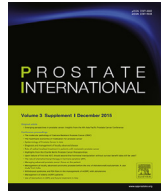




Contents lists available at ScienceDirect

Prostate International

journal homepage: <https://www.journals.elsevier.com/prostate-international>

Research Article

Second primary cancer risk and survival in prostate cancer patients: A nationwide analysis

Jihye Hyun ^{a,†, #}, Jooyoung Lee ^{a,†, #}, Tuan Thanh Nguyen ^b, Se Young Choi ^{c,*}

^a Department of Applied Statistics, Chung-Ang University, Seoul, Korea

^b Department of Urology, Cho Ray Hospital, University of Medicine and Pharmacy, Ho Chi Minh City, Viet Nam

^c Department of Urology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea

ARTICLE INFO

Article history:

Received 23 November 2024

Received in revised form

16 December 2024

Accepted 12 January 2025

Available online xxx

Keywords:

Second primary neoplasms

Prostatic neoplasms

Republic of Korea

Secondary primary malignancies

ABSTRACT

Purpose: Different treatments for prostate cancer (PC) could affect a patient's risk of developing second primary cancers (SPCs). We assessed the incidence of SPC and overall survival (OS) after SPC diagnosis in patients with PC who underwent radical prostatectomy (RP) or radiation therapy (RT) as primary treatment.

Methods: Using the National Health Insurance Service database in South Korea, all male patients with PC between 2002 and 2018 were corrected for selection bias between the RT and RP groups by inverse probability of treatment weighting. The primary outcome was the incidence of SPC, and secondary outcome was OS after SPC diagnosis; cumulative incidence functions for competing risks of each SPC type were evaluated between the RP and RT groups. Cox regression analysis evaluated OS after SPC.

Results: Among 26,254 patients with PC, 20.3% and 79.7% were treated with RT and RP, respectively. Patients with PC had a 7% lower risk of all SPCs than the general male population [standardized incidence ratio (SIR) = 0.93]. Bladder (SIR = 1.65) and thyroid (SIR = 2.75) cancers were more common in both treatment groups. At 10-year follow-up, patients who underwent RP were less likely to have colon cancer than those who underwent RT [risk difference (%) = -0.9]. The former had a lower risk of death following lung (aHRs: 0.70; P = 0.010) and colon (aHRs: 0.53; P = 0.001) SPCs and a higher risk of death following esophageal SPC (aHRs: 6.9; P = 0.008).

Conclusions: SPC incidence and OS after SPC diagnosis may be influenced by the initial PC treatment. The choice of primary treatment for PC should guide the follow-up care and subsequent treatment strategies for SPCs.

© 2025 The Asian Pacific Prostate Society. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Approximately, 5% of the population in developed countries survives a cancer diagnosis.¹ In recent decades, early detection, screening systems, and improved treatments have contributed to the prolonged survival of patients with primary cancer. In the United States, the 5-year survival rates exceed 99% for localized and regional prostate cancer (PC).² A significant increase in the number of cancer survivors has led to a corresponding increase in the

incidence of second primary cancers (SPCs), which are new primary cancers occurring in individuals previously diagnosed with cancer. The causes of SPC are not entirely clear owing to their relatively less frequency among patients with primary cancer and the varied treatments of the initial cancer. Development of SPC may be influenced by genetic predisposition, environmental factors, lifestyle choices, and treatments, such as chemotherapy or radiation therapy (RT), used for the initial cancer.³ Generally, survival rates for SPCs are worse than those for primary cancers.⁴ In the United States, the estimated 5-year mortality specific to SPC is approximately double of that associated with the same primary cancer.⁵

Randomized controlled trials (RCTs) comparing radical prostatectomy (RP) and RT for low- or favorable intermediate-risk localized PC have shown similar oncologic outcomes.⁶ However, there has been no randomized controlled trial report on high-risk PC yet, and the optimal definitive treatment for localized PC remains

* Corresponding author. Department of Urology, Chung-Ang University Hospital, Chung-Ang University College of Medicine 102, Heukseok-ro, Dongjak-gu, Seoul, 06973, Korea.

E-mail address: urosyc@cau.ac.kr (S.Y. Choi).

† Both authors contributed equally to this work as the first authors.

Co-first authors: Jihye Hyun, and Jooyoung Lee.

<https://doi.org/10.1016/j.pnrl.2025.01.004>

p2287-8882 e2287-903X/© 2025 The Asian Pacific Prostate Society. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

undetermined. The different mechanisms of action between RP and RT could predispose patients to different medical conditions after the primary treatment.⁷

This study aimed to evaluate the incidence of SPC and overall survival following an SPC diagnosis in patients with localized PC who were treated with RP or RT as a definitive curative treatment option.

2. Materials and methods

2.1. Database

We used data from the National Health Claims Database provided by the National Health Insurance Service (NHIS). The latter offers comprehensive medical care coverage to 99% of Koreans (over 50 million individuals). The database includes records of inpatient and outpatient diagnoses and prescriptions maintained by the NHIS as a single public insurer. Disease codes were determined according to the Korean Standard Classification of Diseases and Causes of Death, 8th edition (KCD-8).

The crude cancer-specific incidence rates for 24 types of cancer in the general Korean population, stratified by age in 5-year intervals and calendar year, were provided by the Korean Statistical Information Service (KOSIS) database. We included the KOSIS data for crude cancer-specific rates of only males aged 21 to over 85 years, from 2005 to 2018, with the following types of cancer: stomach, lung, colon, liver, bladder, thyroid, pancreatic, gallbladder, bile duct and other biliary, kidney, lip, oral cavity, pharyngeal, and esophageal cancers.

