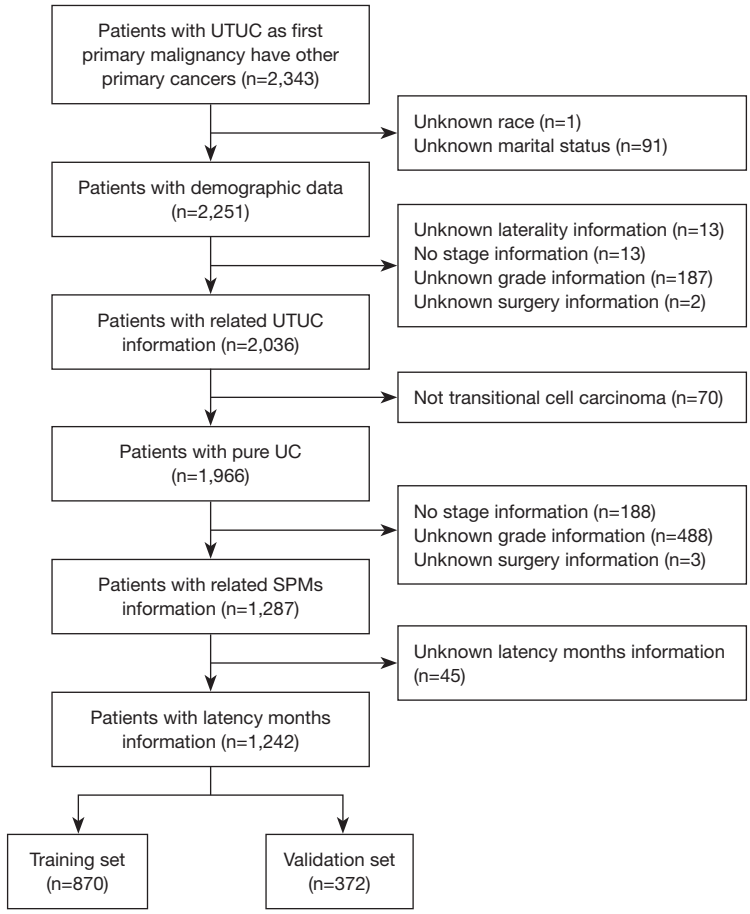

Figure 1 Study flowchart showing the process of constructing nomogram to predict the OS of SPMs after UTUC. UTUC, upper-tract urothelial carcinoma; UC, urothelial carcinoma; SPM, second primary malignancy; OS, overall survival.

across different groups were compared using Pearson's Chi-squared test or Fisher's exact test. Univariate and multivariate Cox regression models were employed to determine hazard ratios (HRs) with 95% confidence intervals (CIs) for OS. A nomogram was developed to predict the 3- and 5-year survival rates of SPM patients, incorporating factors significantly associated with OS and readily available in clinical practice. Model performance was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC), C-index, and calibration plots. All statistical tests were two-sided, with significance set at $P<0.05$. Data analysis was conducted using the statistical software R (version 3.4.3).

Results

Study population

A total of 10,916 patients diagnosed with renal pelvis or ureter cancer as their first primary cancer were identified in the MP-SIR section of the SEER database (from nine registries in the U.S.) between 1975 and 2017. Among them, 3,300 patients were diagnosed with one or more additional primary cancers, resulting in a 30.23% incidence rate of SPMs. Solid tumors were the predominant type of second malignancy in UTUC patients, representing 95.30% of all SPMs. Statistically significant SPMs were further analyzed.

For prognostic significance analysis, de-identified data

Table 1 Effect of age on the risk of second primary cancers in UTUC

Site of second malignancy	<60 years		60–74 years		≥75 years	
	O	SIR	O	SIR	O	SIR
All sites	54	2.44*	426	2.33*	504	2.71*
All solid tumors	52	2.61*	404	2.49*	485	3.01*
Urinary system						
Ureter	1	27.91*	8	18.46*	5	21.25*
Urinary bladder	25	17.42*	182	15.88*	262	19.77*
Renal pelvis	11	16.42*	4	9.52*	4	5.88*
Prostate	6	1.00	51	1.14	52	1.38*
Digestive system						
Splenic flexure	4	5.48*	3	1.32	3	1.97*
Transverse colon	1	3.80*	3	1.87	1	0.67
Small intestine	1	3.42*	1	1.61	1	0.72
Colon excluding rectum	3	2.57*	20	1.34	22	1.08
Cecum	11	2.54*	5	1.61*	6	1.33
Stomach	1	2.27*	4	0.98	5	0.71
Hepatic flexure	2	1.96	2	2.41*	2	0.80
Rectosigmoid junction	2	0.78*	4	0.57	4	1.29
Respiratory system						
Lung and bronchus	6	2.07*	70	2.14*	54	1.81*

