Original Article

Survival outcomes in prostate cancer patients with a prior cancer

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Background: To shed light on the survival outcomes of prostate cancer (PCa) patients diagnosed after a prior cancer and identify prognostic factors for overall survival (OS) and cancer-specific survival (CSS) in PCa patients.

Methods: In the primary group, a total of 1,778 PCa patients with a prior cancer were identified in the Surveillance, Epidemiology, and End Results (SEER) database from 2005 to 2015, retrospectively. Baseline characteristics and causes of death (COD) of these patients were collected and compared. In the second group, a total of 10,296 PCa patients [5,148 patients with PCa as the only malignancy and 5,148 patients with PCa as their second primary malignancy (SPM)] diagnosed between 2010 and 2011 were extracted to investigate the impact of prior cancers on survival outcomes.

Results: In PCa patients with a prior cancer, the most common type of prior cancer was from gastrointestinal system (29.92%), followed by urinary system (21.37%). Patients were more likely to die of the prior caner, and those with prior cancer from respiratory system had the worst survival outcomes. Moreover, the overall ratios in patients with stage (PCa) I–II and III–IV diseases were 0.21 and 1.65, indicating that patients with higher stage diseases were more likely to die of PCa. In the second group, patients with PCa as the SPM had worse OS than those with PCa as the first primary cancer. Lastly, prognostic factors for OS and CSS in PCa patients were explored.

Conclusions: PCa remains to be an important COD for patients with a prior malignancy, especially for those with high-stage diseases. PCa patients with a prior cancer had worse survival outcomes than those without.

Keywords: Prostate cancer (PCa); Surveillance, Epidemiology, and End Results (SEER); survival; prior cancer; prognostic factor

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Introduction

Prostate cancer (PCa) is one of the most common malignancies in genitourinary system globally (1). In 2020, the estimated newly diagnosed cases and deaths are 191,930 and 33,330 in the United States (2). In the United States and some European countries, the incidence rate of PCa has exceeded lung cancer to be the leading cause

of male malignancies. Even though, disease progression of PCa could be well controlled by surgery, radiotherapy and endocrine therapy. It was reported that the 5-year overall survival (OS) rate for PCa was up to 90% in many institutions (3-5).

Overall, the 5-year relative survival rate of cancer survivors has been increasing during the past decades (up to 66%) due to the improvement in cancer detection and treatment (6,7). As a result, the number of cancer survivors is increasing recently. Statistically, the overall estimated cancer survivors in men and women were 7,377,100 and 8,156,120 in 2016 in the United States (8), and this population showed an annual growth trend of 2% (9). Considering the increasing number of cancer survivors, the probability of developing a second primary malignancy (SPM) also increased accordingly (10). Hence, many patients may develop tumors of multiple organs or systems during their lifetime (11).

An SPM is defined as a cancer which arises in a new organ or tissue independently at least 2 months after the initial diagnosis of the prior primary malignancy (12-14). Previous studies have already discussed the critical role of SPM in many cancer types, such as breast cancer (11,15,16), Hodgkin lymphoma (17), cervical cancer (18) and so on. He *et al*. (19) found that there was an excessive risk of developing an SPM in young-onset (age ≤50 years old) colorectal cancer survivors. Additionally, the risk of developing SPMs was reversely correlated to age. Donin *et al*. (20) demonstrated that about 1 in 12 patients would develop a second malignancy during their lifetime, and the most common type of SPMs was lung cancer. Moreover, they discovered that more than half of patients with two primary cancers died of the second malignancy totally.

Most previous studies have focused on the risk of developing an SPM after a known tumor. However, the risk of a specific tumor as an SPM in patients with a prior cancer and survival outcomes for these patients have not been widely discussed. Ji *et al*. (12) found that the most common type of prior cancer in breast cancer patients was gynecologic cancer, followed by gastrointestinal cancer. Besides, treatment for breast cancer significantly decreased the risk of breast cancer specific morality. As PCa was traditionally considered to be an indolent cancer, many cancer survivors or clinicians may not feel it worth treating after weighing the risks and benefits when it was diagnosed after another malignancy (21), and there were rare studies on this topic. Hence, we developed this study on the basis of the Surveillance, Epidemiology, and End Results (SEER) database to achieve a deeper understanding of the survival patterns and risk factors for patients with subsequent PCa. Additionally, we present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tau-20-897).