2.2. Study design

This study was approved by the institutional review board at the Chung-Ang University Hospital. Considering the anonymous nature of data, the requirement of informed consent was waived. The study adhered to the guidelines of the Declaration of Helsinki. Overall, 85,275 patients newly diagnosed with PC from 2004 to 2013 were identified using the KCD-8 code C61. The study excluded patients who had been diagnosed with any cancer prior to the PC diagnosis ($n = 9,801$), those diagnosed with SPC within a year of PC diagnosis ($n = 3,126$), those with inaccurate information in their records ($n = 359$), those who did not receive RP or RP treatment within a year of PC diagnosis ($n = 43,137$), those who received chemotherapy except for androgen deprivation therapy (ADT) prior to RT or RP treatment ($n = 296$), and those who died within a year of PC diagnosis ($n = 385$). Additionally, patients diagnosed with metastatic cancer were excluded ($n = 1,917$). The final number of eligible patients was 26,254 (eFig. 1).

2.3. Outcomes and variables

All patients were followed up from 1 year after PC diagnosis until the occurrence of SPC, death, or December 31, 2018, whichever occurred first. The primary outcome was the occurrence of SPC and SPC subtypes identified using the KCD codes. The initial primary treatments for PC-included RT and RP included open/laparoscopic and robot-assisted RP. The latter was defined as any record of a pathological diagnosis and anesthesia following a PC diagnosis as robot-assisted RP had no corresponding surgical codes in the NHIS. Open/laparoscopic RP and RT were identified using specific surgical codes. Disease and treatment codes are provided in the supplementary material (eTables 1 and 2). We adjusted for the following predictors in the analysis: age at PC diagnosis (<65 years, 65–70 years, and >70 years), year of PC diagnosis (2004–2007, 2008–2010, and 2011–2013), income level (low, middle, and high),

use of ADT (within 3 months prior to or after the primary treatment), and Charlson Comorbidity Index (CCI). The CCI scores were stratified into three categories, namely 0–1, 2–3, and ≥ 4 . For the subset of our cohort diagnosed with both PC and SPC, we considered the following additional variables: age at SPC diagnosis, latency period from PC to SPC diagnosis, RT treatment following SPC diagnosis; hospitalization status; total days of hospitalization within a year of SPC diagnosis; the occurrence of platelet and RBC transfusions within a year of SPC diagnosis; the use of G-CSF within a year of SPC diagnosis; and 1- and 5-year mortality rates after SPC diagnosis.

2.4. Statistical analyses

The standardized incidence ratio (SIR), which serves as a measure of relative risk by comparing the incidence rate of SPC with that in the general population, was calculated to compare the incidence of SPC in male patients with PC to that of cancer in the general male population stratified by PC treatment (either RT or RP). To estimate the SIR, we divided the observed number of SPCs in patients with PC by the expected number of cancer occurrences in the general male population for each cancer type according to PC treatment. The expected number was calculated by summing each age–calendar year–specific cancer incidence rate of the general male population multiplied by each age–calendar year–specific person–year in the study cohort of patients with PC. The 95% confidence intervals (CIs) of the SIR were computed using profile likelihood CIs based on a Poisson regression model.

We used stabilized inverse probability of treatment weighting (IPTW) to correct for selection bias. A logistic regression was used to calculate the propensity score, which represented the probability of a patient receiving RP treatment. We assessed the balance of covariates using standardized mean differences values; those below 0.1 indicated the covariates being well balanced between the two groups.

Next, we used competing risk analysis to accurately evaluate the probability of an SPC type, considering 12 types of SPC and death as competing risks. Cumulative incidence functions (CIFs) were estimated for each type of SPC based on the Aalen–Johansen estimator using weighted data, and the differences in CIF (risk difference, RD) at 5 years and 10 years of follow-up between the RT and RP groups were calculated.⁸ Their 95% CIs were estimated using bootstrapping with 1,000 bootstrap samples. In the subgroup analysis, we further stratified the analysis by age at PC diagnosis (<65, 65–70, and >70 years). To ensure the robustness of our findings, we conducted sensitivity analyses using various approaches for covariate adjustment. Specifically, we employed competing risk models with unweighted data and (non-stabilized) inverse probability-weighted models.

For patients with SPC, adjusted hazard ratios were estimated using multivariate Cox regression models to examine the association between PC treatment and mortality according to the type of SPC, after adjusting for age at PC diagnosis, period of PC diagnosis, income level, CCI, and the usage of ADT for 3 months.

Analyses were conducted using SAS v.7.0 (SAS Institute Inc., Cary, NC, USA) and R software, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Baseline characteristics of patients with PC

Among 26,254 patients with PC, 5,329 (20.3%) were treated with RT and 20,925 (79.7%) with RP. The median follow-up was at 7.2

(5.6–9.5) years for all patients, 6.5 (4.7–8.9) years for the RT group, and 7.3 (5.8–9.6) years for the RP group. The baseline characteristics of all patients are summarized in Table 1. Patients treated with RT were older, with higher income, more comorbidities, and using ADT. For the weighted data, no significant difference between the treatment groups was observed in any of the variables with standardized mean difference values under 0.1.

