Research Paper

Prognostic comparison between radical prostatectomy and radiotherapy in prostate cancer patients at different stages and ages

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ABSTRACT

Radical prostatectomy (RP) and radiotherapy (RT) are both evidence-based nonconservative treatments for prostate cancer (PCa). However, which treatment is better remains controversial. This study aimed to compare the prognostic difference between radical prostatectomy (RP) and radiotherapy (RT) in PCa patients at different stages and ages. Two independent PCa cohorts (the Surveillance, Epidemiology, and End Results, SEER; and the Prostate, Lung, Colorectal, and Ovarian, PLCO) were employed. Cox regression was used to calculate the hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). In both cohorts, patients who received RT exhibited a worse prognostic outcome than those who underwent RP. When stratified analysis was performed by tumor node metastasis (TNM) stage and age at diagnosis in the SEER cohort, the HR of RT versus RP for overall survival increased with TNM stage but decreased with age. Specifically, PCa patients in stage I in the age range of 55–84 years, stage IIA at 70–85+ years, and stage IIB at 75–85+ years had better survival with RT than RP patients ($p < 0.05$). In contrast, patients in stages IIA, IIB, III and IV with respective age ranges of 55–64 years; 50–74 years; 55–59, 65–74 years; and 45–74 years showed worse survival with RT compared with RP ($p < 0.05$). These findings were partially validated in the PLCO dataset. Our results indicated that the choice between RT and RP should be guided by TNM stage and age. These findings may facilitate counseling regarding the prognostic effect of RT and RP for PCa patients.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the most common cause of cancer death among American men [1]. According to cancer statistics in 2018, the incidence of PCa is the fifth most common cancer in China [2]. Radical prostatectomy (RP) and radiotherapy (RT) are both evidence-based non-conservative treatments for PCa [3, 4]. Despite many publications comparing the prognosis between these two treatments, the better option remains unclear for

PCa patients [5–9]. The prognosis of PCa patients is correlated with the age at diagnosis [10]. Our previous study also observed that the age at diagnosis played a key role in the prognosis of PCa patients who received RT [11]. In addition, the tumor node metastasis (TNM) stage exerts much influence on PCa prognosis. However, previous studies placed little emphasis on age and TNM stage, which possibly leads to bias.

This study aimed to compare the prognostic difference between RP and RT in PCa patients at different ages

and various stages of this disease. Two independent PCa cohorts were employed, namely, the Surveillance, Epidemiology, and End Results (SEER) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohorts. The results from this work would benefit clinicians and PCa patients in choosing between RT and RP.

METHODS

Study population

For the SEER cohort, a case listing session was obtained from the SEER program using SEER*Stat 8.2.1 (http://seer.cancer.gov/) [12]. The current SEER project includes 17 population-based cancer registries that represent approximately 28% of the US population. SEER data are available to the public for the purpose of studying cancer-based epidemiology. The SEER cohort was approved by the Surveillance Research Program in NCI's Division of Cancer Control and Population Sciences, with the application number 10809-Nov2017.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial is a randomized trial. This study aimed to evaluate the impact of screening modalities on cancer mortality [13]. Briefly, 154,952 individuals aged 55–74 years were recruited via 10 centers from the US between 1993 and 2001. All participants provided written informed consent, and the study was approved by the Institutional Review Boards at the National Cancer Institute and the 10 recruitment centers. We applied the PLCO cohort to the National Cancer Institute Cancer Data Access System. The project ID is PLCO-411.

Participants provided written informed consent as stated by the SEER and PLCO cohorts. The China Pharmaceutical University Ethics Committee approved the study. This study complied with the Declaration of Helsinki and the regulations of the China Pharmaceutical University Ethics Committee (http://kjc.cpu.edu.cn/dc/c0/c5095a56512/page.htm).

Statistical analysis

Continuous variables are described as the mean (standard deviation) and as the number (percent) for categorical variables. To compare the prognosis between patients who received RP and RT, multi-covariate Cox regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. Age at diagnosis, TNM stage and grade were adjusted for in the SEER cohort. Age at diagnosis, TNM stage, grade, smoking status, education level, race, body mass index (BMI), aspirin

dose, diabetes and family history were adjusted for in the PLCO cohort. The nonlinear relationship between diagnosed age, TNM stage and overall survival was detected by restricted cubic spline regression. All statistical analyses were performed using R (3.5.1).