*, P<0.05. UTUC, upper-tract urothelial carcinoma; O, observed number of cases; SIR, standardized incidence ratio (ratio of observed to expected number of second malignancies).

on UTUC patients from 18 U.S. registries between 2000 and 2016 were retrieved, resulting in 2,343 patients with UTUC as their first of two or more primary malignancies. Ultimately, 1,242 cases were included for detailed analysis. The median follow-up duration was 44 months (Q1–Q3: 17–92 months), with 817 (65.78%) patients experiencing mortality before the last follow-up.

Relationship of patient and demographic variables on SPM risk

(I) Age at diagnosis of UTUC. Patients with UTUC followed by a second cancer were divided into three groups based on their age at the time of diagnosis of the UTUC: <60, 60–74, and ≥75 years. As shown in *Table 1*, the overall risk of SPMs was significantly increased in all three age groups, especially in SPMs of urinary systems. Patients younger than 60 years were nearly 2–5 times more likely to develop a second digestive system malignancy than their older counterparts. The risk of a SPM was highest in the ureter (SIR: 27.91, 18.46, 21.25) in all three age groups followed by urinary bladder and renal pelvis cancer (SIR: 17.42 and 16.42; 15.88 and 9.52; 19.77 and 5.88, respectively).

(II) Race. The overall risk of a second cancer was significantly increased in all racial groups (*Table 2*). The risk was higher in other racial groups compared to Whites and Blacks (SIR: 3.19 *vs.* 2.41 and 3.00 respectively). Similarly, the risk of a SPM was highest in the ureter (SIR: 19.67, 64.68, 41.09) in all three racial groups, followed by urinary bladder cancer (SIR: 16.22, 43.51, 39.89, respectively). In addition, the risk of a second cancer in the lung and bronchus were increased in all racial groups (SIR: 2.03, 2.73, 1.74, respectively).

Table 2 Effect of race on the risk of second primary cancers in UTUC

Site of second malignancy	White		Black		Others	
	O	SIR	O	SIR	O	SIR
All sites	2,940	2.41*	131	3.00*	228	3.19*
All solid tumors	2,798	2.61*	123	3.13*	223	3.50*
Urinary system						
Ureter	46	19.67*	2	64.68*	7	41.09*
Urinary bladder	1,375	16.22*	60	43.51*	124	39.89*
Renal pelvis	33	9.49*	0	0.00	3	14.54*
Penis	6	4.27*	0	0.00	0	0.00
Kidney	39	1.40	1	0.87	6	3.87*
Prostate	284	1.14*	18	1.64	15	1.10
Digestive system						
Splenic flexure	9	2.21*	2	9.91*	0	0.00
Cecum	50	1.79*	0	0	2	1.72
Transverse colon	20	1.79*	1	2.64	0	0.00
Colon excluding rectum	170	1.47*	6	1.45	13	1.84
Large intestine, NOS	10	1.37	0	0	3	7.91*
Stomach	22	0.92	1	0.76	9	2.30*
Descending colon	6	0.91	0	0	4	7.38*
Respiratory system						
Lung and bronchus	384	2.03*	20	2.73*	20	1.74*
Nervous system						
Brain	21	1.84*	0	0.00	1	2.37

*, P<0.05. UTUC, upper-tract urothelial carcinoma; O, observed number of cases; SIR, standardized incidence ratio (ratio of observed to expected number of second malignancies); NOS, not otherwise specified.

(III) Gender. The overall risk of a second cancer was significantly increased in both males and females (*Table 3*). Similarly, the risk of a SPM was highest in the ureter (SIR: 17.71, 42.20) in these two groups, followed by urinary bladder and renal pelvis cancer (SIR: 13.15 and 10.50; 33.72 and 7.36, respectively). In addition, the risk of a second cancer in the cecum, lung and bronchus were increased in both gender (SIR: 1.72 and 1.84; 1.74 and 1.74, respectively).

