Original Research Article

Second Malignant Tumors and Non-Tumor Causes of Death for Patients With Penile Cancer During Their Survivorship

Cancer Control
Volume 29: 1–13

DOI: 10.1177/10732748221134789
journals.sagepub.com/home/ccx
SAGE

Pan Song[1,2,†], Xiaotian Wu[3,†], Luchen Yang[1,†], Kai Ma[1], Zhenghuan Liu[1], Jing Zhou[1], Junhao Chen[1], Qing Zhu[4], and Qiang Dong[1]

Abstract

Background: The aim was to evaluate the causes of death for patients with localized, regional and metastatic penile cancer (PeCa) after diagnosis.

Methods: PeCa patients diagnosed during 2004-2018 in the Surveillance, Epidemiology, and End Results program database were identified. Causes of deaths including PeCa, second malignant tumors (SMTs) and non-tumor diseases were analyzed, as well as the standardized mortality ratio (SMR) of each cause.

Results: For localized PeCa, 800 of 2155 patients died during the follow-up. 24.9% of all deaths were due to PeCa. 18.0% and 57.1% deaths were due to SMTs and non-tumor causes. Main SMTs included cancers of lung and bronchus (n = 40) and skin (n = 11) with significantly increased SMRs of 1.71 (1.22-2.33) and 4.82 (2.41-8.63). Mortality risks of other SMTs were mostly similar with the general populations. Main causes of non-tumor diseases included diseases of heart [n = 172, SMR: 1.66 (1.42-1.93)], COPD and allied cond [n = 38, SMR: 1.63 (1.15-2.24)], and cerebrovascular diseases [n = 33, SMR: 1.71 (1.17-2.4)]. For regional PeCa, 679 of 1310 patients died including 43.5% PeCa, 14.8% SMTs and 26.6% non-tumor causes. The mortality risks of cancers from lung and bronchus [SMR: 2.41 (1.53-3.62)], skin [SMR: 6.41 (2.35-13.95)] and testis [SMR: 149.35 (18.09-539.5)] were significantly increased. Main non-tumor causes of death included diseases of heart [n = 71, SMR: 1.77 (1.38-2.23)], COPD and allied cond [n = 17, SMR: 1.85 (1.08-2.95)] and diabetes mellitus [n = 16, SMR: 3.62 (2.07-5.88)]. For distant diseases, 109 of 132 patients died including 76 (69.7%) died for PeCa itself, 24 (22.0%) died for SMTs and 9 (8.3%) died for non-tumor diseases. The majority of PeCa deaths (67.1%) and SMTs deaths (79.2%) occurred within 1 year after the diagnosis of PeCa.

Conclusions: We firstly analyzed the SMTs and non-tumor causes of death and morality risks of each cause for PeCa patients, which provided valuable information for PeCa patients on disease prevention and health care during their survivorship.

Keywords

penile cancer, causes of death, second malignant tumors, non-tumor diseases, standardized mortality ratio, SEER

Received March 4, 2022. Received revised August 16, 2022. Accepted for publication September 30, 2022.

[1]Department of Urology, The Institution of Urology, West China Hospital of Sichuan University, Chengdu, China
[2]Institute of Oncology Research (IOR), Bellinzona, Switzerland
[3]The Clinical Medical College of Lanzhou University, Lanzhou, China
[4]Department of General Medical, Medical Affairs Division, West China Hospital of Sichuan University, Chengdu, China

[†]These authors contributed equally to this study.

Corresponding Author:
Qiang Dong, Department of Urology, Institute of Urology, West China Hospital of Sichuan University, No. 37, Guoxue Lane, Wuhou District, Chengdu 610041, China.
Email: dqiang666@163.com

Introduction

Penile cancer (PeCa) is a rare malignancy worldwide, accounting for less than 1% of all malignancies in men.[1] The overall incidence rate is approximately .69 cases per 100 000 persons in the US.[2] It was estimated that the number of new PeCa patients was 34 475 and deaths cases was 15 138 each year worldwide.[3] The survival rates still vary greatly with the stages of patients' disease. It was reported that about 40% of new cases were diagnosed with localized PeCa, with a 5-year overall survival rate of approximately 90%.[4] The survival rates decrease dramatically once patients are in the regional or distant metastasis stage. The 5-year overall survival rate is approximately 80% with unilateral inguinal lymph node involvement, 10%-20% with bilateral or pelvic lymph node involvement, and <10% with extranodal extension.[4]

Since the 1990s, substantial progress has been made in the prevention, diagnosis and treatment of PeCa. The prognosis has been greatly improved in PeCa patients, especially those who have not progressed to the metastatic stage. With the prolonged survival time, the proportion of other causes of death such as second malignant tumors (SMTs) and non-tumor diseases has been increasing among all deaths of PeCa patients. Since few previous studies have focused exclusively on other causes of death of PeCa patients, an analysis of causes of death among PeCa patients is warranted. Our study aimed to evaluate the main causes of death including SMTs and non-cancer causes for PeCa patients, and calculate the standardized mortality ratio (SMR) for each reason of death compared with the normal population.

Methods

Data Sources

The data of this study was derived from the Surveillance, Epidemiology, and End Results (SEER) program 18 registries, which is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 27.8% of the U.S. population, and it collects data concerning patient demographics, tumor morphology, stage at diagnosis, primary tumor site, the first course of treatment, and follow-up for vital status. Meanwhile, the data for the general population comes from the Centers for Disease Control and Prevention (CDC) of the United States. All data in this study has been removed identifiable information and can be available freely online. Thus, this study was regarded as exempt research by the institutional review.

Study Population and Study Variables

Patients with PeCa as the first primary malignancy and clear stage information according to the definition of Summary Stage 2000 (1998+) between 2004 and 2018 were included. The patients who had unclear follow-up time, living status at the end of follow-up and detailed causes of death were excluded.

Patients were divided into 3 groups by their stages (localized, regional and distant metastasis). The following variables of all patients and the dead patients were analyzed, including age (15-54, 55-64, 65-74, 75-84, and >85 years), year of diagnosis (2004-2008, 2009-2013, and 2014-2018), race (white, black. American Indian/Alaska native and Asian or Pacific Islander), grade (well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated), main pathological type, Radiotherapy (beam radiation, radioactive implants/brachytherapy and none/unknown) and Chemotherapy (yes and no/unknown).

Outcome Assessments

The causes of death after the diagnosis of PeCa included PeCa deaths, SMTs, and non-cancer deaths were regarded as the main outcomes. The standardized mortality ratio (SMR) with the 95% confidence interval (95% CI) of each cause was also calculated to evaluate the mortality risks compared with the general population. The last follow-up time was December 31, 2018, which was the latest data updated in the SEER database.