Table 2 presents the SIR for all patients, in both RT and RP. The risk for all SPCs excluding PC was 7% lower in patients with PC than in the general male population (SIR = 0.93; 95% CI: 0.90–0.97). Patients treated with RT showed an increased risk of all SPCs excluding PC (SIR = 1.12; 95% CI: 1.04–1.20), whereas those receiving RP showed a reduced risk of all SPCs excluding PC (SIR = 0.89; 95% CI: 0.85–0.92), compared with cancer incidence in the general male population. There was a significant increase in SIRs for urinary bladder cancer (SIR = 1.65; 95% CI: 1.45–1.88), thyroid cancer (SIR = 2.75; 95% CI: 2.30–3.26), and other cancers

(SIR = 1.17; 95% CI: 1.07–1.27), the same patterns being observed in the RT and RP groups. The risks of stomach, lung, colon, liver, gallbladder, bile duct and other biliary, and esophageal complications were lower among patients with PC than in the general male population. Furthermore, there were significantly lower risks of colon cancer in all patients (SIR = 0.88; 95% CI: 0.80–0.96) and in the RP group (SIR = 0.78; 95% CI: 0.70–0.86) than in the RT group (SIR = 1.30; 95% CI: 1.10–1.54).

3.2. Risk of SPCs in patients with PC according to treatment

Table 3 presents the estimated CIF (%) and the RD (%) using competing risk models. At the 5-year follow-up, the risk of pancreas and lip, oral cavity, and pharyngeal cancers was higher in patients who received RP than in those who underwent RT [RD (%) for pancreas = 0.2; 95% CI: 0.1–0.3; and for lip, oral cavity, and pharynx = 0.1, 95% CI: 0.0–0.2]. At the 10-year follow-up, the RP

Table 1

Baseline characteristics of patients with prostate cancer according to treatment prior to and after inverse probability weighting

Patient characteristics	Unadjusted ^a					IPW adjusted ^a			
	Total	RT		SMD	P value ^b	RT		SMD	P ^b
	(n = 26,254)	(n = 5,329)	(n = 20,925)			(n = 5,300)	(n = 2,0940.6)		
Age at PC diagnosis (year)				0.486	<0.001			0.011	0.848
<65	8,646 (32.9%)	1,185 (22.2%)	7,461 (35.7%)			1,741.2 (32.9)	6,888.2 (32.9)		
65–70	8,858 (33.7%)	1,392 (26.1%)	7,466 (35.7%)			1,763.1 (33.3)	7,052.7 (33.7)		
>70	8,750 (33.3%)	2,752 (51.6%)	5,998 (28.7%)			1,795.7 (33.9)	6,999.6 (33.4)		
Period of PC diagnosis				0.085	<0.001			0.045	0.057
2004–2007	5,809 (22.1%)	1,329 (24.9%)	4,480 (21.4%)			1,141.8 (21.5)	4,614.0 (22.0)		
2008–2010	8,507 (32.4%)	1,637 (30.7%)	6,870 (32.8%)			1,844.6 (34.8)	6,850.2 (32.7)		
2011–2013	11,938 (45.5%)	2,363 (44.3%)	9,575 (45.8%)			2,313.7 (43.7)	9,476.4 (45.3)		
Income at diagnosis of PC				0.054	0.002			0.024	0.450
Low	4,704 (17.9%)	898 (16.9%)	3,806 (18.2%)			941.8 (17.8)	3,760.6 (18.0)		
Medium	7,242 (27.6%)	1,415 (26.6%)	5,827 (27.8%)			1,405.8 (26.5)	5,753.0 (27.5)		
High	14,308 (54.5%)	3,016 (56.6%)	11,292 (54.0%)			2,952.4 (55.7)	1,1426.9 (54.6)		
CCI				0.048	0.008			0.006	0.943
0,1	7,589 (28.9%)	1,534 (28.8%)	6,055 (28.9%)			1,515.8 (28.6)	6,035.4 (28.8)		
2,3	9,156 (34.9%)	1,776 (33.3%)	7,380 (35.3%)			1,869.1 (35.3)	7,324.4 (35.0)		
≥4	9,509 (36.2%)	2,019 (37.9%)	7,490 (35.8%)			1,915.2 (36.1)	7,580.8 (36.2)		
Usage of ADT 3 months before or after treatment				0.991	<0.001			0.005	0.752
No	20,310 (77.4%)	2,320 (43.5%)	17,990 (86.0%)			4085.4 (77.1)	16,182.8 (77.3)		
Yes	5,944 (22.6%)	3,009 (56.5%)	2,935 (14.0%)			1,214.6 (22.9)	4,757.8 (22.7)		

Abbreviations: PC, prostate cancer; RT, radiation therapy; RP, radical prostatectomy; SMD, standardized mean difference; IPW, inverse probability weighting; ADT, androgen deprivation therapy; CCI, commodity channel index.

^a Data are presented as number (%).

^b Chi-square test was conducted.