Baseline characteristics of patients

A total of 1,242 cases were randomly divided into a training set (n=870) and a validation set (n=372). No significant differences (P>0.05) were observed in age at UTUC diagnosis, race, gender, marital status, UTUC information (site, grade, laterality, SEER historic stage, therapy information) and SPM information (site, histologic type, grade, SEER historic stage, therapy information) between the two sets (*Table 4*).

Prognostic factors for SPM OS

In order to research the associated factors with the OS, we used univariate and multivariate Cox regression analyses (*Table 5*). Univariate Cox regression analysis demonstrated that age, race, UTUC grade, SEER historic stage, SPM site, histologic type, grade, SEER historic stage, chemotherapy

Table 3 Effect of gender on the risk of second primary cancers in UTUC

Site of second malignancy	Man		Woman	
	O	SIR	O	SIR
All sites	2,170	2.33*	1130	2.79*
All solid tumors	2,072	2.51*	5	3.50*
Urinary system				
Ureter	34	17.71*	559	42.20*
Urinary bladder	1,001	13.15*	21	33.72*
Renal pelvis	28	10.50*	8	7.36*
Penis	6	3.97*	0	0.00
Kidney	37	1.60*	9	1.20
Prostate	317	1.16*	0	0.00
Digestive system				
Small intestine	8	2.34*	1	0.60
Hepatic flexure	10	2.31*	2	0.78
Transverse colon	16	2.18*	5	1.02
Splenic flexure	6	1.94*	5	3.50*
Cecum	30	1.72*	22	1.74*
Colon excluding rectum	131	1.65*	58	1.22
Sigmoid colon	36	1.47*	9	0.82
Stomach	17	0.79	9	2.30*
Respiratory system				
Lung and bronchus	277	1.84*	20	1.74*
Nervous system				
Brain	15	1.80*	7	1.90

*, P<0.05. UTUC, upper-tract urothelial carcinoma; O, observed number of cases; SIR, standardized incidence ratio (ratio of observed to expected number of second malignancies).

and surgery were associated with the OS. Next, multivariate Cox regression analysis revealed age, race, gender, UTUC SEER historic stage, surgery, SPM site, histologic type, grade, SEER historic stage were independent prognostic factors for the OS of SPM.

Construction and validation of OS nomogram

According to the results of univariate and multivariate Cox analyses, we chose the factors with P value <0.05 and readily available in clinical practice to establish a nomogram to predict the 3- and 5-year survival rate (*Figure 2*). Eleven clinical indicators, including age, race, gender, UTUC SEER historic stage, surgery, chemotherapy, SPM site, histologic type, grade, SEER historic stage and latency months were enrolled in our nomogram. In order to evaluate the discriminative ability of the nomogram constructed by us, we calculated the C-index in the training set (0.72, 95% CI: 0.70–0.74) and validation set (0.71, 95% CI: 0.67–0.75). The ROC was plotted and AUC was analyzed for both the training set and validation set (*Figure 3*). The AUCs in the training set used for 3- and 5-year OS predication were 0.73 and 0.723, respectively. In the validation set, values of AUCs for 3- and 5-year OS predication were 0.737 and 0.733. Both the C-index and the ROC indicated that the nomogram we constructed well in

Table 4 Characteristics of SPMs patients after UTUC

Variable	Training set (n=870)	Validation set (n=372)	P value
Age at UTUC diagnosis (years)	69.5±11.0	69.7±10.7	0.85
Latency months	25.1±28.1	24.3±28.5	0.28
Race			0.22
White	753 (86.6)	335 (90.1)	
Black	45 (5.2)	13 (3.5)	
Other	72 (8.3)	24 (6.5)	
Gender			0.13
Man	531 (61.0)	210 (56.5)	
Woman	339 (39.0)	162 (43.5)	
Marital status at UTUC diagnosis			0.58
Unmarried	81 (9.3)	31 (8.3)	
Married	789 (90.7)	341 (91.7)	
UTUC site			0.67
Ureter	308 (35.4)	127 (34.1)	
Renal pelvis	562 (64.6)	245 (65.9)	
UTUC grade			0.38
I	66 (7.6)	29 (7.8)	
II	267 (30.7)	114 (30.6)	
III	282 (32.4)	136 (36.6)	
IV	255 (29.3)	93 (25.0)	
Laterality			0.63
Right	448 (51.5)	186 (50.0)	
Left	422 (48.5)	186 (50.0)	
UTUC SEER historic stage			0.55
Localized	352 (40.5)	140 (37.6)	
Regional	483 (55.5)	217 (58.3)	
Distant	15 (1.7)	9 (2.4)	
Unstaged	20 (2.3)	6 (1.6)	
UTUC radiation			0.70
No	852 (97.9)	363 (97.6)	
Yes	18 (2.1)	9 (2.4)	
UTUC chemotherapy			0.92
No	799 (91.8)	341 (91.7)	
Yes	71 (8.2)	31 (8.3)	