Methods

All the raw data utilized in this study were retrospectively extracted from the SEER database. SEER registry is a public database supported by the US National Cancer Institute to collect relevant information of cancer patients, including demographic characteristics, incidence rates, treatments and survival outcomes. In the beginning, there were only nine regions participated in this project, while approximately 30% of the US population are covered in the database till now. In our study, we signed the user agreement and gained access to the database with the username of 15440-Nov2018. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Additionally, this study was exempt by Institutional Review Board (IRB) approval because the original data were from a public database and individual consent for this retrospective analysis was waived.

Primary group

In the primary group, PCa patients with a prior cancer were extracted from the SEER 9 registry using the "multiple primary-standard incidence ratio" function via the SEER*Stat software (Version 8.3.6; NCI, Bethesda, USA). The initial inclusion criteria were as follows: (I) PCa was the second malignancy of each patient, (II) patients with active follow-up after cancer diagnosis, (III) year of PCa diagnosis was from 2005 to 2015. Additionally, the exclusion criteria were as below: (I) patients with missing or unknown data [race =13, prostate-specific antigen (PSA) =2,586, Gleason score =3,336, stage =2,334, T stage =255, N stage =17, M stage =1, cause of death (COD) =1 and the administration of surgery =5], (II) patients with three or more malignancies in total (n=3), (III) diagnosed by autopsy or death certificate only, (IV) diagnosis interval between PCa and the prior cancer was less than two months.

Afterwards, baseline characteristics and clinicopathological data were extracted for each patient, including age at diagnosis, race, histological type, marital status, types of the prior cancers, American Joint Committee on Cancer (AJCC) 6th TNM stage, Gleason score, PSA level, diagnosis intervals between two cancers, administration of surgery, COD and

follow-up. In this study, age at diagnosis was divided into <65 and ≥65 years old. Race was classified into Black, White and Other (including American Indian/AK Native, Asian/Pacific Islander). PSA was categorized into ≤4, 4–10, 10–20 and >20 ng/mL. Gleason score fell into three categories: ≤6, 7 and 8–10. Furthermore, prior cancers were classified based on different systems, such as gastrointestinal system, urinary system, respiratory system, oral cavity and so on. Finally, for patients who died during the follow-up, COD were categorized into PCa, the prior cancer and other causes.

Firstly, the 5 most common types of the prior cancers were identified according to the frequency of occurrence, and Kaplan-Meier (KM) analyses were performed to probe the survival impacts of these cancers. Then, we calculated the percentage of PCa-related deaths and prior cancer-related deaths in different cancer types. Furthermore, basic and pathological outcomes between patients who died of PCa and those died of the prior cancer were compared. Finally, the ratio of PCa deaths to prior cancer deaths was obtained for each prior cancer type, further stratified by PCa TNM stage.

Second group

In the second group, patients with histologically confirmed, stage I–III PCa from 2010 to 2011 were identified from the SEER 18 registry utilizing the "case listing session" tool. The enrolled patients were grouped into primary prostate cancer (PPC) and subsequent prostate cancer (SPC) according to whether there was a prior cancer before PCa diagnosis. The propensity score matching (PSM) method was developed with a ratio of 1:1 to balance the baseline characteristics. Comparisons between patients with PPC and SPC in survival outcomes were made to explore the impact of the prior cancers on survival. Finally, uni- and multivariate Cox regression analyses were constructed to identify the prognostic factors in PCa patients.

Statistical analysis

Student's *t*-test and chi-square analyses were used for the comparisons in baseline characteristics and clinicopathological data, respectively. Survival outcomes were compared utilizing the KM analyses. The whole analysis was performed via SPSS 23.0 software (SPSS Inc, Chicago, IL, USA) and R software (Version 3.4.1). A two-sided P<0.05 was considered to be statistically significant.

Results

Baseline characteristics of the primary group

A total of 1,778 eligible patients were included in the primary group. The median (interquartile range, IQR) ages at diagnosis of the prior caner and PCa were 64 [58–70] and 68 [63–74] years old. The median (IQR) diagnosis interval between two cancers was 40.5 [19–66] months. Overall, the majority of enrolled patients had their cancer diagnosed at earlier TNM stage (I–II: 76.94% and 86.33% for the prior cancer and PCa, respectively). Besides, the median (IQR) follow-up after PCa diagnosis was 42 (23.00–63.75) months (*Table 1*). In the primary group, the 5 most common types of prior cancer were from gastrointestinal system (29.92%), urinary system (21.37%), skin (19.97%), respiratory system (11.59%) and oral cavity and pharynx (7.31%) (*Table 2*). On the whole, a total of 299 patients died during the follow-up, and patients with prior cancer of respiratory system had the highest mortality (30.58%).