Table 2

Standardized incidence ratios (SIRs) of second primary cancers due to primary treatment of PC, adjusted for age and calendar year

Outcome	Total		Treatment			
			RT		RP	
	SIR (O/E)	95% CI	SIR (O/E)	95% CI	SIR (O/E)	95% CI
All SPCs excluding prostate	0.93 (3117/3340.84)	(0.90, 0.97)	1.12 (738/661.69)	(1.04, 1.20)	0.89 (2379/2679.16)	(0.85, 0.92)
Stomach	0.90 (572/632.97)	(0.83, 0.98)	1.15 (140/122.00)	(0.97, 1.35)	0.85 (432/510.96)	(0.77, 0.93)
Lung	0.74 (554/746.35)	(0.68, 0.81)	0.83 (127/153.02)	(0.69, 0.98)	0.72 (427/593.33)	(0.65, 0.79)
Colon	0.88 (469/532.64)	(0.80, 0.96)	1.30 (136/104.26)	(1.10, 1.54)	0.78 (333/428.38)	(0.70, 0.86)
Liver	0.72 (228/318.22)	(0.63, 0.81)	0.88 (54/61.12)	(0.67, 1.14)	0.68 (174/257.10)	(0.58, 0.78)
Bladder	1.65 (224/135.48)	(1.45, 1.88)	1.94 (56/28.80)	(1.48, 2.50)	1.58 (168/106.68)	(1.35, 1.83)
Thyroid	2.75 (125/45.47)	(2.30, 3.26)	2.61 (19/7.29)	(1.60, 3.96)	2.78 (106/38.17)	(2.28, 3.34)
Pancreatic	1.00 (120/120.47)	(0.83, 1.19)	0.83 (20/24.16)	(0.52, 1.25)	1.04 (100/96.30)	(0.85, 1.26)
Gallbladder, bile duct, and other biliary	0.81 (112/137.61)	(0.67, 0.97)	0.91 (26/28.59)	(0.60, 1.31)	0.79 (86/109.02)	(0.63, 0.97)
Kidney	1.22 (87/71.30)	(0.98, 1.49)	1.14 (15/13.19)	(0.65, 1.81)	1.24 (72/58.11)	(0.97, 1.55)
Lip, oral cavity, and pharyngeal	1.14 (70/61.45)	(0.89, 1.43)	1.05 (12/11.44)	(0.56, 1.76)	1.16 (58/50.01)	(0.89, 1.48)
Esophageal	0.70 (59/84.84)	(0.53, 0.89)	1.16 (19/16.37)	(0.71, 1.76)	0.58 (40/68.48)	(0.42, 0.78)
Other cancers	1.17 (497/426.38)	(1.07, 1.27)	1.35 (114/84.34)	(1.12, 1.62)	1.12 (383/342.04)	(1.01, 1.24)

Abbreviations: SIR, standardized incidence ratio; PC, prostate cancer; O, observed number of SPCs; E, expected number of SPCs; 95% CI, 95% confidence interval; SPC, second primary cancer; RT, radiation therapy; RP, radical prostatectomy.

Table 3 Incidence rate, cumulative incidence estimates (%), and risk differences (%) at the 5- and 10-year follow-ups using competing risk models for each outcome in RP versus RT groups

Outcome	RT (n = 5,329)				RP (n = 20,925)				5-year risk difference, % (95% CI)	10-year risk difference, % (95% CI)
	Events, No.	Incidence rate (per 1,000 person-years), (95% CI)	Cumulative incidence at 5-year follow-up, % (95% CI)	Cumulative incidence at 10-year follow-up, % (95% CI)	Events, No.	Incidence rate (per 1,000 person-years), (95% CI)	Cumulative incidence at 5-year follow-up, % (95% CI)	Cumulative incidence at 10-year follow-up, % (95% CI)		
All SPCs, excluding prostate	738	23.4 (21.7, 25.1)	8.7 (7.5, 9.2)	16.4 (14.1, 17.1)	2,379	16.6 (16.0, 17.3)	8.0 (7.6, 8.4)	14.8 (14.2, 15.4)	-0.7 (-1.2, 0.6)	-1.7 (-2.3, 0.8)
SPC type										
Stomach	140	4.4 (3.8, 5.2)	1.7 (1.3, 2.1)	3.3 (2.4, 3.9)	432	3.0 (2.8, 3.3)	1.5 (1.3, 1.6)	2.8 (2.5, 3.1)	-0.2 (-0.6, 0.3)	-0.5 (-1.1, 0.4)
Lung	127	4.0 (3.4, 4.8)	1.4 (1.0, 1.6)	3.1 (2.2, 3.6)	427	3.0 (2.7, 3.3)	1.4 (1.2, 1.5)	2.6 (2.3, 2.9)	0.0 (-0.3, 0.4)	-0.5 (-1.1, 0.5)
Colon	136	4.3 (3.6, 5.1)	1.6 (1.1, 1.9)	3.0 (2.1, 3.5)	333	2.3 (2.1, 2.6)	1.2 (1.0, 1.3)	2.0 (1.8, 2.3)	-0.4 (-0.7, 0.1)	-0.9 (-1.5, -0.1)
Liver	54	1.7 (1.3, 2.2)	0.6 (0.3, 0.8)	1.0 (0.6, 1.3)	174	1.2 (1.1, 1.4)	0.6 (0.5, 0.7)	1.2 (0.9, 1.4)	0.0 (-0.2, 0.3)	0.2 (-0.1, 0.6)
Urinary bladder	56	1.8 (1.4, 2.3)	0.7 (0.4, 0.9)	1.2 (0.7, 1.5)	168	1.2 (1.0, 1.4)	0.6 (0.5, 0.7)	1.1 (0.9, 1.2)	-0.1 (-0.4, 0.2)	-0.1 (-0.5, 0.3)
Thyroid	19	0.6 (0.4, 0.9)	0.4 (0.2, 0.7)	0.5 (0.3, 0.9)	106	0.7 (0.6, 1.0)	0.4 (0.3, 0.5)	0.5 (0.4, 0.7)	0.0 (-0.3, 0.2)	0.0 (-0.4, 0.3)
Pancreatic	20	0.6 (0.4, 1.0)	0.1 (0.0, 0.2)	0.5 (0.2, 0.9)	100	0.7 (0.6, 0.9)	0.3 (0.2, 0.4)	0.7 (0.6, 0.9)	0.2 (0.1, 0.3)	0.2 (-0.2, 0.6)
Gallbladder and other biliary	26	0.8 (0.6, 1.2)	0.3 (0.1, 0.4)	0.6 (0.2, 0.8)	86	0.6 (0.5, 0.7)	0.3 (0.2, 0.4)	0.6 (0.4, 0.7)	-0.1 (-0.2, 0.2)	0.0 (-0.3, 0.4)
Kidney	15	0.5 (0.3, 0.8)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	72	0.5 (0.4, 0.6)	0.2 (0.2, 0.3)	0.4 (0.3, 0.6)	0.0 (-0.1, 0.2)	0.2 (0.0, 0.4)
Lip, oral cavity, and pharyngeal	12	0.4 (0.2, 0.7)	0.1 (0.0, 0.2)	0.2 (0.1, 0.3)	58	0.4 (0.3, 0.5)	0.2 (0.2, 0.3)	0.3 (0.2, 0.4)	0.1 (0.0, 0.2)	0.1 (-0.1, 0.3)
Esophageal	19	0.6 (0.4, 0.9)	0.3 (0.1, 0.4)	0.3 (0.1, 0.4)	40	0.3 (0.2, 0.4)	0.1 (0.1, 0.2)	0.2 (0.2, 0.3)	-0.1 (-0.3, 0.0)	0.0 (-0.2, 0.1)
Other SPCs	114	3.6 (3.0, 4.3)	1.3 (0.9, 1.7)	2.7 (1.9, 3.4)	383	2.7 (2.4, 3.0)	1.2 (1.1, 1.4)	2.3 (2.1, 2.6)	-0.1 (-0.5, 0.3)	-0.3 (-1.1, 0.5)
Death	1,371	43.4 (41.2, 45.8)	12.4 (11.0, 12.9)	23.1 (20.3, 23.4)	1,946	13.6 (13.0, 14.2)	6.4 (6.1, 6.9)	14.7 (14.2, 15.6)	-6.0 (-6.4, -4.4)	-8.3 (-8.6, -5.4)