Table 4 *(continued)*

Table 4 *(continued)*

Variable	Training set (n=870)	Validation set (n=372)	P value
UTUC surgery			0.82
No	23 (2.6)	9 (2.4)	
Yes	847 (97.4)	363 (97.6)	
SPM site			0.86
Bladder	628 (72.2)	275 (73.9)	
Lung and bronchus	62 (7.1)	28 (7.5)	
Breast	34 (3.9)	17 (4.6)	
Kidney, renal pelvis and ureter	42 (4.8)	16 (4.3)	
Colon	23 (2.6)	9 (2.4)	
Others	81 (9.3)	27 (7.3)	
SPM histologic type			0.85
Transitional cell	647 (74.4)	282 (75.8)	
Adenoma	89 (10.2)	31 (8.3)	
Squamous cell	39 (4.5)	15 (4.0)	
Intraductal	30 (3.4)	14 (3.8)	
Others	65 (7.5)	30 (8.1)	
SPM grade			0.26
I	121 (13.9)	63 (16.9)	
II	329 (37.8)	121 (32.5)	
III	239 (27.5)	110 (29.6)	
IV	181 (20.8)	78 (21.0)	
SPM SEER historic stage			0.73
Localized	677 (77.8)	284 (76.3)	
Regional	130 (14.9)	54 (14.5)	
Distant	37 (4.3)	20 (5.4)	
Unstaged	26 (3.0)	14 (3.8)	
SPM radiation			0.61
No	827 (95.1)	351 (94.4)	
Yes	43 (4.9)	21 (5.6)	
SPM chemotherapy			0.75
No	747 (85.9)	322 (86.6)	
Yes	123 (14.1)	50 (13.4)	
SPM surgery			0.38
No	95 (10.9)	47 (12.6)	
Yes	775 (89.1)	325 (87.4)	

Data are presented as mean ± standard deviation or n (%). SPM, second primary malignancy; UTUC, upper-tract urothelial carcinoma; SEER, Surveillance, Epidemiology, and End Results.

Table 5 Univariate and multivariate Cox analysis of SPMs patients after UTUC in the training and validation sets

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at UTUC diagnosis				
<60 years	Reference	–	Reference	–
≥60, <70 years	1.4 (1.1–1.7)	0.12	1.3 (1.0–1.6)	0.06
≥70, <80 years	3.5 (2.1–6.0)	<0.001	2.9 (1.7–4.8)	<0.001
≥80 years	4.8 (3.1–7.3)	<0.001	4.9 (3.2–7.8)	<0.001
Race				
White	Reference	–	Reference	–
Black	0.8 (0.6–1.1)	0.15	1.1 (0.8–1.6)	0.44
Other	0.7 (0.5–0.9)	0.004	0.6 (0.5–0.9)	0.004
Gender				
Man	Reference	–	Reference	–
Woman	0.9 (0.8–1.1)	0.20	0.8 (0.7–0.9)	0.004
Marital status at UTUC diagnosis				
Unmarried	Reference	–	Reference	–
Married	1.2 (0.9–1.5)	0.19	0.9 (0.7–1.2)	0.55
UTUC site				
Ureter	Reference	–	Reference	–
Renal pelvis	1.0 (0.9–1.2)	0.90	1.1 (0.9–1.2)	0.50
UTUC grade				
I	Reference	–	Reference	–
II	0.8 (0.6–1.1)	0.18	0.8 (0.6–1.1)	0.25
III	1.2 (0.9–1.6)	0.13	1.1 (0.8–1.5)	0.58
IV	1.3 (1.0–1.8)	0.04	1.0 (0.7–1.4)	0.97
Laterality				
Right	Reference	–	Reference	–
Left	0.9 (0.8–1.0)	0.10	0.9 (0.8–1.0)	0.17
UTUC SEER historic stage				
Localized	Reference	–	Reference	–
Regional	1.5 (1.3–1.7)	<0.001	1.2 (1.0–1.4)	0.01
Distant	3.3 (2.1–5.2)	<0.001	2.3 (1.4–3.8)	<0.001
Unstaged	1.3 (0.8–2.1)	0.23	0.9 (0.6–1.5)	0.77
UTUC radiation				
No	Reference	–	Reference	–
Yes	1.4 (0.9–2.1)	0.18	1.0 (0.6–1.6)	0.87
UTUC chemotherapy				
No	Reference	–	Reference	–
Yes	1.3 (1.0–1.6)	0.057	1.3 (1.0–1.7)	0.09

