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The effect of primary urological cancers on survival in men with secondary prostate cancer

Mike Wenzel MD, BSc[1,2] | Christoph Würnschimmel MD[2,3] | Luigi Nocera MD[2,4] | Claudia Collà Ruvolo MD[2,5] | Zhe Tian MSc[2] | Fred Saad MD, PhD[2] | Alberto Briganti MD, PhD[4] | Derya Tilki MD, PhD[3,6] | Markus Graefen MD, PhD[3] | Frederik C. Roos MD, PhD[1] | Philipp Mandel MD, PhD[1] | Felix K.H. Chun MD, PhD[1] | Pierre I. Karakiewicz MD, PhD[2]

[1]Department of Urology, University Hospital Frankfurt, Frankfurt am Main, Germany

[2]Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montréal Health Center, Montréal, Québec, Canada

[3]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany

[4]Division of Experimental Oncology, Department of Urology, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy

[5]Department of Neurosciences, Reproductive Sciences, and Odontostomatology, University of Naples Federico II, Naples, Italy

[6]Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Mike Wenzel, MD, Department of Urology, University Hospital Frankfurt, Theodor- Stern Kai 7, 60590 Frankfurt, Germany.
Email: Mike.Wenzel@kgu.de

Abstract

Background: To test the effect of urological primary cancers (bladder, kidney, testis, upper tract, penile, urethral) on overall mortality (OM) after secondary prostate cancer (PCa).

Methods: Within the Surveillance, Epidemiology and End Results (SEER) database, patients with urological primary cancers and concomitant secondary PCa (diagnosed 2004-2016) were identified and were matched in 1:4 fashion with primary PCa controls. OM was compared between secondary and primary PCa patients and stratified according to primary urological cancer type, as well as to time interval between primary urological cancer versus secondary PCa diagnoses.

Results: We identified 5,987 patients with primary urological and secondary PCa (bladder, n = 3,287; kidney, n = 2,127; testis, n = 391; upper tract, n = 125; penile, n = 47; urethral, n = 10) versus 531,732 primary PCa patients. Except for small proportions of Gleason grade group and age at diagnosis, PCa characteristics between secondary and primary PCa were comparable. Conversely, proportions of secondary PCa patients which received radical prostatectomy were smaller (29.0 vs. 33.5%), while no local treatment rates were higher (34.2 vs. 26.3%). After 1:4 matching, secondary PCa patients exhibited worse OM than primary PCa patients, except for primary testis cancer. Here, no OM differences were recorded. Finally, subgroup analyses showed that the survival disadvantage of secondary PCa patients decreased with longer time interval since primary cancer diagnosis.

Conclusions: After detailed matching for PCa characteristics, secondary PCa patients exhibit worse survival, except for testis cancer patients. The survival disadvantage is attenuated, when secondary PCa diagnosis is made after longer time interval, since primary urological cancer diagnosis.

KEYWORDS
bladder cancer, kidney cancer, mortality, primary prostate cancer, urological cancer

1 | INTRODUCTION

Urological cancers accounted for approximately 20% of all cancers diagnoses in the United States in 2019 and the global burden of urological cancers is increasing.[1,2] Within all urological cancers, prostate cancer (PCa) diagnoses are frequent.[1,3,4] Most contemporary epidemiological studies addressing PCa survival exclusively focused on primary PCa and excluded patients with prior cancers.[5–8] However, an increased risk exists for secondary cancers after prior primary cancers, including secondary PCa.[9–15] Three previous publications suggested that patients with secondary PCa differ in patient and PCa characteristics and are at a survival disadvantage, relative to patients with primary PCa.[16–18] However, none of the three previous studies stratified their survival analyses according primary cancer type. Moreover, urological primary cancers have not been previously addressed. Similarly, analyses did not address the effect of treatment type of secondary PCa or the effect of the time interval between primary urological cancer diagnoses. These points represent important knowledge gaps.

We addressed these voids and relied on the Surveillance, Epidemiology and End Results (SEER) database to investigate the effect of urological primary cancers on mortality in secondary PCa patients. We hypothesized that secondary PCa patients after primary urological cancer may exhibit variable OM according to primary cancer type and/or length of time interval between primary urological cancer and secondary PCa diagnoses.

2 | MATERIAL AND METHODS

2.1 | Study population

Within the SEER database, we identified all patients ≥18 years with secondary PCa diagnosed between 2004 and 2016 after prior diagnosis of urological cancers (bladder cancer [ICD-O-3 code C67.0-67.9], kidney cancer [ICD-O-3 code C64.9], testis cancer [ICD-O-3 code C62.1 and 62.9], penile cancer [ICD-O-3 code C60.0, 60.1, 60.2, 60.8, 60.9], UTUC [ICD-O-3 code C65.9 and C66.9] and urethral cancer [ICD-O-3 code C68.0]).[19] Additionally, we also identified all patients over 18 years old