95% CI, 95% confidence interval; SPC, second primary cancer; RT, radiation therapy; RP, radical prostatectomy

group had a lower risk of colon cancer than the RT group [RD (%) = -0.9; 95% CI: -1.5– -0.1]. Notably, the risk of death was consistently lower in the RP group than in the RT group at both the 5- and 10-year follow-ups [RD (%) for 5-year = -6.0; 95% CI: -6.4– -4.4, and for 10-year = -8.3; 95% CI: -8.6– -5.4]. The CIF across the follow-up period for both RP and RT groups are shown in Fig. 1 (all SPCs excluding PC, stomach, colon, and lung cancers, and death) and eFig. 2 (bladder, thyroid, pancreatic, gallbladder, kidney, lip, oral cavity, esophageal, and other cancers). The risk of colon cancer was consistently higher in the RT group than in the RP group, and this difference increased over the follow-up period. In subgroup analyses, the risks of kidney, lip, oral cavity, and pharyngeal cancers were higher in the RP group than in the RT group, particularly in patients aged <65 years. In the 65–70-year age group, patients who underwent RP had a higher risk of thyroid, lip, oral cavity, and pharyngeal cancers than those who underwent RT. Risk of colon cancer in the RP group was lower than that in the RT group in the >70-year age group (eTable 3). In sensitivity analyses, results regarding the risk of death were robust using different covariate adjustments. However, there were significant differences in the risks of all SPCs (excluding the prostate) at both the 5- and 10-year follow-ups (eTable 4).

3.3. Risk of death in patients with SPCs after PC diagnosis according to treatment

The characteristics of patients with SPCs after PC diagnosis are presented in eTable 5. The average latency period from PC to SPC diagnosis was 5 years [standard deviation (SD): 2.9 years]. Table 4 presents the adjusted HRs (aHRs) of the overall survival of patients with SPC after PC diagnosis according to the type of SPC. For patients with all SPCs (excluding PC) and for those with lung and colon SPCs, the risk of death was lower in the RP group than in the RT group (aHRs for all SPCs excluding PC: 0.86; 95% CI: 0.75–0.99, aHRs for lung: 0.70; 95% CI: 0.53–0.92; $P = 0.010$, and aHRs for colon: 0.53; 95% CI: 0.36–0.78; $P = 0.001$). In contrast, for patients with esophageal SPC, the RP group exhibited higher mortality (aHRs, 6.9; 95% CI: 1.66–28.69; $P = 0.008$) than that of the RT group. In patients with other SPC types, PC treatment was not associated with mortality.

4. Discussion

To the best of our knowledge, this is the first nationwide cohort study to show the different associations between primary treatment for PC and survival according to the type of SPC. The risk of SPC was 7% lower in patients with PC than in the general male population. Bladder and thyroid cancers were detected more frequently in both the RT and RP groups than in the general male population. At the 10-year follow-up, patients treated with RT had a higher risk of colon cancer than those treated with RP. The risk of death after SPC of the lungs and colon was higher in patients who underwent RT than in those who underwent RP. In contrast, the risk of death after SPC of the esophagus was higher in patients who underwent RP than in those who underwent RT. Considering that there was no difference in survival rates among other cancers, previous PC treatment was considered to affect the prognosis of each cancer type.