Table 5 *(continued)*

Table 5 *(continued)*

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
UTUC surgery				
No	Reference	–	Reference	–
Yes	0.7 (0.5–1.1)	0.11	0.6 (0.4–0.9)	0.03
SPM site				
Bladder	Reference	–	Reference	–
Lung and bronchus	2.0 (1.6–2.6)	<0.001	0.9 (0.5–1.5)	0.67
Breast	0.6 (0.4–0.9)	0.02	0.6 (0.2–1.3)	0.19
Kidney, renal pelvis and ureter	1.0 (0.7–1.4)	0.95	0.7 (0.4–1.0)	0.08
Colon	1.4 (0.9–2.1)	0.13	0.7 (0.4–1.4)	0.37
Others	2.1 (1.6–2.6)	<0.001	1.1 (0.7–1.8)	0.76
SPM histologic type				
Transitional cell	Reference	–	Reference	–
Adenoma	1.7 (1.4–2.2)	<0.001	1.6 (1.0–2.6)	0.07
Squamous cell	2.1 (1.5–2.9)	<0.001	1.3 (0.7–2.3)	0.39
Intraductal	0.6 (0.4–1.0)	0.04	1.0 (0.4–2.3)	0.93
Others	1.6 (1.2–2.0)	<0.001	1.3 (0.8–2.0)	0.31
SPM grade				
I	Reference	–	Reference	–
II	1.4 (1.1–1.7)	0.008	1.3 (1.0–1.6)	0.03
III	2.0 (1.6–2.5)	<0.001	1.6 (1.2–2.0)	<0.001
IV	1.9 (1.5–2.4)	<0.001	1.6 (1.2–2.0)	0.001
SPM SEER historic stage				
Localized	Reference	–	Reference	–
Regional	2.1 (1.8–2.5)	<0.001	2.2 (1.7–2.7)	<0.001
Distant	6.2 (4.7–8.3)	<0.001	6.3 (4.4–8.9)	<0.001
Unstaged	2.3 (1.6–3.3)	<0.001	1.5 (1.0–2.3)	0.06
SPM radiation				
No	Reference	–	Reference	–
Yes	1.2 (0.8–1.6)	0.37	0.8 (0.6–1.2)	0.32
SPM chemotherapy				
No	Reference		Reference	
Yes	1.3 (1.1–1.6)	0.007	0.9 (0.7–1.2)	0.52
SPM surgery				
No	Reference	–	Reference	–
Yes	0.6 (0.5–0.7)	<0.001	0.8 (0.7–1.1)	0.18
Latency months	1.0 (1.0–1.0)	0.53	1.0 (1.0–1.0)	0.87

SPM, second primary malignancy; UTUC, upper-tract urothelial carcinoma; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.