RESULTS

Participant characteristics

For the SEER cohort (n = 1,162,819), 148 duplicated participants were initially excluded. Then, participants without follow-up time (n = 12,299), without grade (n = 96,580), without clinical TNM stage (n = 323,315), and without prostatectomy or radiotherapy (n = 31,083) information were excluded. Participants who received both prostatectomy and radiotherapy and those who received other therapies were excluded (n = 292,232). Next, patients with no information on TNM stage were excluded (n = 599,132). Eventually, 131,345 participants were included for further analysis. A flowchart of participant selection is shown in Figure 1A.

For the PLCO cohort (n = 76,682), we initially excluded participants who had a nonresponse form (n = 2,413). Participants without clinical TNM stage were also excluded (n = 65,947). Participants who received both prostatectomy and radiotherapy and those who received other therapies were excluded (n = 1,903). Then, patients with aberrant grade were excluded (n = 23). Finally, participants who underwent prostatectomy or received radiotherapy were used (n = 6,396). A flowchart is presented in Figure 1B.

There were 131,345 participants from the SEER cohort, including 74,663 (56.85%) men undergoing RP and 56,682 (43.16%) men who received RT. A total of 6,396 PCa patients were involved in the PLCO cohort, including 2,961 (46.27%) men treated with RP and 3,435 (53.73%) with RT. Information on the mean age at diagnosis, follow-up time and event-points that occurred in the RP and RT groups is presented in Table 1 for the SEER cohort and Table 2 for the PLCO cohort.

Survival analysis

In the SEER cohort, patients treated with RT showed a worse outcome than those who underwent RP (HR: 1.09, 95% CI: 1.02–1.16, p = 0.0069) (Table 3). This significant association was validated in the PLCO cohort (HR: 1.46, 95% CI: 1.24–1.72, p = < 0.0001) (Table 3). Patients who received both prostatectomy and radiotherapy versus only prostatectomy or radiotherapy in the PLCO cohort showed no significant associations (Supplementary Table 1).

In the next step, stratified analysis was performed according to clinical TNM stage to compare the treatment outcomes of RP and RT for PCa patients in the SEER cohort (Table 4). Of note, PCa patients at TNM stages I, IIA and IIB showed better survival with RT treatment than RP patients ($p = < 0.0001$ for stage I, $p = < 0.0001$ for stage IIA and $p = 0.0048$ for stage IIB). In contrast, those at TNM stages III and IV showed worse prognosis with RT treatment compared with RP ($p = 0.026$ for stage III and $p = < 0.0001$ for stage IV).

Then, stratified analysis was performed according to age at diagnosis in the SEER cohort (Table 5). PCa patients treated with RT showed a better prognosis than those who underwent RP in the 75–79, 80–84 and 85+ year age groups ($p < 0.05$) but a worse prognosis in the 45–49, 50–54, 55–59, 60–64, and 65–69 year age groups ($p < 0.05$). There were no significant differences for patients in the age range of 70–74 years in the comparison between RP and RT.

Subsequently, TNM stage and age were simultaneously considered for stratified analysis. The HR of RT versus RP in overall survival decreased with age (Figure 2A, Table 6). This negative correlation was also found in stages I, IIA, and IIB in the SEER cohort (Figure 2C, 2D, 2E, 2F, Table 6).