Survival outcomes in the primary group

As shown in *Figure 1*, OS was significantly different in patients with different types of prior cancer (P<0.001). PCa patients with prior cancers of respiratory system had the worst survival outcomes [10-year OS: 59.1%, 95% confidence interval (CI), 50.9–68.8%], while those with prior cancers of skin owned the longest OS (10-year OS: 85.8%, 95% CI, 80.9–90.9%).

On COD, 38.13% of patients died of the prior cancer and 16.05% of patients died of PCa (*Figure 2A*). When stratified by cancer types, we found that in patients with cancers of respiratory system, the prior cancer-related death rate was the highest (44.44%) and the PCa-related death rate was relatively lower (12.70%). The highest PCa-related death rate (19.64%) was found in patients with prior urological cancers. Hence, conclusions could be drawn that died of prior cancers was the main COD in these patients. Then, we compared the ratio of PCa deaths to prior cancer deaths in patients. As shown in *Figure 2B*, the overall ratios in patients with stage (PCa) I–II and III–IV diseases were 0.21 and 1.65, indicating that patients with higher stage diseases were more likely to die of PCa. Analogously, similar trends were detected in the majority of cancer types. However, in patients with prior cancers of respiratory system, they may be more likely to die of the first primary malignancy regardless of the PCa TNM stage (the ratio was 0.22 and 0.60 in stage I–II and III–IV diseases, respectively).

Table 1 Demographic and clinical factors of PCa patients with a prior cancer (n=1,778)

Variables	At prior cancer diagnosis	At PCa diagnosis
Age, year		
Mean (SD)	64.31 (8.64)	68.09 (8.33)
Median (IQR)	64.00 (58.00, 70.00)	68.00 (63.00, 74.00)
Race, n (%)		
White	1,415 (79.58)	1,415 (79.58)
Black	277 (15.58)	277 (15.58)
Other	86 (4.84)	86 (4.84)
Marital status, n (%)		
Married	1,411 (79.36)	1,400 (78.74)
Unmarried	189 (10.63)	167 (9.39)
Unknown	178 (10.01)	211 (11.87)
TNM stage, n (%)		
I–II	1,368 (76.94)	1,535 (86.33)
III–IV	410 (23.06)	243 (13.67)
Interval between diagnoses, months		
Mean (SD)	45.46 (31.83)	
Median (IQR)	40.50 (19.00, 66.00)	
Time from PCa diagnosis to death or end of study months		
Mean (SD)		44.09 (23.42)
Median (IQR)		42.00 (23.00, 63.75)

IQR, interquartile range; PCa, prostate cancer; SD, standard deviation.

Table 2 Classification of the prior malignancy, stratified by system

Systems	N (%)	Detailed cancers	Death, n (%)
Gastrointestinal system	532 (29.92)	Esophagus, stomach, liver, colon, rectum and so on	94 (17.67)
Urinary system	380 (21.37)	Bladder, kidney, renal pelvic and ureter	56 (14.74)
Skin	355 (19.97)	Melanoma and other non-epithelial skin cancers	39 (10.99)
Respiratory system	206 (11.59)	Lung, bronchus, larynx and nose	63 (30.58)
Oral cavity and pharynx	130 (7.31)	Tongue, tonsil, mouth and pharynx	33 (18.86)
Others	175 (9.84)	Others	14 (8.00)
Overall	1,778 (100.00)	All of the above	299 (16.82)

In *Table 3*, we found that age at PCa diagnosis (P<0.001), the rates of PSA >20 ng/mL (P<0.001), Gleason score 8–10 (P<0.001), TNM stage III–IV (PCa) diseases (P<0.001) and Tx/N1/Mx or Tx/Nx/M1 (PCa) diseases (P=0.026) were significantly higher in patients who died of PCa when compared with those who died of the prior cancer. Furthermore, the metastatic rate (P<0.001) of the prior cancer was significantly higher in patients who died of a prior cancer.