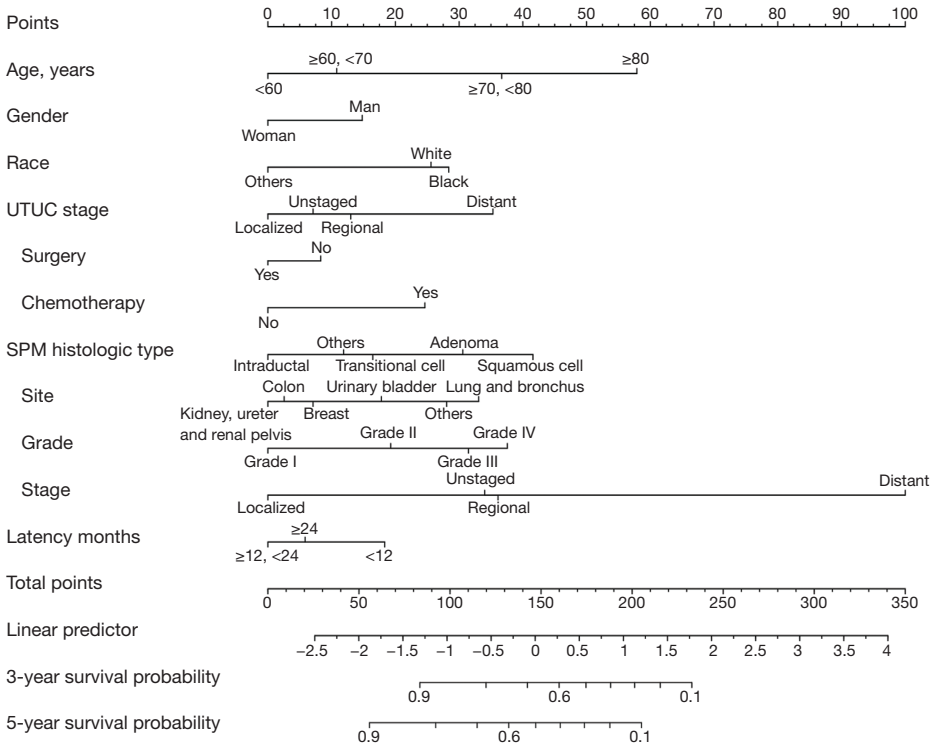

Figure 2 Nomogram to predict 3- and 5-year survival for SPM patients. UTUC, upper-tract urothelial carcinoma; SPM, second primary malignancy.

predicting the OS of SPM.

In order to access the accuracy of our nomogram, the calibration plots were used to evaluate the conformity of our predictions with actual observations. *Figure 4* shows an appropriate agreement in the training set and a great agreement in validation set between the 3- and 5-year OS predictions and actual outcomes.

Discussion

In a study published in *JAMA* by Sung *et al.* (14), it was noted that various types of first primary cancers may increase the likelihood of subsequent primary cancers and could be associated with higher mortality rates. Despite this, there is a scarcity of research focusing on second primary cancers following UTUC. To enhance our understanding of SPMs after UTUC, we examined the SIR of SPMs following the diagnosis of UTUC across different subgroups. Additionally, we developed a nomogram to forecast the 3- and 5-year survival rates of SPMs subsequent to UTUC, aiming to provide valuable insights into the prognosis of these patients.

Given the relatively low incidence of UTUC, it can be challenging for a single institution to amass a substantial patient cohort for in-depth analysis. However, leveraging the SEER database, a reputable public resource, has enabled the examination of cancer data over recent decades, facilitating the analysis of incidence and prognostic outcomes concerning various SPMs following UTUC (19,20). Our study revealed that 30.23% of UTUC patients developed one or more new primary tumors, a notably higher proportion compared to approximately 10% in KCa and 3.69% in PCa patients with SPMs (9,13). Solid tumors constituted the majority (95.30%) of all SPMs, primarily affecting the urinary, digestive, and respiratory systems. Specifically, the ureter, urinary bladder, renal pelvis, lung, and bronchus exhibited consistent increases in the risk of second malignancies across all subgroups.

Regarding SPMs in the digestive system, there was a significantly elevated risk among patients aged 40 to 60 years, Black individuals, and males, aligning with findings from Chakraborty *et al.*'s study (13). However, limited research has explored the causal relationship between demographic parameters and SPM sites, warranting further investigation.