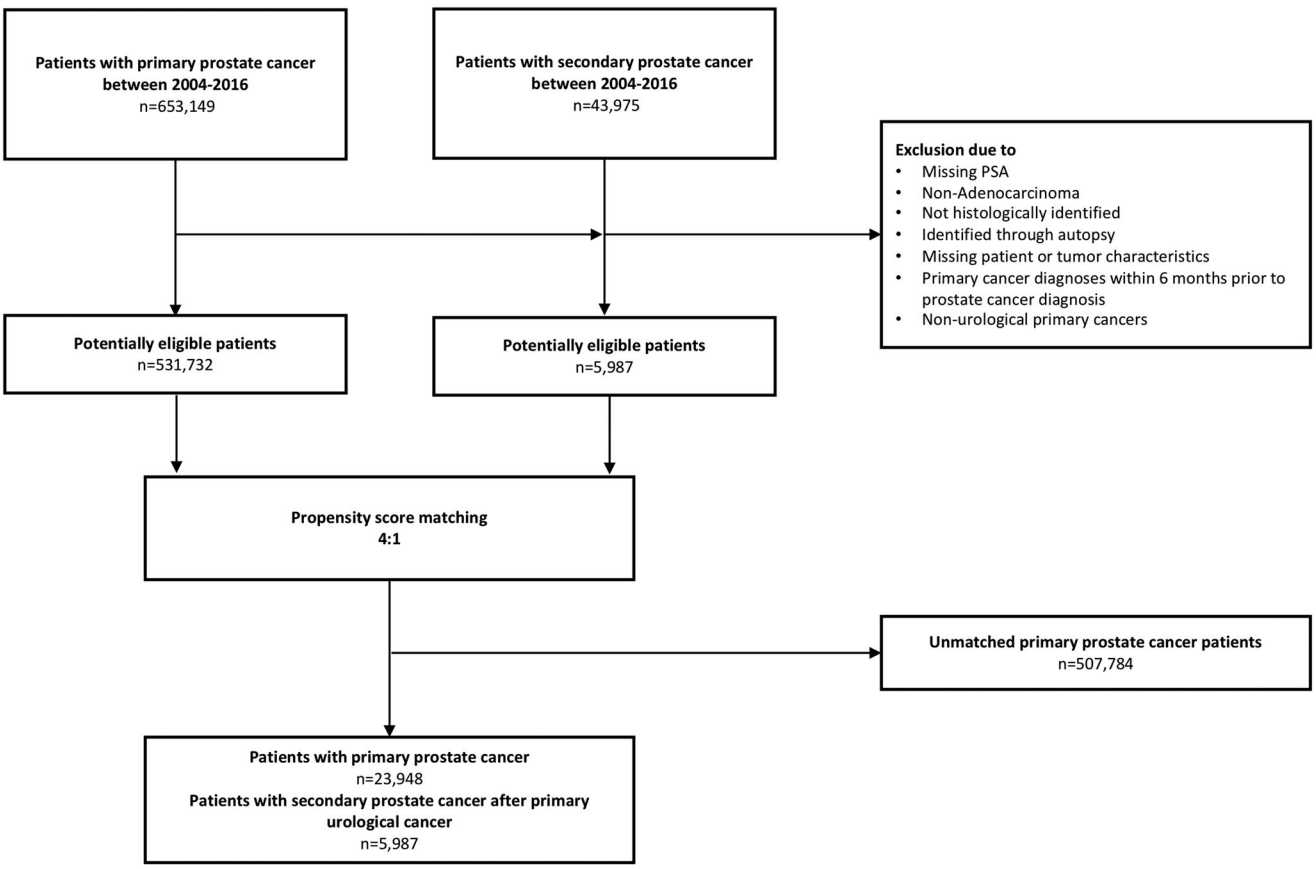

FIGURE 1 Flow chart depicting included patients with primary and secondary prostate cancer after primary urological cancer in analyses

TABLE 1 Descriptive characteristics before matching and after matching for age at prostate cancer diagnosis, year of prostate cancer diagnoses, race/ethnicity, treatment type and TNM stage for primary and secondary prostate cancer patients after primary urological cancers