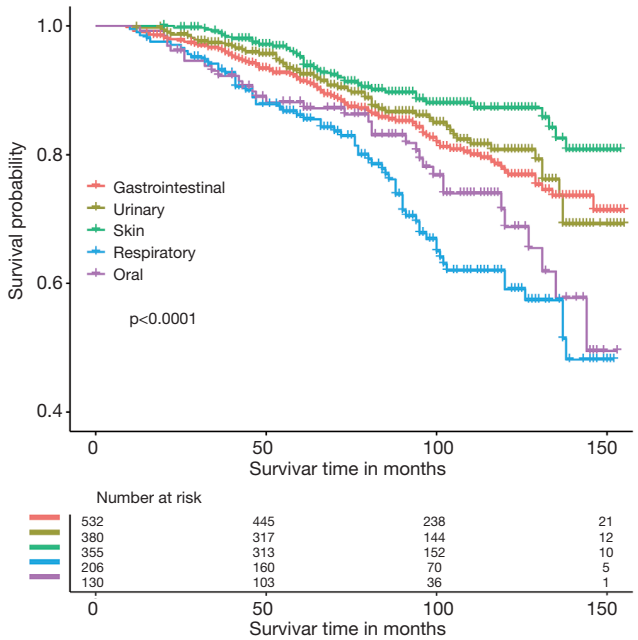

Figure 1 Overall survival of prostate cancer patients with a prior cancer.

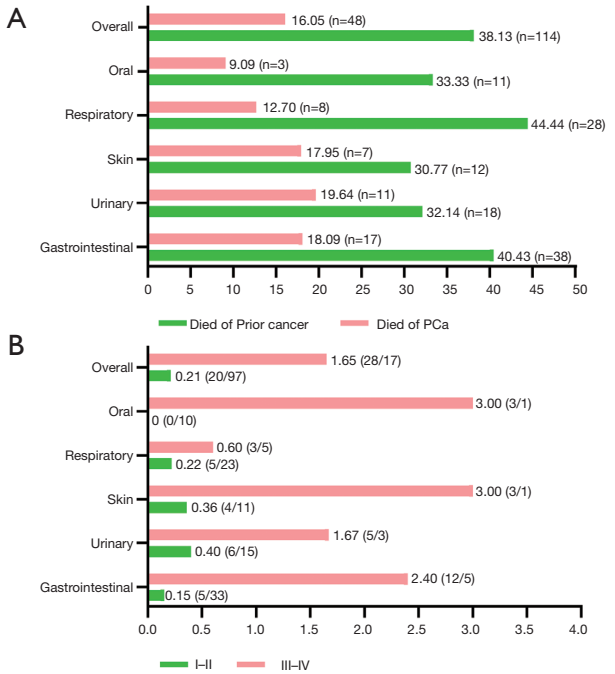

Figure 2 Survival outcomes among patients with different types of prior cancer. (A) The percentage of deaths related to prostate cancer or prior cancer among patients with different types of prior cancer, (B) ratio of prostate cancer deaths to prior cancer deaths.

Survival of patients with PCa as the prior cancer or subsequent primary cancer in the second group

A total of 72,173 patients were enrolled in the second group, including 67,025 patients had PCa as their first primary malignancy and 5,148 patients had PCa as the SPM. As shown in *Table 4*, significant differences were detected between two groups in many variables, including age at diagnosis, race, PSA level, Gleason score, TNM stage, marital status, administration of surgery and radiotherapy (all P<0.05). To reduce the selection bias, a 1:1 PSM was developed and a total of 5,148 pairs of patients were eventually enrolled. As shown in *Figure 3A*,*B*, better survival outcomes were detected in patients with PPC when compared with those with SPC (P<0.05). After PSM, no significant difference was detected in prostate cancer-specific survival (PCSS) between two groups (P=0.66, *Figure 3C*), while significant shorter OS was found in patients with SPC when compared with those with PPC (P<0.001, *Figure 3D*). Lastly, uni- and multivariate Cox regression analyses were conducted to explore prognostic factors associated to OS and PCSS in PCa patients. Multivariate analysis revealed that age at diagnosis, Gleason score, PSA level, TNM stage and administration of surgery were risk factors for cancer-specific survival (CSS) (all P<0.05, *Table 5*). Similarly, age at diagnosis, race, Gleason score, PSA level, sequence of PCa (PPC *vs.* SPC) and administration of surgery were recognized as prognostic factors for OS (all P<0.05, *Table 6*).

Discussion

Nowadays, with the increase of cancer survivors, the risk of developing SPMs has also been increasing accordingly. Additionally, prior cancer played an important role in treatment strategies and clinical trials design (22). It was traditionally accepted that patients with prior cancers should be excluded in clinical trials, which may due to the assumption that prior cancers may impact the survival outcomes (23,24). Consequently, numerous patients with a prior cancer would be excluded from clinical trials, leading to worse accrual and generalizability of clinical trials (22). For example, up to about 20% of lung cancer patients were excluded from taking part in trails if following such a restrictive criterion (25). However, no convincing evidence has been proposed to support this exclusion criteria and address the actual effect of a prior malignancy on cancer survivors. Moreover, the standard incidence ratio of