Radiation-induced secondary malignancy involves a complex process due to a long latency period and limited direct data.⁹ Radiation carcinogenesis involves initiation of premalignant normal cells, inactivation of killing cells, and proliferation of premalignant clones.¹⁰ The sensitivity of various organs in the body is related to the relative sensitivity of the cells that make up those organs. Stochastic effects cannot be avoided;¹⁰ however, direct effects,

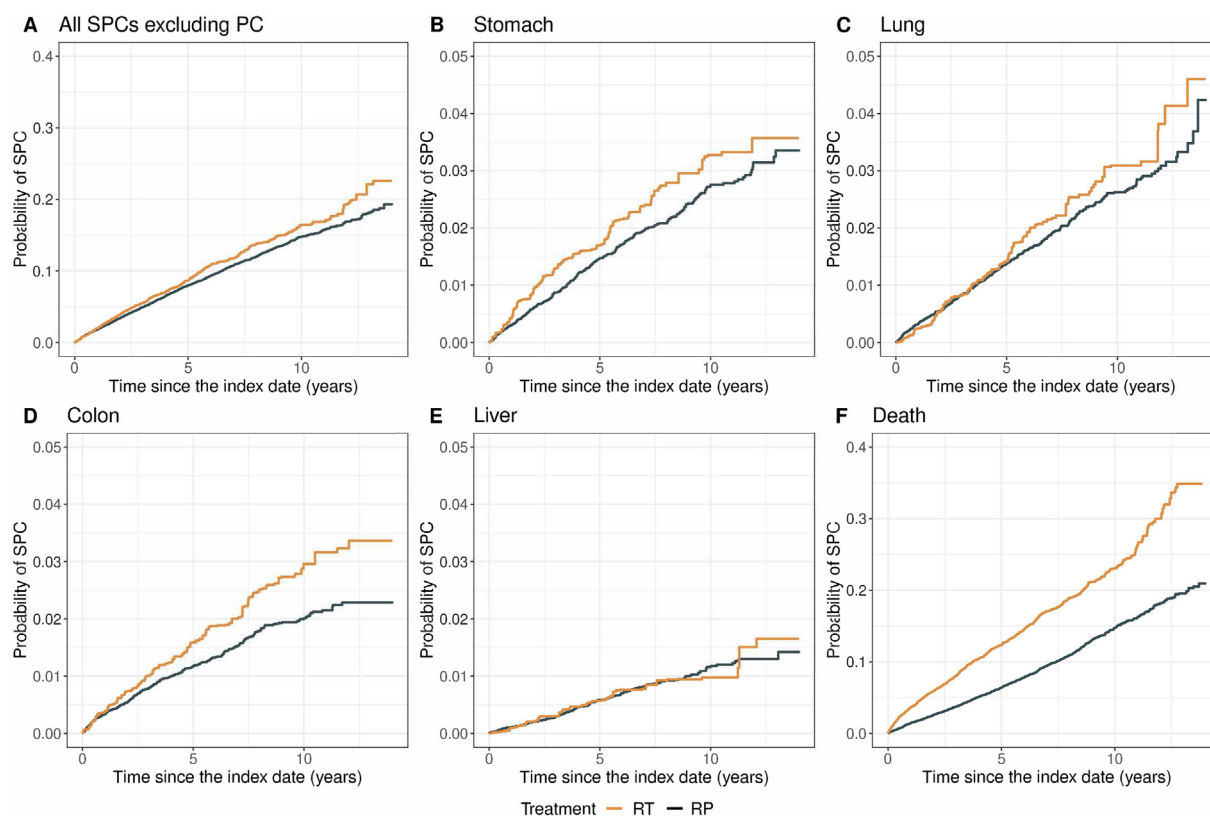


Figure 1. Cumulative incidence estimates for all SPCs excluding PC, stomach, lung, colon, and liver cancers, and death, according to the treatment of patients with PC. The Aalen–Johansen estimates of all SPCs, excluding PC, stomach, lung, colon, and liver cancers, and death, stratified by treatment of patients with PC, using the inverse treatment of probability-weighted data. PC, prostate cancer; SPCs, second primary cancers.

Table 4
Multivariate Cox regression analysis of OS by SPC type in patients with SPC

SPC type	Events, No.		Multivariable model ^a	
	RT	RP	aHR (95% CI) ^b	P
All SPCs excluding prostate	367	824	0.86 (0.75, 0.99)	0.030
Stomach	46	93	0.94 (0.63, 1.39)	0.744
Lung	94	217	0.70 (0.53, 0.92)	0.010
Colon	62	72	0.53 (0.36, 0.78)	0.001
Liver	33	99	0.96 (0.63, 1.45)	0.838
Urinary bladder	17	45	1.31 (0.69, 2.51)	0.414
Pancreatic	16	68	0.72 (0.37, 1.42)	0.346
Gallbladder and other biliary	15	57	1.11 (0.57, 2.15)	0.756
Lip, oral cavity, and pharyngeal	8	19	0.47 (0.12, 1.79)	0.267
Esophageal	6	19	6.90 (1.66, 28.69)	0.008
Other SPCs	70	135	0.60 (0.43, 0.84)	0.003

Abbreviations: aHR, adjusted hazard ratio; 95% CI, 95% confidence interval; OS, overall survival; RT, radiation therapy; RP, radical prostatectomy; SPC, second primary cancer.