		Before matching		After matching		
Variable		Primary PCa *N* = 531,732	Secondary PCa *N* = 5987	Overall *N* = 29,935	Primary PCa *N* = 23,948	Secondary PCa *N* = 5987
Age at PCa diagnosis	Median (IQR)	65 (59–72)	70 (64–76)	70 (64–76)	70 (64–76)	70 (64–76)
Year of PCa diagnosis	Median (IQR)	2010 (2007–2013)	2010 (2007–2013)	2010 (2007–2013)	2010 (2007–2013)	2010 (2007–2013)
Age of primary cancer diagnosis	Median (IQR)	–	64 (56–70)		–	64 (56–70)
Year of primary cancer diagnosis	Median (IQR)	–	2004 (2000–2008)		–	2004 (2000–2008)
PSA, ng/ml	Median (IQR)	6.6 (4.8–10.6)	6.5 (4.5–10.6)	7.0 (4.9–11.3)	7.1 (5.0–11.4)	6.5 (4.5–10.6)
Follow up, in months	Median (IQR)	68 (32–104)	55 (24–90)	59 (26–94)	60 (27–95)	55 (24–90)
cT	cT1	324,967 (61.1)	3558 (59.4)	18,210 (60.8)	14,652 (61.2)	3558 (59.4)
	cT2	164,054 (30.9)	1859 (31.1)	9434 (31.5)	7575 (31.6)	1859 (31.1)
	cT3	14,084 (2.6)	119 (2.0)	494 (1.7)	375 (1.6)	119 (2)
	cT4	4701 (0.9)	54 (0.9)	198 (0.7)	144 (0.6)	54 (0.9)
	cTx	23,926 (4.5)	397 (6.6)	1599 (5.3)	1202 (5)	397 (6.6)
cN stage	cN0	493,330 (92.8)	5596 (93.5)	28,309 (94.6)	22,713 (94.8)	5596 (93.5)
	cN1	15,055 (2.8)	124 (2.1)	525 (1.8)	401 (1.7)	124 (2.1)
	cNx	23,347 (4.4)	267 (4.5)	1101 (3.7)	834 (3.5)	267 (4.5)
M stage	M0	495,768 (93.2)	5608 (93.7)	28,357 (94.7)	22,749 (95.0)	5608 (93.7)
	M1	22,396 (4.2)	211 (3.5)	855 (2.9)	644 (2.7)	211 (3.5)
	Mx	13,568 (2.6)	168 (2.8)	723 (2.4)	555 (2.3)	168 (2.8)
Gleason grade group at diagnosis	I	209,565 (39.4)	2275 (38.0)	11,018 (36.8)	8743 (36.5)	2275 (38.0)
	II	137,937 (25.9)	1363 (22.8)	7652 (25.6)	6289 (26.3)	1363 (22.8)
	III	60,193 (11.3)	671 (11.2)	3696 (12.3)	3025 (12.6)	671 (11.2)
	IV	46,788 (8.8)	597 (10.0)	2921 (9.8)	2324 (9.7)	597 (10)
	V	40,687 (7.7)	491 (8.2)	2512 (8.4)	2021 (8.4)	491 (8.2)
	Unknown	36,562 (6.9)	590 (9.9)	2136 (7.1)	1546 (6.5)	590 (9.9)
D'amico risk group	low	135,502 (25.5)	1411 (23.6)	6927 (23.1)	5516 (23.0)	1411 (23.6)
	intermediate	210,982 (39.7)	2286 (38.2)	12,189 (40.7)	9903 (41.4)	2286 (38.2)
	high	144,985 (27.3)	1636 (27.3)	8376 (28.0)	6740 (28.1)	1636 (27.3)
	Unknown	40,263 (7.6)	654 (10.9)	2443 (8.2)	1789 (7.5)	654 (10.9)
Treatment	RP	178,084 (33.5)	1739 (29.0)	7871 (26.3)	6221 (26.0)	1739 (29.0)
	EBRT	120,891 (22.7)	1461 (24.4)	7282 (24.3)	5860 (24.5)	1461 (24.4)
	BT	39,655 (7.5)	413 (6.9)	2132 (7.1)	1711 (7.1)	413 (6.9)
	BT + EBRT	21,696 (4.1)	201 (3.4)	1000 (3.3)	799 (3.3)	201 (3.4)
	RP + EBRT	15,121 (2.8)	121 (2.0)	576 (1.9)	455 (1.9)	121 (2.0)
	RT + RP	156 (0)	4 (0.1)	15 (0.1)	11 (0)	4 (0.1)
	NLT	140,081 (26.3)	2048 (34.2)	10,093 (33.7)	8125 (33.9)	2.048 (34.2)
	Unknown	16,048 (3.0)	200 (3.3)	966 (3.2)	766 (3.2)	200 (3.3)

(Continues)

TABLE 1 (Continued)

Variable		Before matching		After matching		
		Primary PCa *N* = 531,732	Secondary PCa *N* = 5987	Overall *N* = 29,935	Primary PCa *N* = 23,948	Secondary PCa *N* = 5987
Chemotherapy	Yes	4223 (0.8)	42 (0.7)	153 (0.5)	111 (0.5)	42 (0.7)
Race/ethnicity	Caucasian	363,223 (68.3)	4787 (80.0)	23,847 (79.7)	19,060 (79.6)	4787 (80.0)
	African American	81,905 (15.4)	593 (9.9)	2989 (10.0)	2396 (10.0)	593 (9.9)
	Hispanic	48,835 (9.2)	397 (6.6)	2110 (7.0)	1713 (7.2)	397 (6.6)
	Native	1861 (0.3)	13 (0.2)	55 (0.2)	42 (0.2)	13 (0.2)
	Asian	26,007 (4.9)	194 (3.2)	916 (3.1)	722 (3.0)	194 (3.2)
	Unknown	9901 (1.9)	194 (3.2)	916 (3.1)	722 (3.0)	194 (3.2)
Marital status	Married	354,363 (66.6)	4122 (68.8)	19,992 (66.8)	15,870 (66.3)	4122 (68.8)
	Unmarried	116,788 (22.0)	1190 (19.9)	6541 (21.9)	5351 (22.3)	1190 (19.9)
	Unknown	60,581 (11.4)	675 (11.3)	3402 (11.4)	2727 (11.4)	675 (11.3)
Socioeconomic status	1st quartile	133,678 (25.1)	1469 (24.5)	6163 (20.6)	4694 (19.6)	1469 (24.5)
	2nd–4th quartile	397,946 (74.8)	4518 (75.5)	23,772 (79.4)	19,254 (80.4)	4518 (75.5)
Region	West	270,363 (50.8)	2893 (48.3)	16,816 (56.2)	13,923 (58.1)	2893 (48.3)
	Midwest	51,705 (9.7)	839 (14.0)	4583 (15.3)	3744 (15.6)	839 (14.0)
	North-East	89,653 (16.9)	1152 (19.2)	6419 (21.4)	5267 (22.0)	1152 (19.2)
	South	120,011 (22.6)	1103 (18.4)	2117 (7.1)	1014 (4.2)	1103 (18.4)

Abbreviations: IQR, interquartile range; PCa, prostate cancer.

with biopsy-confirmed primary adenocarcinoma of the prostate, diagnosed between 2004 and 2016 (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9). We excluded patients with unknown histology or unavailable PSA, and patients with diagnoses of primary urological cancer and secondary PCa that were made within a six months or shorter interval, according to previously established methodology.[20,21] Cases identified only at autopsy or death certificate were also excluded. These selection criteria resulted in 5,987 secondary PCa versus 531,732 primary PCa patients (Figure 1, Table 1). Finally, we relied on 1:4 propensity score matching for all 5,987 secondary PCa patients versus 23,948 primary PCa patients (matched for age at diagnoses, year of diagnoses, race/ethnicity, prostate cancer treatment, cT-stage, cN-stage and M-stage (Figure 1). The 1:4 matched cohort was used in all subsequent OM analyses.