Table 3 Clinical and demographic factors associated with prostate cancer death *vs.* prior cancer death

Characteristics	Died from prior cancer	Died from PCa	P value
Number of patients	114	48	
Age at PCa diagnosis, mean ± SD, year	70.97±8.61	77.29±9.07	<0.001
PCa treated, n (%)	22 (19.30)	13 (27.08)	0.272
Gleason score 8–10, n (%)	42 (36.84)	37 (77.08)	<0.001
PSA >20 ng/mL, n (%)	23 (20.18)	25 (52.08)	<0.001
PCa, TNM stage III–IV, n (%)	17 (14.91)	28 (58.33)	<0.001
Prior cancer, TNM stage III–IV, n (%)	45 (39.47)	9 (18.75)	0.011
PCa, Tx/N1/Mx or Tx/Nx/M1, n (%)	8 (7.02)	9 (18.75)	0.026
Prior cancer, Tx/N1-3/Mx or Tx/Nx/M1, n (%)	47 (41.23)	6 (12.50)	<0.001
Interval between diagnoses, mean ± SD, month	34.63±28.50	42.44±32.70	0.130
Kinds of the prior cancers, n (%)			0.683
Gastrointestinal system	38 (33.33)	17 (35.41)	
Urinary system	18 (15.79)	11 (22.92)	
Skin	12 (10.53)	7 (14.58)	
Respiratory system	28 (24.56)	8 (16.67)	
Oral cavity and pharynx	11 (9.65)	3 (6.25)	
Others	7 (6.14)	2 (4.17)	

PCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation.

Table 4 Baseline characteristics of patients with PPC or SPC from the SEER database 2010–2011

Variables	Data before PSM			Data after PSM		
	PPC, n (%)	SPC, n (%)	P value	PPC, n (%)	SPC, n (%)	P value
N	67,025	5,148		5,148	5,148	
Age (year)			<0.001			0.870
<45	427 (0.64)	18 (0.35)		15 (0.29)	18 (0.35)	
45–65	32,361 (48.28)	1,582 (30.73)		1,586 (30.81)	1,582 (30.73)	
≥65	34,237 (51.08)	3,548 (68.92)		3,547 (68.90)	3,548 (68.92)	
Race			<0.001			0.986
White	52,811 (78.79)	4,413 (85.72)		4,414 (85.74)	4,413 (85.72)	
Black	10,761 (16.06)	554 (10.76)		556 (10.80)	554 (10.76)	
Other	3,453 (5.15)	181 (3.52)		178 (3.46)	181 (3.52)	
Grade[1]			0.488			0.954
Grade I	873 (1.30)	61 (1.18)		59 (1.15)	61 (1.18)	
Grade II	27,759 (41.42)	2,087 (40.54)		2,082 (40.44)	2,087 (40.54)	
Grade III	38,300 (57.14)	2,994 (58.16)		2,999 (58.26)	2,994 (58.16)	
Grade IV	93 (0.14)	6 (0.12)		8 (0.16)	6 (0.12)	

Table 4 *(continued)*

Table 4 *(continued)*

Variables	Data before PSM			Data after PSM		
	PPC, n (%)	SPC, n (%)	P value	PPC, n (%)	SPC, n (%)	P value
Histology			0.314			0.785
Adenocarcinoma	66,726 (99.55)	5,120 (99.46)		5,122 (99.49)	5,120 (99.46)	
Non-adenocarcinoma	299 (0.45)	28 (0.54)		26 (0.51)	28 (0.54)	
TNM stage			<0.001			0.999
I	17,643 (26.32)	1,413 (27.45)		1,413 (27.45)	1,413 (27.45)	
II	42,331 (63.16)	3,289 (63.89)		3,288 (63.87)	3,289 (63.89)	
III	7,051 (10.52)	446 (8.66)		447 (8.68)	446 (8.66)	
PSA, ng/mL			<0.001			0.999
≤4	10,215 (15.24)	816 (15.85)		817 (15.87)	816 (15.85)	
4–10	43,021 (64.19)	3,148 (61.15)		3,149 (61.17)	3,148 (61.15)	
10–20	9,204 (13.73)	801 (15.56)		803 (15.60)	801 (15.56)	
>20	4,585 (6.84)	383 (7.44)		379 (7.36)	383 (7.44)	
Gleason score			<0.001			0.988
≤6	31,666 (47.25)	2,272 (44.13)		2,269 (44.08)	2,272 (44.13)	
7	26,257 (39.17)	2,006 (38.97)		2,003 (38.91)	2,006 (38.97)	
8–10	9,102 (13.58)	870 (16.90)		876 (17.02)	870 (16.90)	
Surgery			<0.001			0.897
No	38,930 (58.08)	3,645 (70.80)		3,639 (70.69)	3,645 (70.80)	
Yes	28,095 (41.92)	1,503 (29.20)		1,509 (29.31)	1,503 (29.20)	
Radiation			<0.001			0.921
No/unknown	40,946 (61.09)	2,915 (56.62)		2,910 (56.53)	2,915 (56.62)	
Yes	26,079 (38.91)	2,233 (43.38)		2,238 (43.47)	2,233 (43.38)	
Chemotherapy			0.371			0.297
No/unknown	66,883 (99.79)	5,134 (99.73)		5,139 (99.83)	5,134 (99.73)	
Yes	142 (0.21)	14 (0.27)		9 (0.17)	14 (0.27)	
Marital status			<0.001			0.919
Married	59,502 (88.78)	4,674 (90.79)		4,671 (90.73)	4,674 (90.79)	
Unmarried	7,523 (11.22)	474 (9.21)		477 (9.27)	474 (9.21)	