Statistics Analyses

For the baseline characteristics of 3 groups of patients with different PeCa stages, we analyzed the number of all included patients and observed deaths stratified by the above variables. The SMRs for each variable were calculated by comparing the observed number of deaths to the expected number. The expected number of deaths was based on the total number of patient-year and the excess risk of the general population. The causes of death and related SMRs and 95% CI were also analyzed in localized, regional, and distant metastasis PeCa patients. Statistical significance for SMR is a two-sided test of $P < .05$. All these analyses were performed using SEER*Stat version 8.4.0.1. Pie charts of the proportion of different causes of death were drawn with Microsoft Excel 2016.

Results

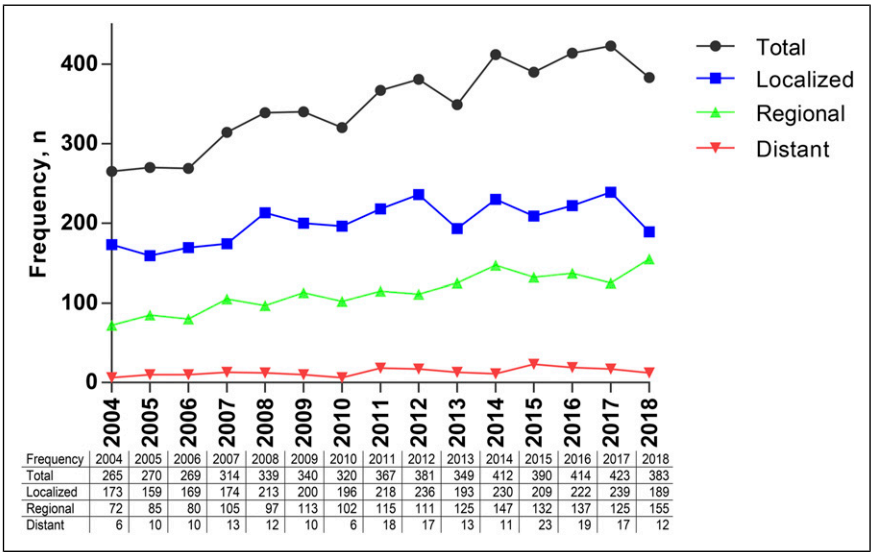
A total of 3597 PeCa patients were included, 1588 (44%) of them died during the follow-up. The majority of patients was in the localized stage (n = 2,155, 60%) and regional stage (n = 1310, 36%), whereas only 4% (n = 132) had distant disease. For patients with localized PeCa, 800 (37.1%) of them died with a SMR of 2.12 (1.97-2.27). 679 (51.8%) regional PeCa patients [SMR: 4.61 (4.27-4.97)] and 109 (82.6%) patients with distant metastatic PeCa [SMR: 27.68 (22.73-33.39)] died during the follow-up.

Baseline characteristics of included patients and the dead cases were presented in Table 1. The trend of new diagnosed PeCa patients from 2000 to 2018 were revealed in Figure 1.

Table 1. Baseline Characteristics of All Patients and Dead Cases During Follow-Up With Localized, Regional, and Distant Penile Cancer.

Characteristic	Localized			Regional			Distant		
	Patients, n	Deaths, n	SMR (95% CI)	Patients, n	Deaths, n	SMR (95% CI)	Patients, n	Deaths, n	SMR (95% CI)
Total	2155	800	2.12[a] (1.97-2.27)	1310	679	4.61[a] (4.27-4.97)	132	109	27.68[a] (22.73-33.39)
Age									
15-54 years	470	80	4.41[a] (3.5-5.49)	329	121	16.05[a] (13.32-19.18)	36	30	106.43[a] (71.81-151.93)
55-64 years	499	128	2.86[a] (2.39-3.4)	337	153	7.48[a] (6.34-8.77)	32	27	48.63[a] (32.05-70.75)
65-74 years	565	210	2.21[a] (1.92-2.53)	330	183	4.67[a] (4.01-5.39)	33	26	35.53[a] (23.21-52.06)
75-84 years	410	222	1.55[a] (1.35-1.76)	217	143	2.61[a] (2.2-3.08)	26	21	10.51[a] (6.51-16.07)
85+ years	211	160	2.10[a] (1.79-2.45)	97	79	3.10[a] (2.45-3.86)	5	5	13.45[a] (4.37-31.39)
Year of diagnosis									
2004-2008	730	143	2.65[a] (2.23-3.12)	353	234	3.11[a] (2.73-3.54)	30	27	17.20[a] (11.34-25.03)
2009-2013	744	284	2.05[a] (1.82-2.3)	442	258	5.32[a] (4.69-6.01)	48	42	32.68[a] (23.55-44.17)
2014-2018	681	373	2.01[a] (1.81-2.23)	515	187	7.88[a] (6.79-9.1)	54	40	36.91[a] (26.37-50.27)
Race									
White	1806	678	2.08[a] (1.92-2.24)	1120	577	4.35[a] (4-4.72)	105	83	26.90[a] (21.43-33.35)
Black	222	84	2.48[a](1.98-3.07)	116	72	7.28[a] (5.7-9.17)	16	15	20.92[a] (11.71-34.51)
American Indian/Alaska native	21	8	3.79[a] (1.64-7.47)	11	3	7.25[a] (1.49-21.18)	3	3	586.91[a] (121.03-1715.19)
Asian or Pacific islander	106	30	1.95[a] (1.31-2.78)	63	27	6.22[a] (4.1-9.05)	8	8	61.02[a] (26.35-120.24)
Grade									
Well differentiated	631	218	1.78[a] (1.55-2.03)	188	86	3.01[a] (2.41-3.71)	7	6	20.27[a] (7.44-44.12)
Moderately differentiated	706	304	2.55[a] (2.27-2.85)	574	317	5.07[a] (4.52-5.65)	38	32	19.92[a] (13.62-28.11)
Poorly differentiated	257	130	2.93[a] (2.44-3.47)	317	192	5.02[a] (4.34-5.79)	44	41	35.67[a] (25.6-48.39)
Undifferentiated	9	2	.7 (.08-2.52)	11	7	5.63[a] (2.27-11.61)	3	2	9.89[a] (1.2-35.72)
Pathological type									
8070/3: Squamous cell carcinoma, NOS	1425	560	2.22[a] (2.04-2.41)	829	447	4.49[a] (4.08-4.93)	84	68	30.34[a] (23.56-38.46)
8071/3: Squamous cell carcinoma, keratinizing, NOS	347	126	2.26[a] (1.88-2.69)	332	165	5.54[a] (4.73-6.46)	19	14	14.96[a] (8.18-25.1)
8051/3: Verrucous carcinoma, NOS	169	49	1.50[a] (1.11-1.98)	39	10	1.54 (.74-2.84)	2	2	98.29[a] (11.9-355.06)
8083/3: Basaloid squamous cell carcinoma	41	12	2.96[a] (1.53-5.18)	34	16	5.50[a](3.14-8.93)	6	5	23.04[a] (7.48-53.77)
Radiotherapy									
Beam radiation	68	30	1.90[a] (1.28-2.72)	198	128	8.26[a](6.89-9.83)	37	29	45.93[a](30.76-65.96)
Radioactive implants/brachytherapy	2	1	4.79 (.12-26.7)	3	1	12.38 (.31-68.98)	0	0	0
None/unknown	2085	769	2.13[a] (1.98-2.28)	1109	550	4.17[a](3.83-4.54)	95	80	24.19[a](19.18-30.11)
Chemotherapy									
Yes	59	22	2.69[a] (1.69-4.08)	298	167	11.38[a](9.72-13.24)	74	58	31.87[a](24.2-41.21)
No/unknown	2096	778	2.10[a] (1.96-2.26)	1012	512	3.86[a](3.53-4.21)	58	51	24.07[a](17.92-31.65)

SMR: standardized mortality ratio; 95% CI: 95% Confidence interval; NOS: Not otherwise specified.
[a]Statistical significance with $P < .05$.