2.2 | Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables. Medians, and interquartile-ranges (IQR) were reported for continuously coded variables. The Chi-square tested the statistical significance in proportions' differences. The t-test and Kruskal-Wallis test examined the statistical significance of means' and distributions' differences.

The first part of the analyses compared patient and PCa characteristics between all identified secondary (n = 5,987) and primary PCa patients (n = 531,732). In the second part of the analyses, we focused on overall mortality (OM), after propensity score matching. Kaplan-Meier illustrated OM in the overall comparison, as well as in all subsequent OM subgroup analyses. Additionally, multivariable Cox regression quantified hazard ratios (HR) of secondary versus primary PCa patients, after further adjustment for covariates: PSA, socioeconomic status, Gleason grade group and D'Amico risk group. All tests were two sided with a level of significance set at $p < .05$ and R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.

3 | RESULTS

3.1 | Descriptive characteristics of the study population

Before matching, 5,987 patients with secondary PCa and 531,732 primary PCa cancer patients were eligible. Median age at PCa diagnosis was 65 years for primary versus 70 years for secondary PCa (Table 1, <0.001). Median age of primary urological cancer diagnosis before secondary PCa was 64 years. The median age at

TABLE 2 Baseline and prostate cancer characteristics of the 10 most common nonurological cancers before secondary prostate cancer

	Median age at primary cancer diagnosis (IQR)	Median age at secondary prostate cancer diagnosis (IQR)	Median PSA at diagnosis in ng/ml (IQR)	RP versus EBRT treatment (%)	Overall deaths	Died from secondary prostate cancer (%)	Died from primary cancer (%)
Bladder cancer *n* = 3287	66 (59–72)	72 (66–78)	6.6 (4.4–11.2)	25.6 vs. 23.6%	1057	159 (15.0)	246 (23.3)
Kidney cancer *n* = 2127	62 (56–68)	68 (63–74)	6.4 (4.7–10.2)	28.3 vs. 25.9%	472	70 (14.8)	129 (27.3)
Testis cancer *n* = 391	42 (36–53)	61 (56–67)	5.7 (4.3–8.7)	44.8 vs. 13.0%	48	14 (29.2)	18 (37.5)
UTUC *n* = 125	67 (61–72)	72 (67–78)	7.1 (4.9–14.5)	18.4 vs. 23.2%	38	6 (15.8)	5 (13.2)
Penile cancer *n* = 47	62 (58–70)	71 (67–76)	7.8 (5.1–14.7)	14.9 vs. 25.5%	12	3 (25.0)	7 (58.3)
Urethral cancer *n* = 10	61 (53–72)	75 (62–80)	8.5 (5.7–12.3)	30.0 vs. 20.0%	2	0 (0)	0 (0)
Overall *n* = 5987	64 (56–70)	70 (64–76)	6.5 (4.5–10.6)	27.6 vs. 23.7%	1623	251 (15.5)	401 (24.7)

Abbreviations: EBRT, external beam radiation therapy; PSA, prostate-specific antigen, RP, radical prostatectomy.

diagnosis of primary urological cancer ranged from respectively 42 (primary testis cancer) to 66 years (bladder cancer). Conversely, the median age at secondary PCa ranged from 61 (testis cancer) to 75 years (primary urethral cancer, Table 2). Median PSA at diagnosis virtually showed no differences between secondary and primary PCa patients: 6.5 versus 6.6 ng/ml. Within all urological cancers before secondary PCa, median PSA at secondary PCa diagnosis ranged from 5.7 (testis cancer) to 9.3 ng/ml (urethral cancer). Patients with secondary PCa more frequently harbored Gleason grade group 4 (10.0 vs. 8.8%) or 5 (8.2 vs. 7.7%), relative to primary PCa patients ($p < .001$). However, no clinically meaningful differences in rates of cT-stage, cN-stage and M-stage between primary and secondary PCa groups were observed. Important differences existed according to use of local therapy: patients with secondary PCa more frequently received no local therapy than primary prostate cancer patients (34.2 vs. 26.3%). Moreover, patients with secondary PCa less frequently received radical prostatectomy ([RP] 29.0 vs. 33.5%, $p < .001$). External beam radiation therapy (EBRT) rates showed only marginal differences (24.4 vs. 22.7%, $p < .001$). After stratification according to type of primary cancer in secondary PCa patients, rates of RP ranged from 9.5 (penile cancer) to 44.8% (testis cancer) and rates of EBRT ranged from 13.0 (testis cancer) to 25.9% (kidney cancer).

3.2 | Propensity score matched (1:4) survival analyses

After propensity score matching, median survival of all 5,987 secondary PCa patients was 132 months versus not reached in 23,948 primary PCa patients, with respective ten-year OM rates of 44.2 in secondary PCa patients versus 33.1% (Figure 2A). This survival disadvantage translated into a 1.5-fold higher risk of OM. After further multivariable adjustment a 1.6-fold higher OM was observed (Table 3) in secondary PCa patients, relative to primary PCa patients.