[1]Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated. SEER, Surveillance, Epidemiology, and End Results; PPC, primary prostate cancer; SPC, subsequent prostate cancer; PSA, prostate-specific antigen; PSM, propensity score matching; SD, standard deviation; SPC, subsequent primary cancer.

developing PCa after a prior cancer in the United States has been increasing in the past three decades (Figure S1). Considering that there are increasing cancer survivors develop PCa during the long-term follow up, it is necessary to investigate the survival outcomes of this population.

In this study, we found that the most common cancer type of prior cancers in PCa survivors was from gastrointestinal system. More patients died from their

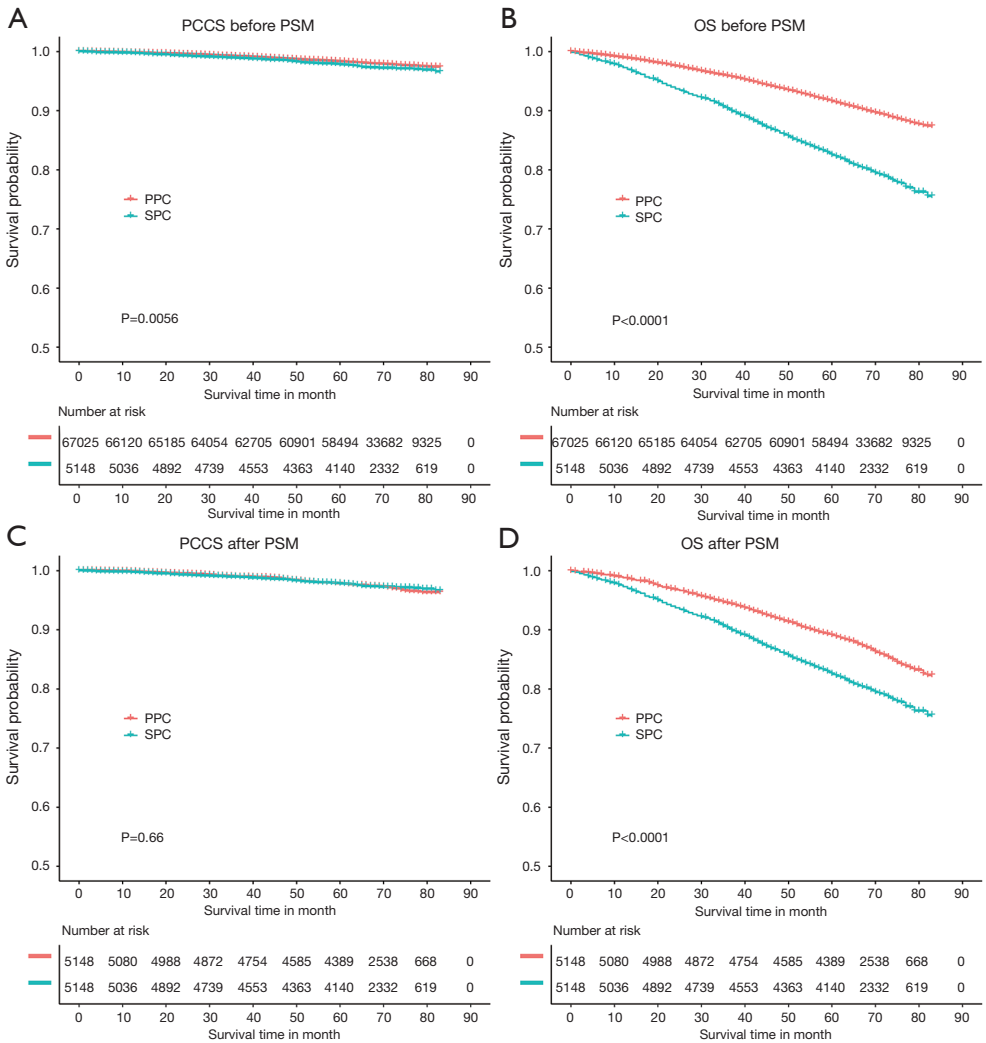

Figure 3 Kaplan-Meier survival curves of patients with prostate cancer as the second primary cancer or the prior cancer. (A,B) PCSS and overall survival before PSM; (C,D) PCSS and overall survival after PSM. PCSS, prostate cancer-specific survival; PSM, propensity score matching.

prior cancer rather than PCa (38.13% *vs.* 16.05%) with a median follow-up of 42 months, and this tendency existed in various systems. However, the ratio of PCa deaths to prior cancer deaths was greater than 1 in all systems except for respiratory system, suggesting that PCa remained to be an important COD in men with a prior caner, especially for those with stage III–IV PCa diseases. Nevertheless, in patients with a prior cancer of respiratory system, both patients and clinicians should focus on the treatment of the prior cancer rather than PCa, regardless of the stage of PCa. Certainly, PCa patients with prior cancer of respiratory system had the shortest OS, while those with prior cancers of skin owned the longest OS. Similarly, Ji *et al.* (12) reported that breast cancer patients with prior cancers of lung had the worst OS, and those with prior melanoma had the best OS, with a median follow-up of 20.96 months. It was due to the fact that lung cancer was more lethal than many other cancers (26) and prior skin cancer in PCa patients could only affect the OS slightly. Laccetti *et al.