^a In the multivariate Cox models, we adjusted for variables including age at PC diagnosis (in years), period of prostate cancer diagnosis, income level, commodity channel index, and androgen deprivation therapy usage (3 months).

^b Reference was the RT group.

caused by ionization of the particles and the rays, and indirect effects, caused by free radicals produced during radiolysis of water and oxygen, can occur.¹¹ Radiation exposure increased the risk of developing SPCs as per the epidemiological studies on Japanese atomic bomb survivors.¹² In addition, a significant radiation-associated increase in the risk of cancer in adolescence and young adulthood has been reported.¹² Radiation dose, time, and distance could be another consideration for SPC.^{13,14} Significant increase in SPC of colon in RT than in RP could be caused by rectal cancer being

near the prostate. For SPCs, we hypothesize that genetic predispositions, such as Lynch syndrome, could influence the development of cancers like colorectal cancer.¹⁵ The higher incidence of colon cancer in RT patients compared with the general population may suggest that RT affects genetic mutations.¹⁶

Prognosis of SPC may be a different concern from the incidence of SPC. Radiation was found to provoke submucosal fibrosis, causing stricture and adhesion.¹⁷ Previous RT history could cause difficulty in dissection during surgeries, and hence cause more complications.¹⁸ The gastrointestinal tract is a radiosensitive organ and could be a major limiting factor when determining tolerance to radiotherapy.¹⁹ Previous radiation exposure history can influence the decision-making of most radiologists.²⁰ Sufficient and higher re-irradiation dose could contribute to more favorable outcomes in some types of SPC.²¹ Radio-resistance could be associated with several biological changes of the tumor cells and the tumor microenvironment.²² Further, while RT had shown only immunosuppressive effects previously, its immunostimulatory effects were revealed recently.²³ Finally, a higher ratio of invasive and variant histology with poor prognosis of SPC of bladder was observed after RT rather than RP.²⁴ Therefore, different circumstances may influence the prognosis after SPC diagnosis for each cancer type.

It is hard to assume a fundamental correlation between the incidence of SPC with RP, because there does not appear to be a chronic mechanism by which RP directly induces SPCs. First, it is possible that the observed differences were due to chance. For instance, at the 5-year follow-up, the risk of pancreatic cancer and lip, oral cavity, and pharyngeal cancers was higher in patients who received RP than in those who underwent RT. These cancers are not commonly observed, with only 120 cases of pancreatic cancer and 70 cases of lip, oral cavity, and pharyngeal cancers among 26,254

patients. Second, differences in detection rates may have contributed. Patients undergoing RP are often followed up in urology departments, where comprehensive systemic evaluations may lead to higher detection rates of SPCs.

Our study has some limitations. First, the NHIS database, which compared RT and RP, included a retrospective cohort. Although IPTW analyses were used to control potential confounders, some factors could not be controlled in a nationwide dataset. In particular, the NHIS database did not provide PC stage and grade. We considered that metastatic disease would be excluded and that local or locally advanced PC would be included. Second, NHIS records for robot-assisted RP could not be found as it was a non-covered service. Therefore, we used a combination of anesthetic and pathology codes as an operational definition without surgical codes for robot-assisted RP. Third, this database does not include detailed data regarding the stage or treatment after SPC diagnosis. Fourth, data on RT were not included. Regarding RT, technological advancements have significantly improved treatment efficacy, quality of life, and reduced adverse effects.²⁵ Intensity-modulated RT offers highly precise tumor-targeted dose delivery, minimizing the damage to adjacent tissue, but its longer beam-on time could increase the exposure of peripheral healthy tissue to ionizing radiation of low dose.²⁶ In modern RT era, the issue of SPC has arisen.²⁷ However, during our study period, three-dimensional conformal RT was the most commonly used technique, and intensity-modulated RT only became the predominant method after 2019 in South Korea.²⁸ Large-scale prospective datasets for comparing the incidence and prognosis of SPC may provide a solution. Nevertheless, considering the rarity and latency of SPC, a retrospective study using nationwide data was practical to ensure adequate follow-up measures and sample size.

5. Conclusion

Although the risk of total SPC among patients treated with primary RT or RP was lower than that in the general age-matched male population, there was significant increase in the SIRs of bladder and thyroid cancers in both the groups. Patients who underwent RT had a higher risk (0.9 %) of SPC of the colon than those who underwent RP at 10-year follow-up. In SPC of the lung, colon, and esophagus, PC treatment was associated with survival after SPC diagnosis. Therefore, primary treatment for PC should be considered for the follow-up of SPC, and for proper treatment after SPC diagnosis.

Authors' contributions

Se Young Choi and Jooyoung Lee contributed to study concept and design.

Se Young Choi contributed to acquisition of data.

Jihye Hyun, Se Young Choi, and Jooyoung Lee contributed to analysis and interpretation of data.

Jihye Hyun, Jooyoung Lee, and Se Young Choi contributed to drafting of the manuscript.

Tuan Thanh Nguyen contributed to critical revision of the manuscript for important intellectual content.

Jooyoung Lee and Se Young Choi contributed to obtaining funding.

Se Young Choi contributed to supervision.

Data sharing

The raw sequencing data are not publicly available as these compromise patient consent and ethics regulations in South Korea.