Additionally, this finding was validated in the PLCO cohort (Figure 2B). Specifically, in TNM stage I,

patients aged 55–85+ years (HR: 0.20–0.59, $p < 0.05$) showed better survival with RT than RP patients (Table 6). In TNM stage IIA, patients aged 70–85+ years (HR: 0.41–0.58, $p < 0.05$) showed better survival with RT than RP. In contrast, patients aged 55–64 years (HR: 2.04–2.93, $p < 0.05$) showed worse survival with RT than with RP (Table 6). In TNM stage IIB patients, those aged 75–85+ years (HR: 0.25–0.52, $p < 0.05$) showed better survival with RT than RP patients. In contrast, patients aged 50–74 years (HR: 1.39–2.45, $p < 0.05$) showed worse survival with RT than with RP (Table 6). In TNM stage III, patients aged 80–84 years (HR: 0.48, 95% CI: 0.23–0.97, $p = 0.041$) showed better survival with RT than RP patients. In contrast, patients aged 55–74 years (HR: 2.36–4.79, $p < 0.05$) showed worse survival with RT than with RP (Table 6). In TNM stage IV, patients aged 45–74 years (HR: 1.66–5.85, $p < 0.05$) showed worse survival with RT than with RP. PCa patients in other age groups within stages showed no significant differences between RP and RT (Table 6).

DISCUSSION

In this study, we compared the prognosis of PCa patients with RT and RP in two databases involving more than 130,000 subjects. We investigated the different prognoses of discrepant treatments using the SEER database. Furthermore, the results were confirmed in the PLCO database. Compared to RP, as
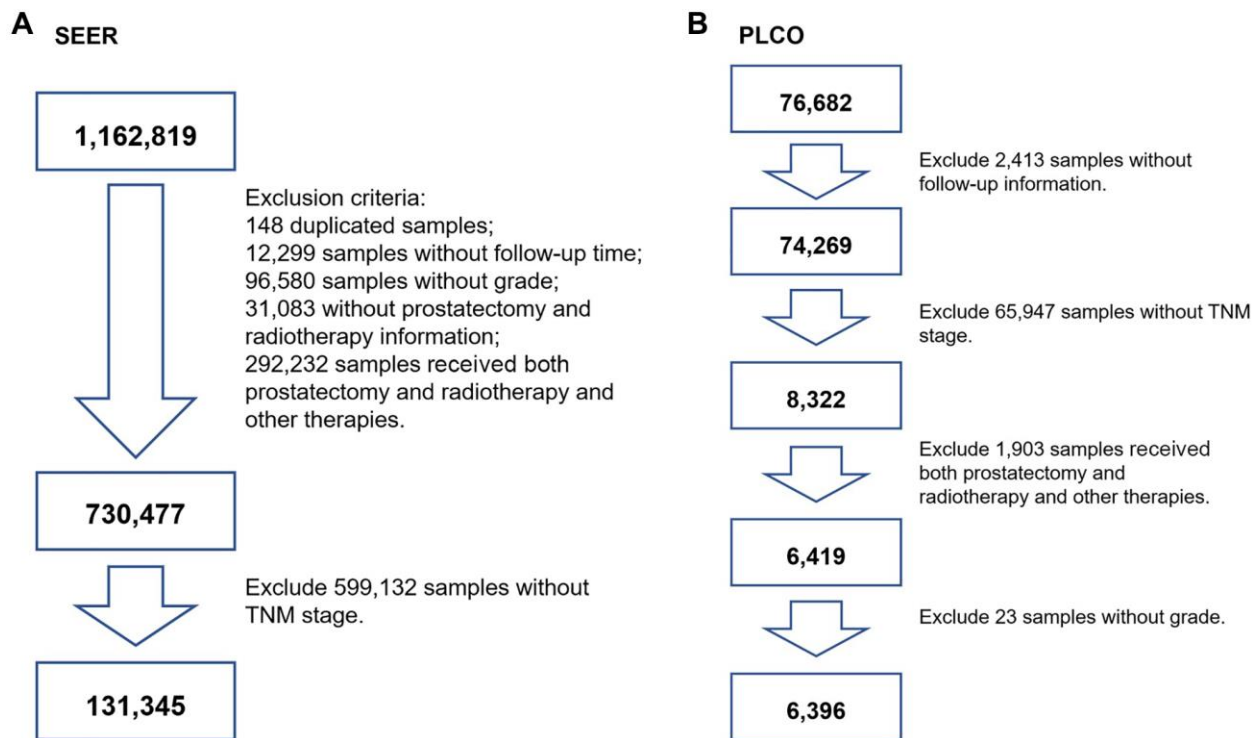

Figure 1. The flowchart of screening participants using the SEER and PLCO cohort. (**A**) for SEER screening, (**B**) for PLCO screening. TNM stage: tumor node metastasis stage.