Frequency	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total	265	270	269	314	339	340	320	367	381	349	412	390	414	423	383
Localized	173	159	169	174	213	200	196	218	236	193	230	209	222	239	189
Regional	72	85	80	105	97	113	102	115	111	125	147	132	137	125	155
Distant	6	10	10	13	12	10	6	18	17	13	11	23	19	17	12

Figure 1. The number of newly diagnosed of penile cancer from 2004 to 2018.

Causes of Death for Patients With Localized Penile Cancer

Among the 800 cases of death, 199 (24.9%) died for PeCa, 144 (18.0%) died for other tumor causes, and the rest 457 (57.1%) deaths were due to non-tumor causes. 75.9% of all PeCa deaths were within 3 years after diagnosis. The mortality rate of the general population who died for PeCa was rather low, which led to the extremely high SMR from the ratio of observed and expected. The majority of SMTs deaths (n = 106, 73.6%) occurred with 5 years after the diagnosis of PeCa. The main SMTs were lung and bronchus cancer [n = 40, SMR: 1.71 (1.22-2.33)], all cancers of digestive system [n = 25, SMR: 1.12 (.72-1.65)]. The main non-cancer causes of death were diseases of heart [n = 172, SMR: 1.66 (1.42-1.93)], chronic obstructive pulmonary disease (COPD) and allied cond [n = 38, SMR: 1.63 (1.15-2.24)], cerebrovascular diseases [n = 33, 22% of all deaths, SMR: 1.71 (1.17-2.4)] and diabetes mellitus [n = 26, SMR: 2.30 (1.5-3.37)]. The mortality risks of lung and bronchus cancer, skin tumor, diseases of heart, COPD and allied cond, cerebrovascular diseases, diabetes mellitus, nephritis, nephrotic syndrome and nephrosis, other infectious and parasitic diseases, hypertension, chronic liver disease and cirrhosis and atherosclerosis were significantly increased when compared with the general population. All these results are shown in Table 2. The mortality rate of all causes of death, PeCa, SMTs and non-tumor causes of patients after diagnosis is shown in Figure 2A and the percentage composition of the main causes of death is presented in Figure 3A.

Causes of Death for Patients With Regional Penile Cancer

For patients with regional PeCa, 348 (51.3%) of all 679 deaths were due to PeCa itself. There were 118 SMTs deaths and 213 non-cancer deaths, accounting for 17.4% and 31.4% of all deaths. For the PeCa deaths, 89.1% of them occurred within 3 years after diagnosis. With the low PeCa mortality rate of the general population, the SMR of PeCa death reached a terribly high level. The main SMTs were lung and bronchus cancer [n = 23, SMR: 2.41 (1.53-3.62)]. The mortality risks of lung and bronchus cancer, and skin tumor [SMR: 6.41 (2.35-13.95)] were significantly increased. The most common non-cancer cause of death was diseases of heart [n = 71, SMR: 1.77 (1.38-2.23)], COPD and allied cond [n = 17, SMR: 1.85 (1.08-2.95)], diabetes mellitus [n = 16, SMR: 3.62 (2.07-5.88)] and cerebrovascular diseases [n = 13, SMR: 1.77 (.94-3.03)]. The mortality risks of diseases of heart, COPD and allied cond, diabetes mellitus, nephritis, nephrotic syndrome and nephrosis [n = 9, SMR: 2.88 (1.32-5.47)] and septicemia [n = 8, SMR: 3.83 (1.65-7.54)] were significantly increased when compared with the general population. All these results are shown in Table 3. The mortality rate of patients after diagnosis and is shown in Figure 2B and the percentages of the main causes of death is revealed in Figure 3B.

Causes of Death for Patients With Distant Metastatic Penile Cancer

For the included 132 patients with distant metastasis PeCa, 109 of them died during the follow-up with a significantly increased SMR of 27.68 (22.73-33.39). 100 deaths (91.7%) were due to malignant cancers including 76 cases (69.7%) dead of PeCa. 67.1% (n = 51) of all PeCa deaths occurred within 1 year and 98.7% (n = 75) dead within 3 years after diagnosis. There were 24 patients (22%) who died for SMTs, mainly including cancers from 4 lung and bronchus, 2 prostate, and 2 skin, 2 lymphoma and 3 other

Table 2. Main causes of death for patients with localized penile cancer.