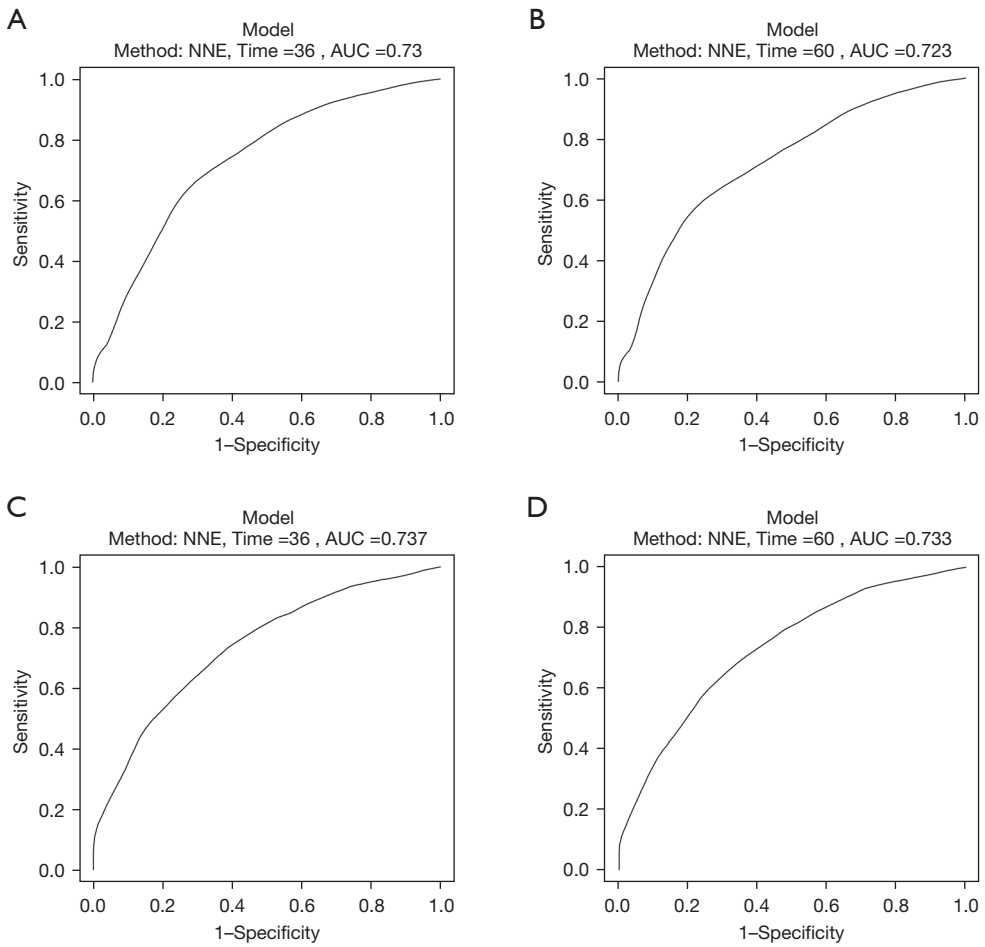

Figure 3 ROC analysis to assess 3-year (A) and 5-year (B) survival for SPM patients in the training set; the ROC curve to assess 3-year (C) and 5-year (D) survival in the validation set. Time =36: 36 months (3 years); time =60: 60 months (5 years). NNE, nearest neighbor estimation; AUC, area under the curve; ROC, receiver operating characteristic; SPM, second primary malignancy.

The data analysis results suggest the importance of vigilant monitoring for urinary and respiratory system tumors—particularly in UTUC patients as their first primary cancer—to detect potential subsequent primary cancers and enhance prognosis. Furthermore, certain demographic groups may benefit from long-term surveillance for digestive system tumors to optimize patient outcomes.

The relationship between the first primary cancer and subsequent primary cancers remains a topic of uncertainty. One prevailing hypothesis suggests a shared etiology between the two primary cancers, indicating that they may mutually influence each other's occurrence. This hypothesis gains more credibility when the incidence of one cancer increases after the diagnosis of the other (i.e., when A precedes B, the risk of B rises, and vice versa). In our study, patients initially diagnosed with UTUC exhibited an elevated likelihood of developing other primary cancers within the urinary system. Similarly, KCa and PCa patients also demonstrated a higher incidence of UTUC as a second primary malignancy (21,22). Furthermore, certain primary cancers in the digestive system were associated with a subsequent occurrence of UTUC (23). The findings from these studies suggest a potential underlying pathogenic link among these cancers, supporting the concept of reciprocal risk. While the exact mechanisms remain unclear, hypotheses include environmental factors [such as smoking or alcohol consumption as contributors to various tumor types (24)] and genetic risk factors [e.g., mismatch-repair deficiency associated with increased risks for multiple cancers (25)]. Further research is needed to elucidate