3.3 | Propensity score matched (1:4) survival analyses according to treatment type

We repeated the Kaplan-Meier and Cox regression analyses, after stratification according to local PCa treatment type in patients treated with RP, EBRT or no local treatment (NLT) across all primary urological cancer types. Here, presence of secondary PCa resulted in worse OM, relative to primary PCa patients. Specifically, ten-year OM rates were respectively 24.7 versus 15.2%, 46.6 versus 37.8% and 62.1 versus 56.5% for RP, EBRT and NLT treated secondary versus primary PCa patients (Figure 2B-D). In multivariable Cox regression models, the respective HRs were 2.0 after RP, 1.4 after

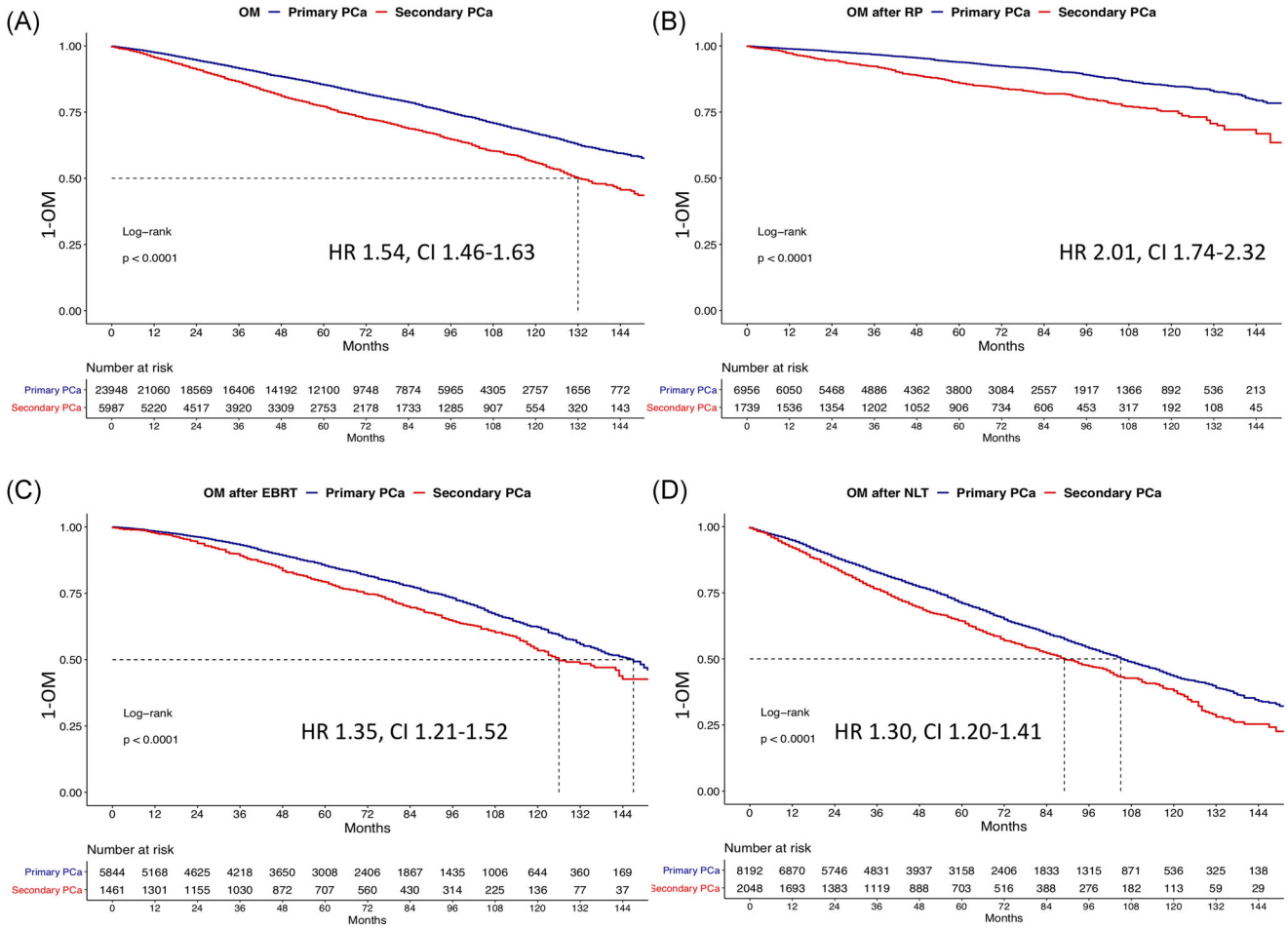

FIGURE 2 Kaplan–Meier plots depicting overall mortality (OM) for primary and secondary prostate cancer after primary urological cancers for (A) the overall cohort (B) patients treated with radical prostatectomy (RP) (C) patients treated with external beam radiation therapy (EBRT) and (D) patients stratified according to any kind of local treatment (LT) versus nonlocal treatment (NLT). CI, confidence interval; HR, hazard ratio; NLT, no local treatment [Color figure can be viewed at wileyonlinelibrary.com]

EBRT and 1.4 after NLT in secondary PCa patients, relative to primary PCa patients (Table 3, all $p < .01$).

3.4 | Propensity score matched (1:4) survival analyses according to primary urological cancer type

In Kaplan-Meier plots, ten-year OM rates (Figures 3–4) in secondary PCa patients were respectively 49.2 versus 39.0%, 39.5 versus 27.7%, 22.1% versus 16.4%, 42.4 versus 30.5%, 50.1 versus 26.4% for bladder, kidney, testis, UTUC and penile cancer versus primary PCa patients. Due to small sample size, ten-year OM rates could not be computed for urethral cancer. Five-year OM rates of primary urethral cancer with subsequent secondary PCa were 25 versus 11.9% for primary PCa patients. Similarly, insufficient numbers of observations were recorded for penile cancer. The specific multivariable HRs were 1.6, 1.8 and 1.7 for respectively secondary PCa patients with primary bladder, kidney, UTUC cancer (all $p < .01$, Table 3). The exception consisted of testis cancer. Specifically, in primary testis cancer patients with secondary PCa an OM difference was not detected in either univariable or multivariable Cox regression models (both $p > .05$).