Table 1. Clinical and pathoanatomic characteristics of Surveillance, Epidemiology, and End results (SEER) (*n* = 131, 345).

Variables	Prostatectomy (*n* = 74, 663)	Radiation (*n* = 56, 682)
Age (years)	62.94 ± 8.54	67.53 ± 7.97
Survival time (months)	24.12 ± 13.84	24.83 ± 13.65
End-point events	2, 531 (3.39%)	2, 356 (4.16%)
TNM		
I	10, 092 (13.5%)	16, 279 (28.7%)
II	49, 470 (66.3%)	37, 042 (65.4%)
III	12, 507 (16.8%)	1, 410 (2.5%)
IV	2, 594 (3.5%)	1, 951 (3.4%)
Grade		
Well differentiated; Grade I	1, 179 (1.6%)	591 (1.0%)
Moderately differentiated; Grade II	25, 508 (34.2%)	20, 815 (36.7%)
Poorly differentiated; Grade III	47, 872 (64.1%)	35, 137 (62.0%)
Undifferentiated; anaplastic; Grade IV	104 (0.1%)	139 (0.2%)
T		
T1a	2, 682 (3.6%)	0 (0.0%)
T1b	1, 416 (1.9%)	0 (0.0%)
T1c	2, 228 (3.0%)	38, 171 (67.3%)
T1NOS	653 (0.9%)	0 (0.0%)
T2a	7, 797 (10.4%)	3, 917 (6.9%)
T2b	1, 420 (1.9%)	1, 934 (3.4%)
T2c	38, 918 (52.1%)	2, 085 (3.7%)
T2NOS	5, 275 (7.1%)	8, 418 (14.9%)
T3a	9, 890 (13.2%)	665 (1.2%)
T3b	3, 752 (5.0%)	605 (1.1%)
T3NOS	104 (0.1%)	446 (0.8%)
T4	476 (0.6%)	309 (0.5%)
TX	52 (0.1%)	132 (0.2%)
N		
N0	72, 789 (97.5%)	55, 652 (98.2%)
N1	1, 740 (2.3%)	840 (1.5%)
NX	134 (0.2%)	190 (0.3%)
M		
M0	73, 849 (98.9%)	55, 316 (97.6%)
M1a	54 (0.1%)	62 (0.1%)
M1b	563 (0.8%)	1, 039 (1.8%)
M1c	151 (0.2%)	232 (0.4%)
M1NOS	46 (0.1%)	33 (0.1%)

Table 2. Clinical and pathoanatomic characteristics the Prostate, Lung, Colorectal, and Ovarian (PLCO) (*n* = 6, 396).

Variables	Prostatectomy (*n* = 2, 961)	Radiation (*n* = 3, 435)
Age (years)	66.04 ± 4.59	70.50 ± 5.31
Survival time	144.13 ± 21.56	143.75± 22.31
End-point events	284	493
TNM		
I	4 (0.1%)	6 (0.2%)
II	2939 (99.3%)	3303 (96.2%)
III	17 (0.6%)	86 (2.5%)
IV	1 (0.0%)	40 (1.2%)
Grade		
Slight Anaplasia (G1)	77 (2.6%)	142 (4.1%)
Moderate Anaplasia (G2)	2447 (82.6%)	2774 (80.8%)
Marked Anaplasia (G3-4)	437 (14.8%)	519 (15.1%)
Gleason		
2–4	67 (2.3%)	110 (3.2%)
5–6	1416 (47.8%)	1834 (53.4%)
7–10	1456 (49.2%)	1471 (42.8%)
Not Available (99)	22 (0.7%)	20 (0.6%)
T		
T1 (3)	1 (0.0%)	0 (0.0%)
T1a (4)	21 (0.7%)	17 (0.5%)
T1b (5)	18 (0.6%)	22 (0.6%)
T1c (6)	1816 (61.3%)	2112 (61.5%)
T2 (7)	89 (3.0%)	46 (1.3%)
T2a (8)	619 (20.9%)	654 (19.0%)
T2b (9)	319 (10.8%)	443 (12.9%)
T2c (10)	61 (2.1%)	40 (1.2%)
T3 (11)	4 (0.1%)	23 (0.7%)
T3a (12)	8 (0.3%)	38 (1.1%)
T3b (13)	3 (0.1%)	19 (0.6%)
T3c (14)	2 (0.1%)	12 (0.3%)
T4 (15)	0 (0.0%)	7 (0.2%)
TX (1)	0 (0.0%)	2 (0.1%)
N		
N0 (2)	2261 (76.4%)	2899 (84.4%)
N1 (3)	0 (0.0%)	17 (0.5%)
N2 (4)	0 (0.0%)	0 (0.0%)
NX (1)	687 (23.2%)	512 (14.9%)
Not Available (99)	13 (0.4%)	7 (0.2%)
M		
M0 (2)	2532 (85.5%)	3066 (89.3%)
M1a (3)	0 (0.0%)	3 (0.1%)
M1b (4)	1 (0.0%)	18 (0.5%)
M1c (5)	0 (0.0%)	1 (0.0%)
MX (1)	421 (14.2%)	341 (9.9%)
Not Available (99)	7 (0.2%)	6 (0.2%)