Causes of death	Total			<1 year			<1-5 year			5-10 years			>10 years		
	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)
All causes of death	800	377.82	2.12[a] (1.97-2.27)	167	58.34	2.86[a] (2.44-3.33)	422	183.12	2.30[a] (2.09-2.54)	167	107.68	1.55[a] (1.32-1.8)	44	28.68	1.53[a] (1.11-2.06)
All malignant cancers	343	86.5	3.97[a] (3.56-4.41)	80	13.45	5.95[a] (4.72-7.4)	204	42.35	4.82[a] (4.18-5.53)	48	24.48	1.96[a] (1.45-2.6)	11	6.22	1.77 (.88-3.16)
Male genital system	213	10.72	19.86[a] (17.29-22.72)	58	1.71	33.97[a] (25.79-43.91)	129	5.2	24.82[a] (20.72-29.49)	25	2.99	8.37[a] (5.42-12.36)	1	.83	1.2 (.03-6.7)
Penis	199	.08	2495.58[a] (2160.87-2867.44)	53	.01	4477.48[a] (3353.94-5856.66)	125	.04	3293.53[a] (2741.5-3924.09)	21	.02	898.28[a] (556.05-1373.11)	0	.01	0 (0-561.23)
Prostate	9	10.59	.85 (.39-1.61)	2	1.69	1.18 (.14-4.28)	2	5.14	.39 (.05-1.41)	4	2.95	1.36 (.37-3.47)	1	.82	1.22 (.03-6.78)
Urinary system	8	6.29	1.27 (.55-2.51)	3	.96	3.14 (.65-9.16)	4	3.05	1.31 (.36-3.36)	1	1.81	.55 (.01-3.08)	0	.47	0 (0-7.81)
Urinary bladder	4	3.8	1.05 (.29-2.7)	2	.58	3.47 (.42-12.54)	1	1.83	.55 (.01-3.04)	1	1.1	.91 (.02-5.09)	0	.29	0 (0-12.7)
Kidney and renal Pelvis	1	2.33	.43 (.01-2.39)	1	.36	2.81 (.07-15.63)	0	1.14	0 (0-3.24)	0	.67	0 (0-5.54)	0	.17	0 (0-21.87)
Other urinary organs	3	.09	33.47[a] (6.9-97.82)	0	.01	0 (0-278.54)	3	.04	69.99[a] (14.43-204.54)	0	.03	0 (0-140.81)	0	.01	0 (0-503.78)
Digestive system	25	22.34	1.12 (.72-1.65)	3	3.41	.88 (.18-2.57)	18	10.89	1.65 (.98-2.61)	3	6.4	.47 (.1-1.37)	1	1.63	.61 (.02-3.42)
Liver and intrahepatic bile duct	8	3.71	2.16 (.93-4.25)	0	.53	0 (0-6.92)	7	1.78	3.93[a] (1.58-8.09)	1	1.11	.9 (.02-5.03)	0	.28	0 (0-13.01)
Pancreas	7	5.47	1.28 (.51-2.63)	1	.82	1.22 (.03-6.82)	5	2.65	1.89 (.61-4.4)	1	1.59	.63 (.02-3.5)	0	.42	0 (0-8.88)
Esophagus	4	2.93	1.37 (.37-3.5)	0	.45	0 (0-8.21)	3	1.44	2.08 (.43-6.09)	0	.84	0 (0-4.41)	1	.21	4.84 (.12-26.98)
Colon and rectum	3	7.41	.4 (.08-1.18)	2	1.18	1.7 (.21-6.13)	0	3.65	0 (0-1.01)	1	2.06	.48 (.01-2.7)	0	.52	0 (0-7.13)
Stomach	2	1.83	1.1 (.13-3.96)	0	.29	0 (0-12.81)	2	0.9	2.23 (.27-8.06)	0	.51	0 (0-7.2)	0	.13	0 (0-28.41)
Intrahepatic bile duct	2	.76	2.63 (.32-9.49)	0	.11	0 (0-34.14)	1	.36	2.77 (.07-15.41)	1	.23	4.36 (.11-24.32)	0	.06	0 (0-59.14)
Respiratory system	43	24.31	1.77[a] (1.28-2.38)	7	3.87	1.81 (.73-3.73)	25	12.07	2.07[a] (1.34-3.06)	8	6.76	1.18 (.51-2.33)	3	1.62	1.85 (.38-5.41)
Lung and bronchus	40	23.39	1.71[a] (1.22-2.33)	7	3.72	1.88 (.76-3.87)	24	11.62	2.07[a] (1.32-3.07)	6	6.5	.92 (.34-2.01)	3	z	1.93 (.4-5.64)
Skin excluding basal and squamous	11	2.28	4.82[a] (2.41-8.63)	1	.35	2.88 (.07-16.03)	6	1.12	5.38[a] (1.97-11.7)	3	.66	4.57 (.94-13.37)	1	.16	6.17 (.16-34.36)
Brain and other nervous system	2	1.76	1.14 (.14-4.11)	0	.26	0 (0-13.99)	2	.86	2.34 (.28-8.44)	0	.51	0 (0-7.23)	0	.13	0 (0-28.57)
Lymphoma	3	3.5	.86 (.18-2.5)	0	.54	0 (0-6.79)	1	1.71	.58 (.01-3.25)	2	.99	2.01 (.24-7.27)	0	.25	0 (0-14.66)

(continued)

Table 2. (continued)

Causes of death	Total			<1 year			<1-5 year			5-10 years			>10 years		
	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)
Myeloma	2	1.93	1.04 (.13-3.75)	0	.29	0 (0-12.63)	1	.93	1.07 (.03-5.97)	1	.55	1.81 (.05-10.08)	0	.15	0 (0-24.97)
Leukemia	3	3.89	.77 (.16-2.25)	0	0.6	0 (0-6.15)	2	1.9	1.05 (.13-3.8)	1	1.11	.9 (.02-5.02)	0	.28	0 (0-13.08)
Miscellaneous malignant cancer	28	6.79	4.12[a] (2.74-5.96)	7	1.05	6.64[a] (2.67-13.67)	13	3.32	3.91[a] (2.08-6.69)	4	1.92	2.08 (.57-5.32)	4	.49	8.13[#](2.21-20.81)
Non-cancer causes															
Diseases of heart	172	103.44	1.66[a] (1.42-1.93)	29	16.31	1.78[a] (1.19-2.55)	91	50.31	1.81[a] (1.46-2.22)	40	29.08	1.38 (.98-1.87)	12	7.74	1.55 (.8-2.71)
COPD and allied cond	38	23.29	1.63[a] (1.15-2.24)	8	3.59	2.23 (.96-4.4)	20	11.32	1.77[a] (1.08-2.73)	9	6.65	1.35 (.62-2.57)	1	1.74	.57 (.01-3.2)
Cerebrovascular diseases	33	19.34	1.71[#](1.17-2.4)	7	3.04	2.31 (.93-4.75)	10	9.33	1.07 (.51-1.97)	9	5.46	1.65 (.75-3.13)	7	1.51	4.63[#](1.86-9.54)
Diabetes mellitus	26	11.32	2.30[a] (1.5-3.37)	6	1.72	3.49[#](1.28-7.6)	7	5.47	1.28 (.51-2.64)	11	3.25	3.38[a] (1.69-6.05)	2	.88	2.28 (.28-8.24)
Nephritis' nephrotic syndrome and nephrosis	16	8.25	1.94[a] (1.11-3.15)	3	1.28	2.34 (.48-6.83)	11	4	2.75[a] (1.37-4.92)	1	2.33	.43 (.01-2.39)	1	.63	1.58 (.04-8.79)
Pneumonia and influenza	14	9.33	1.5 (.82-2.52)	5	1.5	3.34[a] (1.08-7.79)	6	4.54	1.32 (.49-2.88)	3	2.6	1.16 (.24-3.38)	0	0.7	0 (0-5.3)
Other infectious and parasitic diseases including HIV	13	3.13	4.16[a] (2.21-7.11)	5	.49	10.17[a] (3.3-23.74)	3	1.55	1.93 (.4-5.64)	5	.88	5.71[a] (1.85-13.33)	0	.21	0 (0-17.77)
Accidents and adverse effects	11	12.11	.91 (.45-1.63)	2	1.82	1.1 (.13-3.96)	4	5.84	.69 (.19-1.75)	3	3.52	.85 (.18-2.49)	2	.93	2.16 (.26-7.79)
Hypertension without heart disease	10	4.22	2.37[#](1.14-4.36)	2	.62	3.22 (.39-11.62)	1	1.99	.5 (.01-2.8)	5	1.24	4.04[a] (1.31-9.42)	2	.36	5.52 (.67-19.96)
Chronic liver disease and cirrhosis	9	3.8	2.37[a] (1.08-4.49)	2	.57	3.53 (.43-12.76)	4	1.85	2.16 (.59-5.53)	2	1.11	1.8 (.22-6.49)	1	.27	3.65 (.09-20.36)

AbbreviationsSMR: standardized mortality ratio; CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease.
[a]Statistical significance with $P < .05$.