The proportions of patients that died of secondary PCa after primary urological cancers (Table 2) ranged from 15.0 (kidney cancer) to 29.2% (testis cancer). Similarly, the proportions of patients that died of primary cancer ranged from 13.2 (UTUC) to 58.3% (penile cancer). Urethral cancer patients died from non-cancer specific reasons. Unfortunately, these cancer-specific rates could not be translated into Kaplan-Meier-derived actuarial estimates due to unavailable time to death.

3.5 | Propensity score matched (1:4) survival analyses according to time interval length since initial cancer diagnosis and secondary PCa diagnoses

Time interval length since initial cancer and secondary PCa diagnoses was stratified between 7 and 60 versus 61-120 versus ≥121 months. In Kaplan-Meier plots that addressed the comparison between secondary PCa diagnosed between 7 and 60 months after primary

TABLE 3 Univariable und multivariable Cox regression models after adjustment for PSA, socioeconomic status, Gleason grade group, and D'amico risk stratification

	Univariable		Multivariable	
	HR (CI)	*p* value	HR (CI)	*p* value
Cancers				
Primary prostate cancer	**Ref**	–	–	–
All urological cancers	1.54 (1.46–1.63)	<.001	1.60 (1.51–1.69)	<.001
Secondary after bladder cancer	1.48 (1.38–1.59)	<.001	1.55 (1.44–1.66)	<.001
Secondary after kidney cancer	1.65 (1.49–1.84)	<.001	1.76 (1.58–1.96)	<.001
Secondary after testis cancer	1.35 (0.97–1.87)	.07	1.14 (0.81–1.61)	.4
Secondary after UTUC	1.60 (1.10–2.32)	.01	1.74 (1.18–2.58)	<.01
Secondary after penile cancer	1.69 (0.87–3.31)	.1	1.70 (0.82–3.49)	.2
Treatments				
Primary prostate cancer and RP	**Ref**	–	–	–
Secondary RP	2.01 (1.74–2.32)	<.001	2.03 (1.75–2.35)	<.001
Primary prostate cancer and EBRT	**Ref**	–	–	–
Secondary EBRT	1.35 (1.21–1.52)	<.001	1.37 (1.22–1.53)	<.001
Primary prostate cancer and no local treatment	**Ref**	–	–	–
secondary prostate no local treatment	1.30 (1.20–1.41)	<.001	1.36 (1.25–1.47)	<.001
Time intervals				
Primary prostate cancer	**Ref**	–	–	–
Secondary cancer 7–60 months before prostate cancer	1.53 (1.42–1.65)	<.001	1.62 (1.50–1.75)	<.001
Secondary cancer 61–120 months before prostate cancer	1.36 (1.21–1.52)	<.001	1.39 (1.24–1.55)	<.001
Secondary cancer >120 months before prostate cancer	1.22 (1.08–1.37)	.001	1.24 (1.10–1.40)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; UTUC, upper tract urinary cancer.

urological cancer diagnosis, relative to primary PCa, the respective ten-year OM rates were 45.4% versus 33.9%. These OM rates translated into a multivariable HR of 1.6 ($p < .001$). In Kaplan-Meier plots, ten-year OM rates for interval length 61-120 and ≥121 months between secondary and primary PCa patients were respectively 42.3 versus 36.7% and 42.9 versus 37.6% months. The respective multivariable HRs of 61-120 and ≥121 months were 1.6 and 1.4.

4 | DISCUSSION

Secondary PCa received little attention in the urologic literature.[15–17] For example, in a previous study that was based on a SEER cohort, median year of primary cancer diagnosis was 1989 and median year of subsequent secondary PCa diagnosis was 1995. A more recent report by Klippenstein et al. focused on 1,552 secondary PCa patients exclusively treated with RP. In all of the three previous studies, secondary PCa patients exhibited worse survival than primary PCa patients. Specifically, no previous study investigated OM rates according to primary urological cancer diagnosis and the effect of treatment type, as well as of time interval between primary urological cancer and subsequent secondary PCa. We addressed these voids and made several noteworthy observations.

First, we found that the median age at secondary PCa diagnosis was on average five years later than that of primary PCa patients (70 vs. 65 years). It is also of note that secondary PCa occurred on average six years after primary urological cancer diagnosis (median age 64). However, only small differences were found between secondary and primary PCa patients according Gleason grade groups (e.g., Gleason grade group 4:10.0 vs. 8.8% or 5: 8.2 vs. 7.7%). Moreover, no meaningful differences were observed in median PSA at PCa diagnosis between secondary and primary PCa (6.6 vs. 6.5 ng/ml). To the best of our knowledge, we are first to report baseline PCa characteristics of patients with secondary PCa after