PSA (ng/mL)		
0–4	496 (16.8%)	421 (12.3%)
4.1–10	1891 (63.9%)	2167 (63.1%)
10.1–20	353 (11.9%)	474 (13.8%)
20.1–50	65 (2.2%)	150 (4.4%)
50.1–100	9 (0.3%)	30 (0.9%)
100+	2 (0.1%)	16 (0.5%)
Not available	145 (4.9%)	177 (5.2%)
Smoke		
Never smoked	1031 (34.8%)	1124 (32.7%)
Current or former smoker	1861 (62.9%)	2218 (64.6%)
Not available	69 (2.3%)	93 (2.7%)
Education		
Less Than 8 Years	23 (0.8%)	37 (1.1%)
8-11 Years	150 (5.1%)	226 (6.6%)
12 Years or Completed High School	530 (17.9%)	583 (17.0%)
Post High School Training Other Than College	343 (11.6%)	375 (10.9%)
Some College	556 (18.8%)	704 (20.5%)
College Graduate	593 (20.0%)	631 (18.4%)
Postgraduate	689 (23.3%)	783 (22.8%)
Not available	77 (2.6%)	96 (2.8%)
Race		
White, Non-Hispanic	2648 (89.4%)	2893 (84.2%)
Black, Non-Hispanic	138 (4.7%)	234 (6.8%)
Hispanic	45 (1.5%)	64 (1.9%)
Asian	42 (1.4%)	123 (3.6%)
Pacific Islander	10 (0.3%)	23 (0.7%)
American Indian	7 (0.2%)	5 (0.1%)
Missing	71 (2.4%)	93 (2.7%)
BMI	27.22 ± 3.68	27.41 ± 4.02
Aspirin		
None	1392 (47.0%)	1496 (43.6%)
1/Day	623 (21.0%)	879 (25.6%)
2+/Day"	136 (4.6%)	147 (4.3%)
1/Week	38 (1.3%)	38 (1.1%)
2/Week	99 (3.3%)	122 (3.6%)
3-4/Week	297 (10.0%)	306 (8.9%)
<2/Month	195 (6.6%)	220 (6.4%)
2-3/Month	107 (3.6%)	123 (3.6%)
Not available	74 (2.5%)	104 (3.0%)
Diabetes		
No	2737 (92.4%)	3073 (89.5%)
YES	137 (4.6%)	249 (7.2%)
Not available	87 (2.9%)	113 (3.3%)
Family history of Prostate Cancer		
No	2481 (83.8%)	2927 (85.2%)
Yes, Immediate Family Member	349 (11.8%)	346 (10.1%)
Possibly - Relative Or Cancer Type Not Clear	44 (1.5%)	51 (1.5%)

Not available	87 (2.9%)		111 (3.2%)
Comorbidity			
0	1209 (40.8%)		1103 (32.1%)
1	989 (33.4%)		1163 (33.9%)
2	516 (17.4%)		698 (20.3%)
≥3	247 (8.3%)		471 (13.7%)

Table 3. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) of prostate cancer (PCa) deaths for men who received radiotherapy (RT) versus those who underwent radical prostatectomy (RP) in SEER and PLCO.