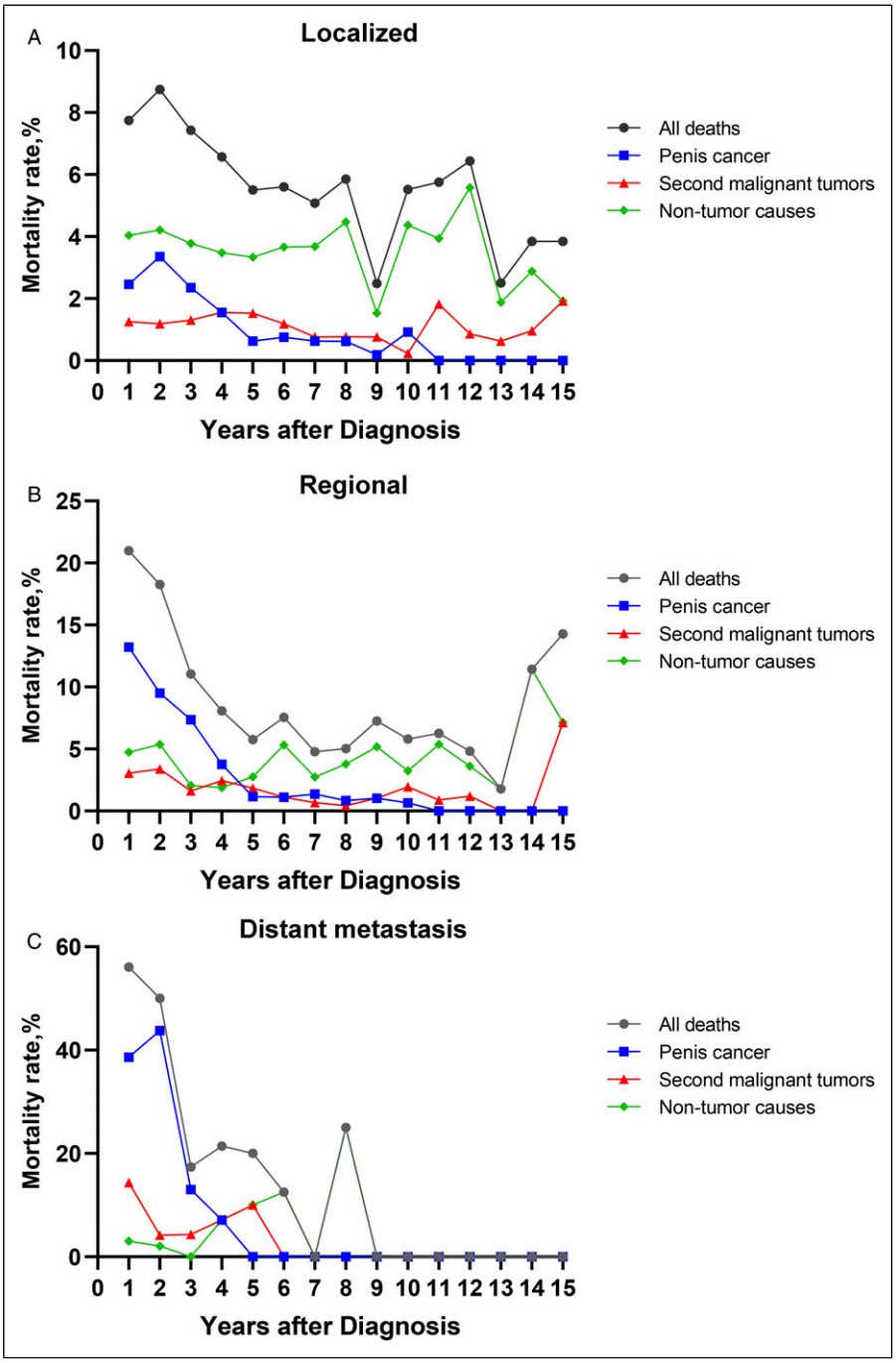


Figure 2. Mortality rate of all causes of death, PeCa, SMTs and non-tumor causes for patients diagnosed with localized, regional and distant metastasis penile cancer. (A) Patients with localized penile cancer; (B) patients with regional penile cancer; (C) patients with distant metastasis penile cancer.

urinary organs. 19 (79.2%) of SMTs deaths occurred within 1 year of the diagnosis of PeCa. As for the non-cancer deaths, only 9 cases of deaths were observed, including 5 deaths from diseases of heart, 1 septicemia death, 1 other infection and parasitic diseases deaths, and 2 other causes of death. These results are presented in Table 4 and Figure 3C. The mortality rate of all causes of death, PeCa, SMTs and non-tumor causes for patients after diagnosis is shown in Figure 2C.

Discussion

With the high and increasing survival rate of PeCa, deaths from other causes account for a very high proportion of total