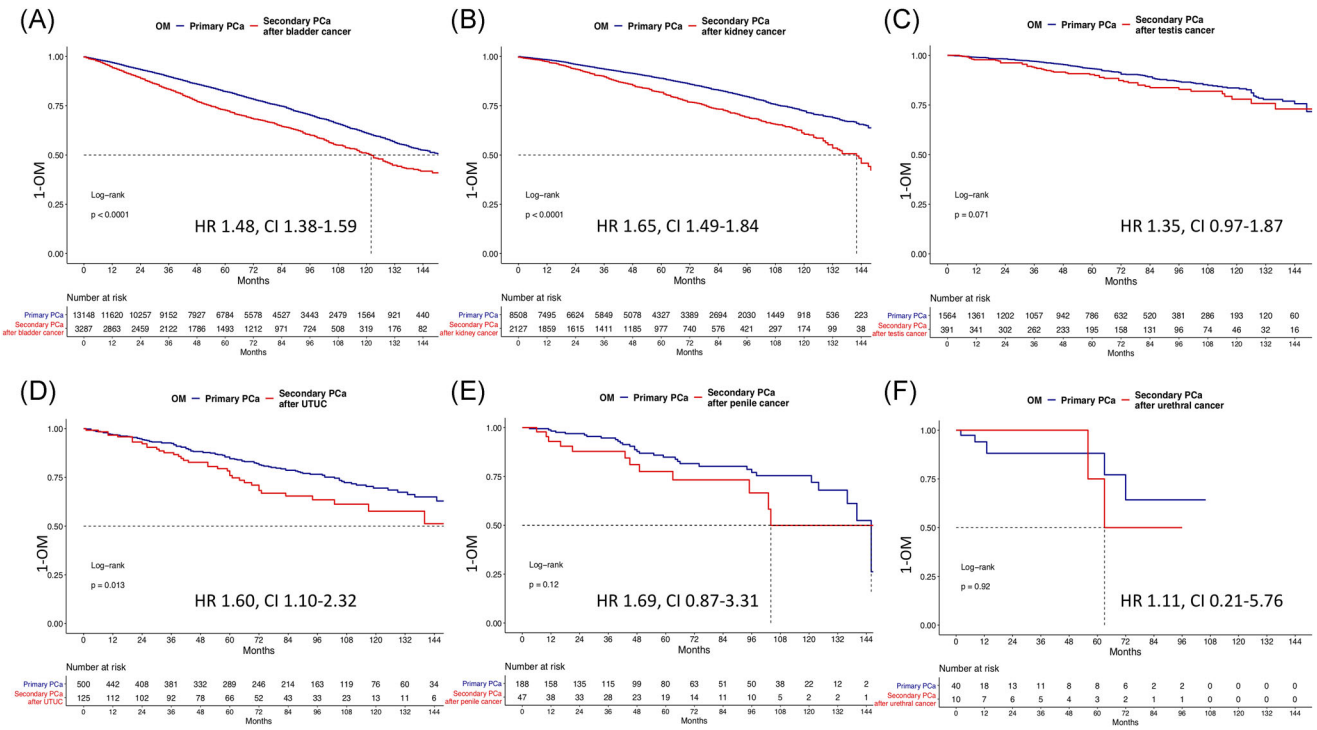

FIGURE 3 Kaplan–Meier plots depicting overall mortality (OM) for primary and secondary prostate cancer after (A) primary bladder cancer (B) primary kidney cancer (C) primary testis cancer (D) primary penile cancer (E) primary upper tract urinary carcinoma (UTUC) (F) primary urethral cancer. CI, confidence interval; HR, hazard ratio [Color figure can be viewed at wileyonlinelibrary.com]

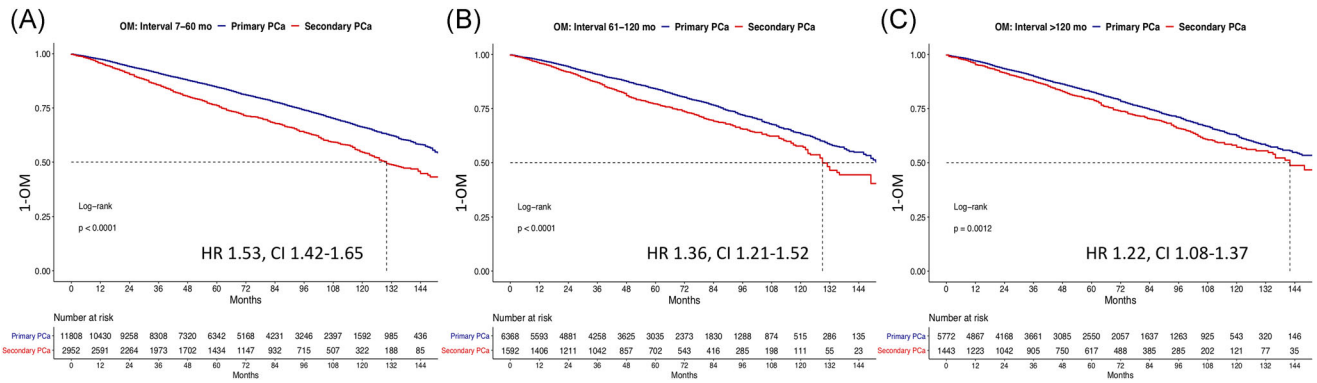

FIGURE 4 Kaplan Meier plots depicting overall mortality (OM) for primary and secondary prostate cancer after primary urological cancers according to the time interval between primary cancer and secondary prostate cancer (A) 7–60 months B) 61–120 months (E) >120 months. CI, confidence interval; HR, hazard ratio [Color figure can be viewed at wileyonlinelibrary.com]