Dataset	No. of patients (deaths/total)	HR	95%CI	p	HR	95%CI	p
SEER	4887/131,345	1.19	1.13–1.26	< 0.0001[a]	1.09	1.02–1.16	0.0069[b]
PLCO	777/6,396	1.50	1.30–1.73	< 0.0001[a]	1.46	1.24–1.72	< 0.0001[c]

[a]unadjusted.

[b]adjusted age at diagnosis (5-year groups), tumor node metastasis (TNM) stage (continuous) and grade (continuous).

[c]adjusted age at diagnosis (5-year groups), TNM stage (continuous), grade (continuous), smoke (categorical), education levels (continuous), race (categorical), body mass index (continuous), aspirin does (continuous), diabetes (categorical) and family history (categorical).

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; PLCO, the Prostate, Lung, Colorectal, and Ovarian.

Table 4. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) of prostate cancer (PCa) deaths for men who received radiotherapy (RT) versus those who underwent radical prostatectomy (RP) in SEER stratified by TNM stage.

TNM stage	No. of patients (deaths/total)	HR[a]	95%CI[a]	p[a]	HR[b]	95%CI[b]	p[b]
I	984/26,371	0.31	0.27–0.35	< 0.0001	0.35	0.30–0.40	< 0.0001
IIA	1056/32,631	0.82	0.72–0.93	0.0025	0.67	0.58–0.76	< 0.0001
IIB	1547/53,881	2.15	1.94–2.38	< 0.0001	0.85	0.76–0.95	0.0048
III	299/13,917	2.86	2.20–3.71	< 0.0001	1.38	1.04–1.84	0.026
IV	1001/4,545	1.83	1.61–2.07	< 0.0001	1.78	1.59–2.05	< 0.0001

[a]unadjusted.

[b]adjusted age at diagnosis (5-year groups) and grade (continuous).

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

Table 5. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) of prostate cancer (PCa) deaths for men who received radiotherapy (RT) versus those who underwent radical prostatectomy (RP) in SEER stratified by age groups.

Age (years)	No. of patients (deaths/total)	HR[a]	95%CI[a]	p[a]	HR[b]	95%CI[b]	p[b]
45–49	46/3,461	3.80	2.13–6.79	< 0.0001	6.40	3.50–11.68	< 0.0001
50–54	179/10,892	3.09	2.30–4.14	< 0.0001	5.32	3.95–7.16	< 0.0001
55–59	347/19,949	2.43	1.97–3.00	< 0.0001	4.04	3.22–5.06	< 0.0001
60–64	611/27,645	1.92	1.64–2.25	< 0.0001	3.36	2.84–3.98	< 0.0001
65–69	861/30,593	1.36	1.19–1.56	< 0.0001	2.15	1.86–2.49	< 0.0001
70–74	864/20,527	0.77	0.68–0.88	0.0002	1.09	0.94–1.27	0.21
75–79	808/11,239	0.42	0.37–0.49	< 0.0001	0.52	0.45–0.61	< 0.0001
80–84	658/4,414	0.32	0.28–0.38	< 0.0001	0.34	0.29–0.40	< 0.0001
85+	504/1,767	0.44	0.36–0.55	< 0.0001	0.39	0.32–0.49	< 0.0001

[a]unadjusted.

[b]adjusted tumor node metastasis (TNM) stage (continuous) and grade (continuous).

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

age increases, the prognosis of RT improves, while as the malignancy of PCa increases, the prognosis of RT worsens. For each patient, our study suggested better treatment according to age and TNM stage information.