* (24) demonstrated that the most common type of prior cancer in patients with locally advanced lung cancer was PCa (25%), and prior PCa did not adversely affect OS in those patients. They claimed that locally advanced lung cancer patients with a prior cancer should not be excluded from clinical

Table 5 Uni- and multivariate Cox regression model analysis of CSS

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age, year			<0.001			0.012
<65	Reference			Reference		
≥65	2.777	1.985–3.885	<0.001	1.562	1.104–2.211	0.012
Race			0.059			
White	Reference					
Black	0.598	0.371–0.965	0.035			
Other	0.612	0.272–1.376	0.235			
Grade[1]			<0.001			0.226
Grade I–II	Reference			Reference		
Grade III–IV	3.851	2.789–5.319	<0.001	1.548	0.763–3.137	0.226
Marital status			0.257			
Married	Reference					
Unmarried	0.764	0.479–1.217	0.257			
Gleason score			<0.001			<0.001
≤6	Reference			Reference		
7	1.956	1.351–2.830	<0.001	1.018	0.492–2.105	0.962
8–10	9.800	7.025–13.673	<0.001	3.363	1.600–7.063	0.001
PSA, ng/mL			<0.001			<0.001
≤4	Reference			Reference		
4–10	1.210	0.755–1.939	0.428	0.958	0.597–1.538	0.860
10–20	3.817	2.349–6.202	<0.001	2.028	1.225–3.356	0.006
>20	9.855	6.094–15.938	<0.001	3.613	2.180–5.989	<0.001
TNM stage			<0.001			0.070
I	Reference			Reference		
II	4.137	2.690–6.363	<0.001	1.300	0.690–2.452	0.417
III	5.245	3.125–8.804	<0.001	1.986	0.936–4.211	0.074
Histology			0.151			
Adenocarcinoma	Reference					
Non-adenocarcinoma	2.300	0.737–7.176	0.151			
Diagnosis			0.660			
PPC	Reference					
SPC	0.948	0.747–1.203	0.660			

Table 5 *(continued)*

Table 5 *(continued)*

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Surgery			<0.001			<0.001
No	Reference			Reference		
Yes	0.297	0.205–0.430	<0.001	0.366	0.239–0.561	<0.001

[1]Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated. CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; PPC, primary prostate cancer; PSA, prostate-specific antigen; PSM, propensity score matching; SD, standard deviation; SPC, subsequent primary cancer.