prior urological cancers. In consequence, our results cannot be directly compared to previous investigations. However, Dinh et al., who relied on patients identified between 1973 and 2011, reported an older median age at primary cancer diagnosis (68 vs. 64 years), as well as older age at secondary PCa diagnosis (73 vs.70 years).[17] In consequence, the current patients were younger at both primary urological and secondary PCa diagnoses, relative to the more historical cohort of Dinh et al. However, it is also noteworthy that median age at primary urological cancer and secondary PCa diagnosis varied across the six primary urological cancer groups. A specific explanation for this variability cannot be provided. It may be postulated that more aggressive early cancer detection may play a role. The exception to all established age distributions for primary urological cancers consists of the current cohort of primary testis cancer patients with secondary PCa, in whom the median age at diagnosis was 42 years. It contrasts with the median age, as well the age distribution of testis cancer patients in general, which ranged from 27 to 43 (median 34) years in a recent SEER database report.[22] Due to a limited amount of detail regarding the primary testis cancer diagnosis, a factual explanation for this discrepancy cannot be provided.

Second, we also made important observations regarding OM in patients with secondary PCa. Specifically, after 1:4 matching for TNM

stage, age, year of diagnosis, treatment modality and race/ethnicity, secondary PCa patients were at 1.5-fold higher risk of OM, compared to primary prostate cancer patients. Similarly, in subgroup analyses stratified according to treatment type an OM disadvantage of similar magnitude was also observed. For example, the OM disadvantage ranged from 1.3 to 1.4 to 2.0-fold for NLT, EBRT and RP treatment. The OM disadvantage recorded in RP patients, is in agreement with Klippenstein et al. who focused on a European (Martini Clinic) cohort of secondary PCa patients (n = 1,552) treated with RP.[16] However, the magnitude of the OM disadvantage was the lowest in secondary PCa patients, treated with NLT or EBRT and may be explained by the fact that these patients have a higher risk of other cause mortality (OCM), due to on average older age and more severe comorbidities, regardless of a secondary or primary prostate cancer.[23,24] Conversely, in secondary PCa patients treated with RP, a generally lower OCM may lead to a higher risk to die from the primary urological cancer or secondary prostate cancer.

Third, we also observed important variability in OM rates among secondary PCa patients according to type of primary urological cancer. Specifically, ten-year OM ranged from 22% in primary testis cancer to 50% in primary penile cancer patients with secondary PCa. In secondary PCa patients after primary testis cancer diagnosis, absolute OM rates did not show clinically meaningful differences (22 vs. 16%). The most plausible explanation for this observation relates to a significantly younger age of primary testis cancer patients at secondary PCa diagnosis, which was 61 years instead of 70 years for the entire cohort of 5,987 secondary PCa patients. It is of interest that several studies investigated the increased incidence of secondary PCa in primary testis cancer patients.[25–27] The effect of testosterone level and testosterone supplements was investigated, but no association was identified.[4,28,29] In consequence, the observations regarding younger age at secondary PCa diagnosis in primary testis cancer patients may be explained by an early detection due to younger average age of those individuals and a higher cancer awareness, relative to all other individuals with secondary PCa after primary urological cancer. Finally, sample size limitations (n = 10) prevented meaningful comparisons between secondary PCa after primary urethral and penile cancer.

Finally, we made important observations regarding OM according to specific time interval between primary urological cancer and secondary PCa diagnosis. Specifically, the OM disadvantage of secondary PCa after prior urological cancer was less pronounced, when the time interval was longest between both cancer diagnoses (HR: 1.5). Conversely, the OM disadvantage was most pronounced when the time interval was shortest (HR: 1.2). These observations indicate that diagnostic and/or therapeutic measures applied to secondary PCa patients after a lengthy time interval since primary urological cancer diagnosis, may be more aggressive than when the time interval is short.

Taken together, our findings indicate that OM rates of secondary PCa patients after primary urological cancer are significantly higher, relative to primary PCa patients, despite matching and adjusting for risk factors. Matching and adjusting was applied to account for differences between secondary PCa patients with primary urological cancer, relative to primary PCa patients, in whom unfavorable Gleason grade groups at diagnosis were more frequent and in whom age at PCa diagnosis was more advanced. This OM disadvantage was strongest in secondary PCa patients with primary kidney cancer and weakest in bladder cancer. Moreover, OM disadvantage was most pronounced when time interval between the diagnosis of the primary cancer and the secondary PCa was shortest. None of these observations were previously reported. In consequence, future validations with more detailed primary urologic cancer characteristics should be performed.

Our work has limitations and should be interpreted in the context of its retrospective and population-based design. Second, the nature of our data does not allow to define specific mortality time points to estimate Kaplan-Meier derived analyses. Instead, only OM was available. This limitation is shared with all previous publications focusing on secondary cancers after specific primary cancers in large-scale databases.[30–32] Limited stage and grade information was available for each of the six examined primary cancer. Third, important variables such as performance status or comorbidities are not available in the SEER database and might affect OM rates.

5 | CONCLUSION

After detailed matching for PCa characteristics, secondary PCa patients exhibit worse survival, except for testis cancer patients. The survival disadvantage is attenuated, when secondary PCa diagnosis is made after longer time interval, since primary urological cancer diagnosis.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required.

DATA AVAILABILITY STATEMENT

All data generated for this analysis were from the SEER 18 database. The code for the analyses will be made available after request.

ORCID

Mike Wenzel http://orcid.org/0000-0002-4338-0889
Christoph Würnschimmel https://orcid.org/0000-0001-7891-4791
Luigi Nocera http://orcid.org/0000-0003-3354-8139
Claudia Collà Ruvolo http://orcid.org/0000-0001-8110-7341
Derya Tilki http://orcid.org/0000-0001-7033-1380

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