In the last decade, many studies have been conducted to compare the prognosis after RT and RP. Petrelli et al. summarized 17 studies and conducted a meta-analysis. The results found lower overall mortality and cancer-
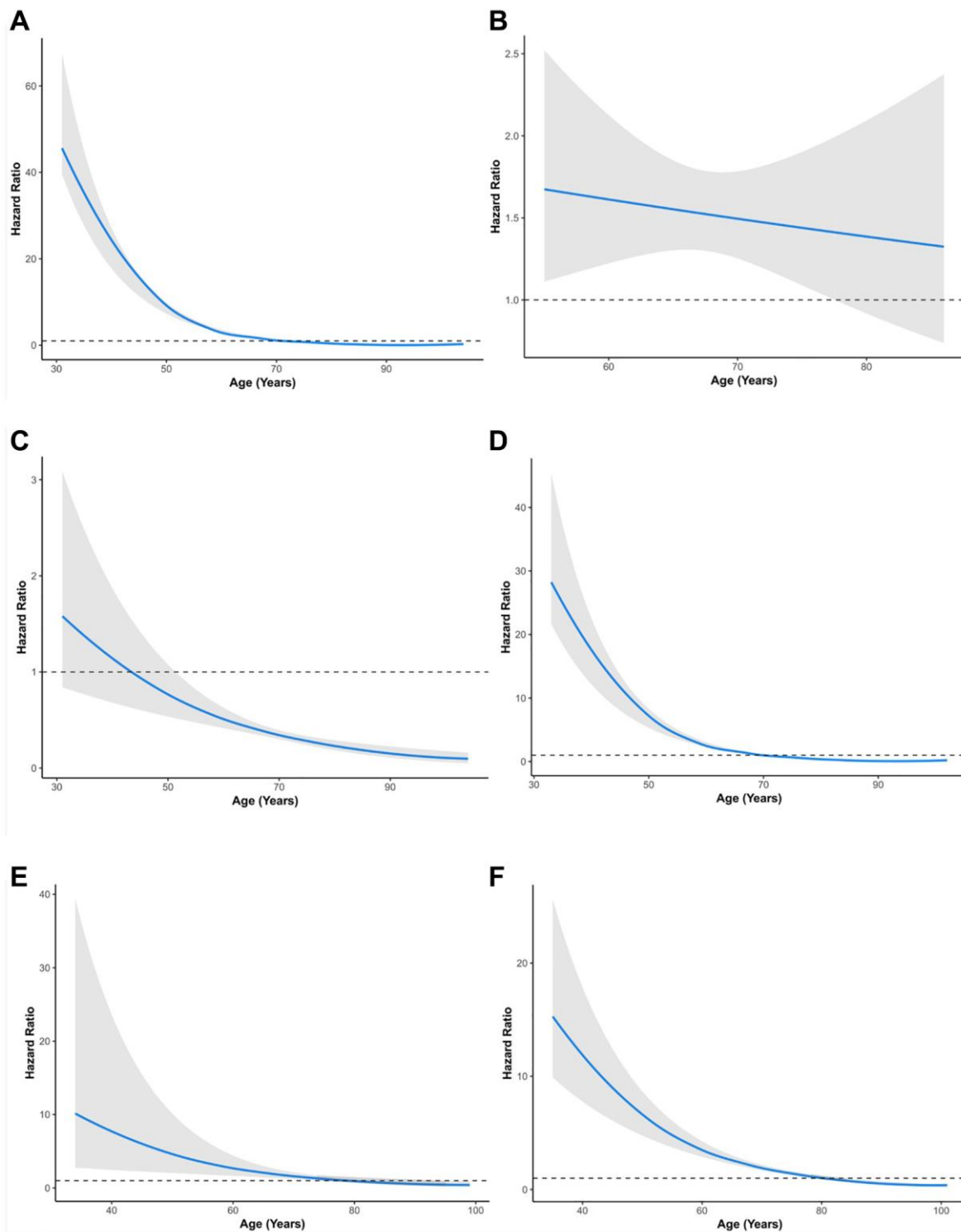

Figure 2. Relationship between age and hazard ratio of RT versus RP for patients with prostate cancer. (**A**) All groups in SEER. (**B**) All groups in PLCO. (**C**) Stage I group in SEER. (**D**) Stage II group in SEER. (**E**) Stage III group in SEER. (**F**) Stage IV group in SEER. SEER, Surveillance, Epidemiology, and End Results; PLCO, the Prostate, Lung, Colorectal, and Ovarian. The solid lines are multivariable adjusted hazard ratios. The shaded areas are the 95% confidence intervals. The dotted lines are coordinate 1 on the vertical axis.