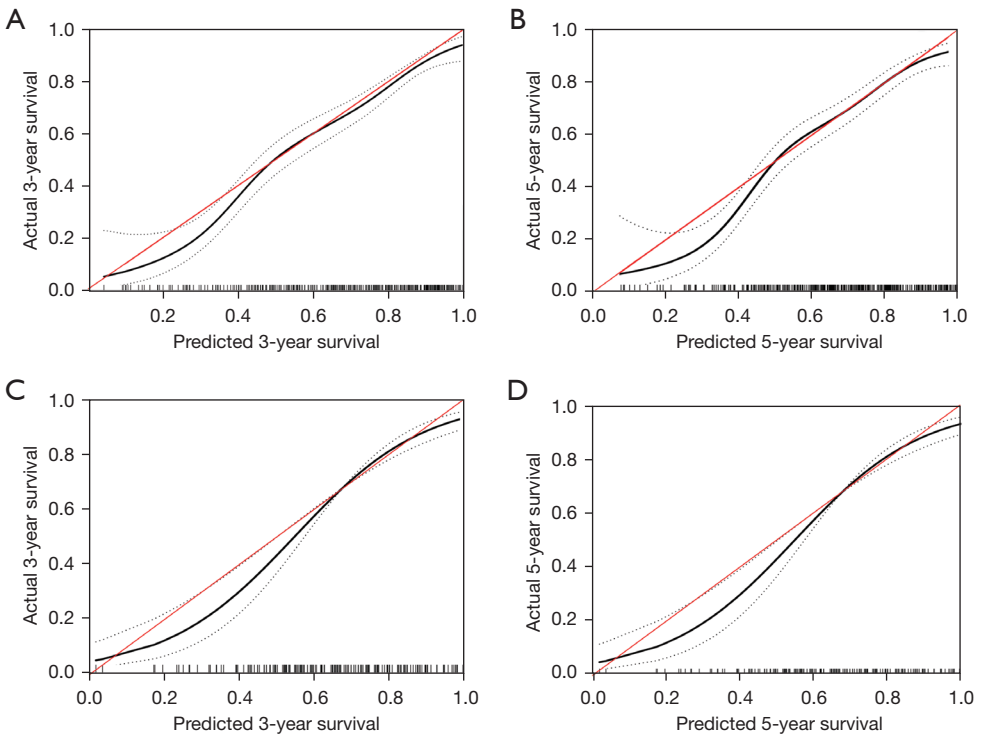

Figure 4 The calibration curve to evaluate the 3-year (A) and 5-year (B) survival for SPM patients in training set; the calibration curve to evaluate the 3-year (C) and 5-year (D) survival for SPMs patients in the validation set. Black curve: nomogram-predicted OS is plotted on the x-axis; actual OS is plotted on the y-axis. The imaginary line (red line) indicates a perfect calibration model in which the predicted probabilities are identical to the actual survival outcomes. SPM, second primary malignancy; OS, overall survival.

the precise mechanisms driving these associations and to deepen our understanding of the complex interplay between different primary cancers.

Numerous studies have utilized nomograms to assess the prognosis of second primary cancers (9,26,27); however, a similar approach has not been reported in the literature for evaluating the prognosis of UTUC. To investigate the prognosis of SPMs following UTUC, we identified 11 parameters—including age, gender, race, UTUC stage, surgical intervention, chemotherapy details, SPM histologic type, SPM site, SPM grade, SPM stage, and latency months—to predict the prognosis of SPM patients. Our nomogram demonstrated strong performance in predicting the survival outcomes of SPM patients.

Despite the valuable insights gained from our study, there are several limitations to consider. Firstly, the retrospective nature of our cohort warrants further validation through prospective, randomized clinical trials to corroborate our findings. Secondly, the availability of metastatic information was limited to data between 2000 and 2016, and the predominance of White patients in our cohort suggests the need for validation in diverse populations, such as an Asian cohort. Additionally, important confounding factors like smoking status, quality performance status, laboratory parameters, tumor volume, comorbidities, index data and other detailed treatment information (such as adjuvant bacillus Calmette-Guerin and intravesical mitomycin C) were not captured in our database, highlighting the need for more comprehensive data collection in future studies. Lastly, the complex relationship between first primary cancer and subsequent primary cancer remains incompletely understood [e.g., unmarried status may reduce survival time in UTUC patients (28), but it did not have an impact on SPM patients in this study], necessitating ongoing long-term research efforts for deeper insights.

Conclusions

Our study represents the first comprehensive analysis of second primary malignancy incidence in UTUC patients

using the SEER database and introduces a nomogram for predicting SPM prognosis. While our model showed promising performance in assessing SPM survival outcomes, its efficacy should be further evaluated through multi-center research studies to validate its clinical utility.

Acknowledgments

The authors express thanks to the SEER website for providing us with the downloaded data.
Funding: This research was funded by the Natural Science Foundation of Zhejiang Province, China (No. LY24H260001).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-515/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-515/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-515/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Zhang X, Chen W, Li C, Wan X, Xu P, Zhang T. A nomogram for overall survival of second primary cancers following upper-tract urothelial carcinoma: a SEER population-based study. Transl Cancer Res 2024;13(8):4131-4145. doi: 10.21037/tcr-24-515