Table 6 Uni- and multivariate Cox regression model analysis of OS

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age, year			<0.001			<0.001
<65	Reference			Reference		
≥65	2.971	2.599–3.396	<0.001	2.008	1.747–2.307	<0.001
Race			0.014			0.013
White	Reference			Reference		
Black	1.227	1.067–1.411	0.004	1.155	1.003–1.330	0.046
Other	0.948	0.728–1.235	0.691	0.760	0.583–0.991	0.042
Grade[1]			<0.001			0.763
Grade I–II	Reference			Reference		
Grade III–IV	1.582	1.433–1.747	<0.001	1.035	0.829–1.292	0.763
Marital status			0.150			
Married	Reference					
Unmarried	1.120	0.960–1.307	0.150			
Gleason score			<0.001			<0.001
≤6	Reference			Reference		
7	1.465	1.311–1.637	<0.001	1.235	0.972–1.569	0.084
8–10	2.756	2.448–3.103	<0.001	1.854	1.435–2.395	<0.001
PSA, ng/mL			<0.001			<0.001
≤4	Reference			Reference		
4–10	1.146	0.986–1.332	0.077	0.963	0.828–1.120	0.625
10–20	2.100	1.776–2.483	<0.001	1.378	1.152–1.648	<0.001
>20	3.381	2.824–4.049	<0.001	1.877	1.548–2.277	<0.001

Table 6 *(continued)*

Table 6 *(continued)*

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
TNM stage			<0.001			0.299
I	Reference			Reference		
II	1.641	1.461–1.843	<0.001	1.143	0.939–1.390	0.183
III	0.979	0.792–1.210	0.845	1.057	0.790–1.414	0.710
Histology			0.077			
Adenocarcinoma	Reference					
Non-adenocarcinoma	1.606	0.949–2.717	0.077			
Diagnosis			<0.001			<0.001
PPC	Reference			Reference		
SPC	1.549	1.410–1.703	<0.001	1.580	1.438–1.737	<0.001
Surgery			<0.001			<0.001
No	Reference			Reference		
Yes	0.263	0.226–0.305	<0.001	0.347	0.292–0.412	<0.001

[1]Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated. CI, confidence interval; OS, overall survival; HR, hazard ratio; PPC, primary prostate cancer; PSA, prostate-specific antigen; PSM, propensity score matching; SD, standard deviation; SPC, subsequent primary cancer.

trials, and they should be offered aggressive, potentially curative therapies if otherwise appropriate. We supposed that lung cancer played a leading role in survival outcomes in patients with both PCa and lung cancer. In our study, we recommended that PCa patients with prior cancers must be carefully considered for clinical trials.

Our results showed that patients with SPC had shorter OS when compared with those with PPC (P<0.0001), while no significant difference was detected in PCSM (P=0.66). Zhou *et al*. (22) found that patients having PCa as an SPM had inferior OS than those having PCa as the only malignancy. Moreover, similar survival outcomes were found in those with other malignancies, including thyroid, bladder, kidney and renal pelvic, eye and orbits, breast and so on. In the study conducted by Ji *et al*. (12) concluded that patients with subsequent breast cancer had worse OS and breast CSS than those with primary breast cancer. However, no obvious difference was found in the CSS despite the statistical significance. Interestingly, significant better OS was detected in patients with second primary colorectal cancer than those with initial primary colorectal cancer (27). Moreover, Liu *et al*. (28) found that younger patients with lung cancers with a prior caner had the same or not-inferior OS than those without a prior cancer (P<0.05). We believed that these survival differences were due to the differences between PCa and lung cancer or colorectal cancer itself. Additionally, in this study, multivariate Cox regression revealed that sequence of PCa (PPC *vs.* SPC) was an independent prognostic factor for OS, but not for CSS, which was consistent with the result in KM-analysis. Therefore, researchers should be familiar with the past medical history of each patient, and pay more attention to patients with a prior cancer in clinical decisions.

However, there were some potential limitations that could not be ignored. Firstly, some data were missing in SEER database which limited further comprehensive analysis of the research, such as comorbidities (obesity, diabetes), cycle of radiotherapy and chemotherapy, chemotherapy drugs and so on. Secondly, treatment types of the prior cancer may affect the survival and occurrence of SPM (29). Lastly, although a PSM method was used in this study, unavoidable selection bias still existed due to the retrospective design. Thus, prospective and large sample size studies are needed to validate our findings in the future.

In conclusion, PCa is still an important COD for patients with a prior cancer, especially for those with high-stage diseases. In PCa patients with a prior cancer, the OS will be

affected by the prior cancer significantly, indicating that we should be more prudential in clinical decision-making.

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Footnote

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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). This study was exempt by Institutional Review Board (IRB) approval because the original data were from a public database and individual consent for this retrospective analysis was waived.

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