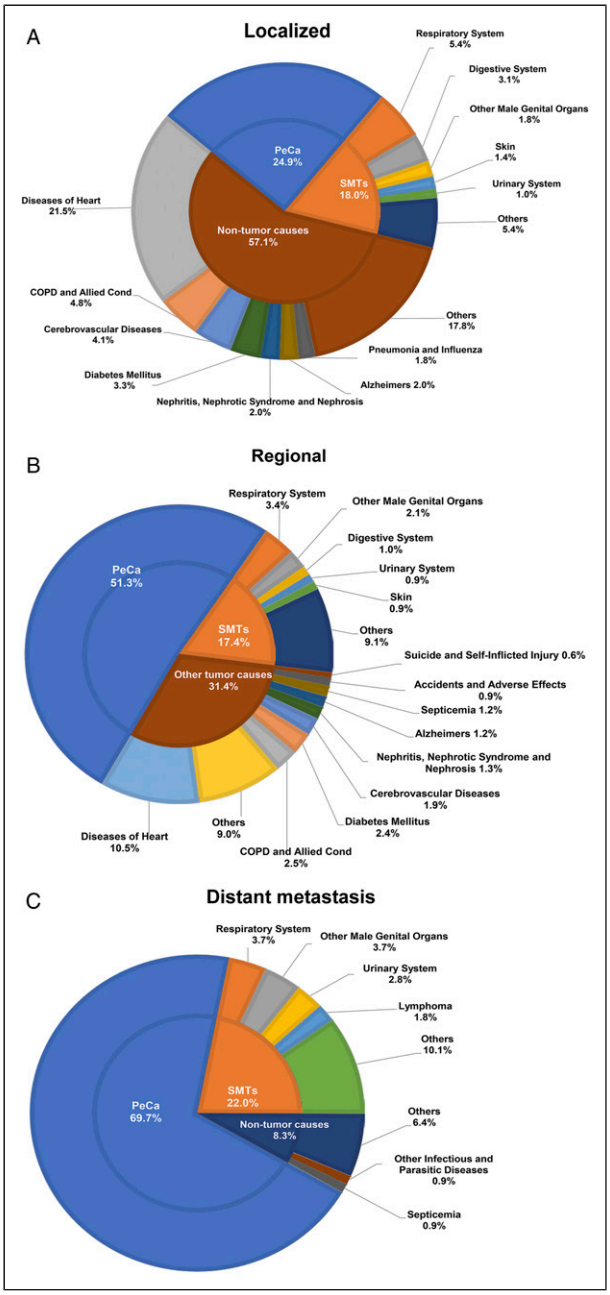


Figure 3. The percentages of main causes of death in penile cancer patients. (A) Patients with localized penile cancer; (B) patients with regional penile cancer; (C) patients with distant metastasis penile cancer.

deaths and tend to increase.[5] Therefore, other causes of death including SMTs and non-tumor diseases should be taken seriously. Besides, whether these causes have relationships with the diagnosis of PeCa is unclear. In current literature, studies on the SMTs for the primary PeCa were quite rare. Our study, as far as we can know, is the first study focusing on the SMTs and non-cancer causes of death for primary PeCa patients. We also relate these causes to the time period after diagnosis of penile cancer and provide results stratified by tumor stage and patient characteristics to provide valuable insights into the prognosis and management of penile cancer.

According to the basic characteristic of dead patients, people diagnosed with penile cancer between 15 and 54 years had obviously higher SMRs than other age groups. As the number of deaths among 15-54 years old were not obviously higher than other age groups, this result was due to the lower excess risk of the general population. For the general population among 15-54 years, most of them have better physical conditions and a lower rate of all kinds of deaths when compared with the population with elderly age. We also found that the mortality risk continued to decrease with the year of diagnosis from 2.65 in 2004-2008 to 2.01 in 2014-2018 in localized disease. This may be the result of improved cancer treatment and disease management after diagnosis for PeCa over time. However, this result was reversed in regional and distant metastatic disease. White people accounted for a higher proportion of all deaths, but black people had a higher risk of death in localized and regional diseases. Previous studies reported that the mortality rate of blacks was higher than that of whites among American penile cancer patients.[6] This may be due to earlier exposure of blacks to HPV through early sexual contact, leading to an earlier diagnosis of penile cancer.[6,7]

For localized and regional diseases, deaths from SMR accounted for a certain percentage of total deaths. A study identified 3641 PeCa patients in the Swedish Family-Cancer Database from 1958 to 2015. They found that SMTs occurred in 16.8% of primary PeCa patients and 45.9% of these patients dead for SMTs rather than PeCa.[8] The main SMTs included prostate cancer, colorectum cancer, lung cancer, bladder cancer, skin squamous cell cancer and stomach cancer. These results were similar to ours. This study also reported that SMTs was associated with HPV and smoking.[8] Another study with 1634 men with PeCa found a 2-3-fold increased risk of a second human papillomavirus (HPV) associated cancer of the oral cavity, oropharynx and anal canal among PeCa patients.[9] For the occurrence of PeCa, there were some important risk factors of PeCa including lack of circumcision, smegma retention, chronic balanitis, lichen sclerosis, obesity, smoking, HPV infection and immune-compromised states.[10,11] It may be the consequences of treatment for penile cancer and the more widely spread of HPV.[12-14]

For the non-tumor deaths, it accounted for a large proportion among all deaths in localized and regional stages. A previous study reported that 65.7% of deaths were due to non-cancer causes among PeCa patients without SMTs and only 28.4% were due to penile cancer.[8] Cardiovascular disease is still a major cause of death in PeCa patients. Statistics in recent years from a study had shown that more than 20% of PeCa patients died from cardiovascular disease.[15] It was also reported that the risk of cancer patients dying from cardiovascular diseases was inversely related to the age at diagnosis.[15] For this kind of cancer with a good prognosis but still a high risk of cardiovascular death, patients may benefit from

Table 3. Main causes of death for patients with regional penile cancer.