Declaration of generative AI and AI-assisted technologies in the writing process

There is no need to add a statement.

Funding

This research was supported by the National Research Foundation of Korea funded by the Korean government (MSIT) [grant number 2022R1C1C1011806] and supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) [grant number NRF-2023R1A2C1003830].

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnrl.2025.01.004>.

References

1. Australian Institute of Health Welfare. In: Cancer in Australia 2019. Cancer series no. 119. Cat. no. CAN 123. Canberra: AIHW; 2019.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA A Cancer J Clin* 2023;73:17–48.
3. Phipps AI, Chan AT, Ogino S. Anatomic subsite of primary colorectal cancer and subsequent risk and distribution of second cancers. *Cancer* 2013;119:3140–7.
4. Jayasekara H, Hodge AM, Haydon A, et al. Prediagnosis alcohol intake and metachronous cancer risk in cancer survivors: a prospective cohort study. *Int J Cancer* 2021;149:82–838. <https://doi.org/10.1002/ijc.33603>.
5. Keegan THM, Bleyer A, Rosenberg AS, Li Q, Goldfarb M. Second primary malignant neoplasms and survival in adolescent and young adult cancer survivors. *JAMA Oncol* 2017;3:1554–7.
6. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375:1415–24.
7. Hyun J, Ha MS, Oh SY, et al. Urinary tract infection after radiation therapy or radical prostatectomy on the prognosis of patients with prostate cancer: a population-based study. *BMC Cancer* 2023;23:395.
8. Young JG, Stensrud MJ, Tchetgen Tchetgen EJ, Hernan MA. A causal framework for classical statistical estimands in failure-time settings with competing events. *Stat Med* 2020;39:1199–236.
9. Travis LB, Rabkin CS, Brown LM, et al. Cancer survivorship—genetic susceptibility and second primary cancers: research strategies and recommendations. *J Natl Cancer Inst* 2006;98:15–25.
10. Sachs RK, Shuryak I, Brenner D, Fakir H, Hlatky L, Hahnfeldt P. Second cancers after fractionated radiotherapy: stochastic population dynamics effects. *J Theor Biol* 2007;249:518–31.
11. Morgan WF, Sowa MB. Non-targeted effects induced by ionizing radiation: mechanisms and potential impact on radiation induced health effects. *Cancer Lett* 2015;356:17–21.
12. Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res* 2007;168:1–64.
13. Di Betta E, Fariselli L, Bergantin A, et al. Evaluation of the peripheral dose in stereotactic radiotherapy and radiosurgery treatments. *Med Phys* 2010;37:3587–94.
14. Kaveh K, Manem VSK, Kohandel M, Sivaloganathan S. Modeling age-dependent radiation-induced second cancer risks and estimation of mutation rate: an evolutionary approach. *Radiat Environ Biophys* 2015;54:25–36.
15. Bauer CM, Ray AM, Halstead-Nussloch BA, et al. Hereditary prostate cancer as a feature of Lynch syndrome. *Fam Cancer* 2011;10:37–42.
16. Sun M, Moquet J, Ellender M, et al. Potential risks associated with the use of ionizing radiation for imaging and treatment of colorectal cancer in Lynch syndrome patients. *Fam Cancer* 2023;22:61–70.
17. McBride WH, Mason KA, Davis C, Withers HR, Smathers JB. Adhesion formation in experimental chronic radiation enteropathy. *Int J Radiat Oncol Biol Phys* 1989;16:737–43.
18. May DN, Parker WP. Review of principles of salvage radical prostatectomy. *AME Med J* 2021;6:3.
19. Ashburn JH, Kalady MF. Radiation-induced problems in colorectal surgery. *Clin Colon Rectal Surg* 2016;29:85–91.

20. Pandharipande PV, Eisenberg JD, Avery LL, et al. Journal club: how radiation exposure histories influence physician imaging decisions: a multicenter radiologist survey study. *AJR Am J Roentgenol* 2013;200:1275–83.
21. Lee HI, Kim JH, Ahn SH, et al. Re-irradiation for recurrent or second primary head and neck cancer. *Radiat Oncol J* 2021;39:279–87.
22. Suwa T, Kobayashi M, Nam JM, Harada H. Tumor microenvironment and radioresistance. *Exp Mol Med* 2021;53:1029–35.
23. Walle T, Martinez Monge R, Cerwenka A, Ajona D, Melero I, Lecanda F. Radiation effects on antitumor immune responses: current perspectives and challenges. *Ther Adv Med Oncol* 2018;101758834017742575.
24. Monda S, Pratsinis M, Lui H, et al. Secondary bladder cancer after prostate cancer treatment: an age-matched comparison between radiation and surgery. *Eur Urol Focus* 2023;10:448–53. <https://doi.org/10.1016/j.euf.2023.09.002>.
25. Lee TH, Pyo H, Yoo GS, et al. Prostate-specific antigen kinetics in hypofractionated radiation therapy alone for intermediate- and high-risk localized prostate cancer. *Prostate Int* 2023;11:173–9.
26. Hall EJ, Wu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003;56:83–8.
27. Jahreiss MC, Aben KKH, Hoogeman MS, et al. The risk of second primary cancers in prostate cancer survivors treated in the modern radiotherapy era. *Front Oncol* 2020;10605119.
28. Lee J, Kim WC, Yoon WS, Rim CH. Implications of radiotherapy utilization in Korea from 2010 to 2019. *J Kor Med Sci* 2021;36e117.