Causes of death	Total			<1 year			1-5 years			>5 years		
	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)
All causes of death	679	147.4	4.61[a] (4.27-4.97)	275	27.55	9.98[a] (8.84-11.23)	310	67.93	4.56[a] (4.07-5.1)	94	51.92	1.81[a] (1.46-2.22)
All malignant cancers	466	34.65	13.45[a] (12.26-14.73)	213	6.56	32.48[a] (28.27-37.15)	225	16.42	13.71[a] (11.97-15.62)	28	11.67	2.40[a] (1.59-3.47)
Male genital system	362	4.07	88.89[a] (79.97-98.54)	179	.79	225.26[a] (193.47-260.79)	168	1.88	89.54[a] (76.51-104.15)	15	1.4	10.70[a] (5.99-17.65)
Penis	348	.03	11 020.00[a] (9892.46-12,240.84)	173	.01	29 605.21[a] (25 357.89-34 360.42)	162	.01	11 182.19[a] (9526.53-13042.87)	13	.01	1155.76[a] (615.39-1976.38)
Prostate	8	4.02	1.99 (.86-3.92)	2	.78	2.55 (.31-9.21)	4	1.85	2.16 (.59-5.53)	2	1.38	1.45 (.18-5.22)
Testis	2	.01	149.35[a] (18.09-539.5)	1	0	370.55[a] (9.38-2064.6)	1	.01	152.52[a] (3.86-849.81)	0	0	0 (0-891.78)
Urinary system	6	2.51	2.39 (.88-5.21)	1	.46	2.18 (.06-12.16)	4	1.15	3.47 (.94-8.87)	1	.89	1.12 (.03-6.23)
Kidney and renal Pelvis	3	.95	3.17 (.65-9.27)	0	.18	0 (0-20.85)	2	.45	4.46 (.54-16.13)	1	.32	3.12 (.08-17.36)
Urinary bladder	2	1.5	1.34 (.16-4.83)	1	.27	3.71 (.09-20.65)	1	.68	1.48 (.04-8.23)	0	.55	0 (0-6.72)
Digestive system	7	8.97	.78 (.31-1.61)	1	1.69	.59 (.01-3.3)	4	4.27	.94 (.26-2.4)	2	3.01	.66 (.08-2.4)
Colon and rectum	3	2.95	1.02 (.21-2.97)	0	.57	0 (0-6.44)	2	1.41	1.41 (.17-5.11)	1	.97	1.03 (.03-5.77)
Esophagus	2	1.21	1.65 (.2-5.95)	0	.23	0 (0-16.24)	1	.58	1.72 (.04-9.57)	1	.41	2.47 (.06-13.75)
Respiratory system	23	9.9	2.32[a] (1.47-3.49)	4	1.91	2.1 (.57-5.37)	13	4.8	2.71[a] (1.44-4.63)	6	3.19	1.88 (.69-4.09)
Lung and bronchus	23	9.53	2.41[a] (1.53-3.62)	4	1.84	2.18 (.59-5.58)	13	4.62	2.81[a] (1.5-4.81)	6	3.07	1.95 (.72-4.25)
Skin excluding basal and squamous	6	.94	6.41[a] (2.35-13.95)	2	.17	11.79[a] (1.43-42.6)	4	.43	9.23[a] (2.51-23.62)	0	.33	0 (0-11.07)
Lymphoma	2	1.41	1.42 (.17-5.14)	0	.26	0 (0-14.17)	2	.65	3.05 (.37-11.03)	0	.49	0 (0-7.53)
Leukemia	2	1.56	1.28 (.16-4.63)	0	.29	0 (0-12.84)	2	.72	2.76 (.33-9.97)	0	.55	0 (0-6.74)
Miscellaneous malignant cancer	51	2.72	18.75[a] (13.96-24.66)	25	.51	48.95[a] (31.68-72.26)	24	1.28	18.76[a] (12.02-27.92)	2	.93	2.15 (.26-7.77)
Non-cancer causes												
Diseases of heart	71	40.11	1.77[a] (1.38-2.23)	20	7.57	2.64[#](1.61-4.08)	32	18.45	1.73[a] (1.19-2.45)	19	14.09	1.35 (.81-2.11)
COPD and allied cond	17	9.21	1.85[a] (1.08-2.95)	4	1.69	2.37 (.65-6.08)	8	4.24	1.89 (.82-3.72)	5	3.29	1.52 (.49-3.55)
Diabetes mellitus	16	4.42	3.62[a] (2.07-5.88)	5	.83	6.00[a] (1.95-14.01)	6	2.07	2.89[a] (1.06-6.3)	5	1.51	3.31[a] (1.08-7.73)
Cerebrovascular diseases	13	7.34	1.77 (.94-3.03)	3	1.39	2.16 (.44-6.3)	6	3.34	1.79 (.66-3.91)	4	2.61	1.53 (.42-3.92)
Nephritis, nephrotic syndrome and nephrosis	9	3.13	2.88[a] (1.32-5.47)	3	.59	5.07[a] (1.05-14.81)	5	1.44	3.48[a] (1.13-8.12)	1	1.1	.91 (.02-5.08)

(continued)

Table 3. (continued)

Causes of death	Total			<1 year			1-5 years			>5 years		
	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)
Septicemia	8	2.09	3.83[a] (1.65-7.54)	5	0.4	12.66[a] (4.11-29.53)	1	.96	1.04 (.03-5.77)	2	.73	2.74 (.33-9.89)
Alzheimers	8	4.79	1.67 (.72-3.29)	3	.84	3.56 (.74-10.42)	2	2.02	.99 (.12-3.57)	3	1.93	1.56 (.32-4.55)
Chronic liver disease and cirrhosis	4	1.62	2.47 (.67-6.32)	3	.31	9.67[a] (1.99-28.25)	0	.79	0 (0-4.64)	1	.52	1.94 (.05-10.8)
Accidents and adverse effects	6	4.84	1.24 (.45-2.7)	0	.91	0 (0-4.04)	3	2.26	1.33 (.27-3.88)	3	1.67	1.8 (.37-5.25)
Suicide and self-inflicted injury	4	1.38	2.9 (.79-7.42)	1	.27	3.71 (.09-20.68)	1	.67	1.49 (.04-8.28)	2	.44	4.57 (.55-16.51)

CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; SMR: standardized mortality ratio.
[a]Statistical significance with $P < .05$.

Table 4. Main Causes of Death for Patients With Distant Penile Cancer.

	Total			<1 year			1-3 years			>3 years		
Causes of death	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)	Observed, n	Expected, n	SMR (95% CI)
All causes of death	109	3.94	27.68[a] (22.73-33.39)	74	1.85	40.10[a] (31.49-50.34)	28	1.09	25.61[a] (17.02-37.01)	7	1	7.00[a] (2.82-14.43)
All malignant cancers	100	.98	102.30[a] (83.23-124.42)	70	.45	154.76[a] (120.65-195.54)	27	.29	92.21[a] (60.76-134.16)	3	.23	12.91[a] (2.66-37.72)
Respiratory system	4	.28	14.38[a] (3.92-36.81)	3	.13	22.93[a] (4.73-67.01)	0	.09	0 (0-42.56)	1	.06	16.48 (.42-91.8)
Lung and bronchus	4	.27	14.98[a] (4.08-38.34)	3	.13	23.85[a] (4.92-69.69)	0	.08	0 (0-44.28)	1	.06	17.24 (.44-96.06)
Soft tissue including heart	2	.01	331.85[a] (40.19-1198.77)	1	0	351.01[a] (8.89-1955.69)	1	0	554.76[a] (14.05-3090.9)	0	0	0 (0-2682.36)
Skin excluding basal and squamous	2	.02	85.91[a] (10.4-310.32)	1	.01	87.34[a] (2.21-486.61)	1	.01	146.53[a] (3.71-816.42)	0	.01	0 (0-736.74)
Male genital system	80	.12	650.98[a] (516.18-810.2)	55	.05	1065.43[a] (802.63-1386.8)	24	.03	713.33[a] (457.04-1061.38)	1	.04	26.58 (.67-148.08)
Prostate	2	.12	16.48[a] (2-59.52)	2	.05	39.26[a] (4.75-141.82)	0	.03	0 (0-111.09)	0	.04	0 (0-99.09)
Penis	76	0	84 751.04[a] (66 774.18-106078.56)	51	0	126 908.70[a] (94 491.86-166861.5)	24	0	92 697.90[a] (59 393.29-137,927.13)	1	0	4237.74[a] (107.29-23,611.17)
Urinary system	3	.06	46.59[a] (9.61-136.15)	2	.03	64.45[a] (7.81-232.82)	0	.02	0 (0-199.1)	1	.01	67.40[a] (1.71-375.54)
Miscellaneous malignant cancer	7	.07	93.72[a] (37.68-193.1)	7	.04	198.90[a] (79.97-409.8)	0	.02	0 (0-166.27)	0	.02	0 (0-213.09)
Non-cancer causes												
Septicemia	1	.06	16.57 (.42-92.3)	1	.03	37.63 (.95-209.66)	0	.02	0 (0-218.26)	0	.02	0 (0-218.46)
Other infectious and parasitic diseases including HIV	1	.04	26.85 (.68-149.58)	1	.02	57.29[a] (1.45-319.22)	0	.01	0 (0-340.04)	0	.01	0 (0-412.29)
Diseases of heart	5	1.05	4.75[a] (1.54-11.09)	1	.49	2.02 (.05-11.26)	1	.28	3.52 (.09-19.64)	3	.27	10.95[a] (2.26-32)
Other cause of death	2	.57	3.53 (.43-12.75)	1	.27	3.69 (.09-20.57)	0	.15	0 (0-25.01)	1	.15	6.75 (.17-37.6)

SMR: standardized mortality ratio; CI: confidence interval.
[a]Statistical significance with $P < .05$.

clinical intervention by a cardiologist at the time of diagnosis. There were some relationships between diabetes mellitus and PeCa. Previous studies reported that diabetes was associated with phimosis, which could increase the risk of penile cancer.[16-18] Men with diabetes, mainly type 2 diabetes, were associated with an increased incidence of penile squamous cell carcinoma compared with men without diabetes.[19] Localized and advanced PeCa and the associated treatments have profound physical and psychological effects on the survivors' quality of life. Due to potentially crippling surgery, patients with penile cancer increased psychological stress and therefore have an increased need for psychosocial care.[20-22] However, in our study, we didn't find a significantly increased risk of suicide and self-inflicted injury.[22]

For patients with distant metastatic PeCa, the prognosis was poor with a mortality rate of 82.6%. The main cause of death in patients was the penile cancer tumor itself. Other causes of death only account for only a small fraction of all deaths. Therefore, active and effective treatment for metastatic penile cancer is still the most important measure to prevent deaths and prolong survival durations.

Our study is the first to provide the most comprehensive comparison and description of the risk of death from all causes in PeCa patients using tumor stage and time after diagnosis. However, there were some limitations in our study. Firstly, we used Summary Stage 2000 (1998+) to distinguish local, regional and distant diseases, but these classifications maybe not the same in different periods. Therefore, the results of this study can't fully represent the current staging results. Secondly, some important information of patients in this database was available, such as the basic illness, detailed treatments and socioeconomic status, etc. The information might have certain impacts on the survival and prognosis of patients. Our results might be influenced by the missing information. Thirdly, the sample size selection was not estimated by power calculations. It was also a limitation of our study.

Conclusion

Our study provided a detailed analysis of the causes of death for patients with locally, regionally, and distant metastatic PeCa after diagnosis. This information could be useful for disease prevention and health care during patients' survivorship.

Author Contributions

P.S., X.W. and L.Y.: project development, data collection and analysis, manuscript writing. K.M., Z.L.: data collection and analysis, manuscript writing. J.Z., J.C. and Q.Z.: manuscript writing. Q.D.: project development. All authors confirm that they read and approved the final draft for submission. All authors are also responsible for the manuscript content.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a Key Project of National Natural Science Foundation of China; Grant ID: 8177060452; Project of Science and Technology Department of Sichuan Province, Grant ID: 2021YFS0117; and Project of Science and Technology Department of Chengdu City, Sichuan Province, Grant ID: 2021YF0500717SN.

Ethical Approval

All data were obtained from the public available database. All patients' data we obtained from the database was de-identified. Therefore, our study was exempted by the ethics committee of West China Hospital of Sichuan University.

Data Availability Statement

The data of this study are available in the SEER database (https://seer.cancer.gov/). The raw data has been uploaded as Supplementary materials.

ORCID iD

Qiang Dong https://orcid.org/0000-0003-0343-8254

Supplemental Material

Supplemental material for this article is available online.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30.
2. Thomas A, Necchi A, Muneer A, et al. Penile cancer. *Nat Rev Dis Prim*. 2021;7:11.
3. Erratum. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2020;70:313.
4. Thomas A, Necchi A, Muneer A, et al. Penile cancer. *Nat Rev Dis Primers*. 2021;7:1-24.
5. Zaorsky NG, Churilla TM, Egleston BL, et al. Causes of death among cancer patients. *Ann Oncol*. 2017;28:400-407.
6. Hernandez BY, Barnholtz-Sloan J, German RR, et al. Burden of invasive squamous cell carcinoma of the penis in the United States, 1998-2003. *Cancer*. 2008;113:2883-2891.
7. Kahn JA, Lan D, Kahn RS. Sociodemographic factors associated with high-risk human papillomavirus infection. *Obstet Gynecol*. 2007;110:87-95.
8. Zhang L, Hemminki O, Chen T, et al. Familial clustering, second primary cancers and causes of death in penile, vulvar and vaginal cancers. *Sci Rep*. 2019;9:11804.
9. Glombik D, Oxelbark A, Sundqvist P, et al. Risk of second HPV-associated cancers in men with penile cancer. *Acta Oncol*. 2021;60:667-671.
10. Micali G, Nasca MR, Innocenzi D, Schwartz RA. Penile cancer. *JAAD*. 2006;54:369-391.

11. Douglawi A, Masterson TA. Updates on the epidemiology and risk factors for penile cancer. *Transl Androl Urol*. 2017;6:785-790.
12. Hemminki K, Dong C, Vaittinen P. Second primary cancer after in situ and invasive cervical cancer. *Epidemiology*. 2000;11:457-461.
13. Teng C-J, Huon L-K, Hu Y-W, et al. Secondary primary malignancy risk in patients with cervical cancer in Taiwan: A nationwide population-based study. *Medicine (Baltim)*. 2015; 94:e1803.
14. Arnold M, Liu L, Kenter GG, Creutzberg CL, Coebergh JW, Soerjomataram I. Second primary cancers in survivors of cervical cancer in The Netherlands: Implications for prevention and surveillance. *Radiother Oncol*. 2014;111:374-381.
15. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J*. 2019;40:3889-3897.
16. Bromage SJ, Crump A, Pearce I. Phimosis as a presenting feature of diabetes. *BJU Int*. 2008;101:338-340.
17. Chopra R, Fisher RD, Fencl R. Phimosis and diabetes mellitus. *J Urol*. 1982;127:1101-1102.
18. Crowe GG. Diabetes presenting with phimosis. *Lancet*. 1971;2:50.
19. Reinholdt K, Thomsen LT, Munk C, et al. Incidence of HPV-related anogenital intraepithelial neoplasia and cancer in men with diabetes compared with the general population. *Epidemiology*. 2021;32:705-711.
20. Dräger DL, Protzel C, Hakenberg OW. Identifying psychosocial distress and stressors using distress-screening instruments in patients with localized and advanced penile cancer. *Clin Genitourin Cancer*. 2017;15:605-609.
21. Cassileth BR, Lusk EJ, Tenaglia AN. Patients' perceptions of the cosmetic impact of melanoma resection. *Plast Reconstr Surg*. 1983;71:73-75.
22. Ficarra V, Righetti R, D'Amico A, et al. General state of health and psychological well-being in patients after surgery for urological malignant neoplasms. *Urol Int*. 2000;65:130-134.