Table 6. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) of prostate cancer (PCa) death for men who received radiotherapy (RT) versus those who underwent radical prostatectomy (RP) in SEER stratified by age according to TNM stage.

TNM stage	Age (years)	No. of patients (deaths/total)	HR[a]	95% CI[a]	p[a]	HR[b]	95% CI[b]	p[b]
Stage I	45–49	11/669	0.97	0.3–3.19	0.96	0.99	0.29–3.30	0.99
	50–54	32/1, 994	0.85	0.42–1.7	0.64	0.87	0.43–1.74	0.69
	55–59	76/3, 879	0.60	0.38–0.94	0.026	0.59	0.38–0.93	0.022
	60–64	117/5, 520	0.48	0.33–0.69	< 0.0001	0.47	0.33–0.68	< 0.0001
	65–69	163/6, 239	0.40	0.29–0.54	< 0.0001	0.40	0.29–0.54	< 0.0001
	70–74	172/4, 302	0.25	0.18–0.34	< 0.0001	0.25	0.18–0.34	< 0.0001
	75–79	173/2, 321	0.29	0.21–0.39	< 0.0001	0.29	0.21–0.39	< 0.0001
	80–84	145/879	0.37	0.24–0.57	< 0.0001	0.37	0.24–0.57	< 0.0001
	85+	93/393	0.22	0.05–0.89	0.034	0.20	0.05–0.83	0.026
Stage IIA	45–49	6/456	2.56	0.47–14.01	0.28	2.54	0.46–14.01	0.28
	50–54	23/1, 697	1.23	0.54–2.81	0.62	1.25	0.55–2.86	0.59
	55–59	62/3, 587	2.96	1.54–5.69	0.0011	2.93	1.53–5.63	0.0012
	60–64	130/6, 089	2.03	1.30–3.16	0.0017	2.04	1.31–3.18	0.0016
	65–69	207/7, 902	0.98	0.71–1.34	0.89	0.98	0.71–1.34	0.89
	70–74	205/6, 733	0.58	0.43–0.80	0.0009	0.58	0.43–0.80	0.0009
	75–79	203/4, 245	0.58	0.41–0.81	0.0016	0.58	0.41–0.82	0.0021
	80–84	135/1, 430	0.29	0.21–0.41	< 0.0001	0.29	0.21–0.41	< 0.0001
	85+	83/388	0.41	0.25–0.67	0.0007	0.41	0.25–0.67	0.0004
stage IIB	45–49	13/1, 910	2.28	0.30–17.54	0.43	2.28	0.28–18.39	0.44
	50–54	50/5, 645	2.54	1.14–5.64	0.022	2.45	1.09–5.55	0.031
	55–59	107/9, 536	2.54	1.59–4.06	< 0.0001	2.34	1.45–3.80	0.0005
	60–64	173/11, 768	3.35	2.46–4.56	< 0.0001	3.52	2.55–4.85	< 0.0001
	65–69	260/11, 799	2.20	1.72–2.82	< 0.0001	2.17	1.69–2.81	< 0.0001
	70–74	283/6, 910	1.37	1.09–1.73	0.0078	1.39	1.09–1.76	0.0074
	75–79	266/3, 582	0.49	0.38–0.62	< 0.0001	0.52	0.40–0.67	< 0.0001
	80–84	210/1, 594	0.23	0.18–0.30	< 0.0001	0.24	0.18–0.31	< 0.0001
	85+	182/645	0.25	0.17–0.36	< 0.0001	0.25	0.17–0.36	< 0.0001
Stage III	45–49	2/333	–	–	–	–	–	1.0
	50–54	8/1, 220	3.04	0.37–24.8	0.30	2.99	0.36–24.58	0.31
	55–59	24/2, 351	5.02	1.99–12.66	0.0006	4.79	1.89–12.12	0.0009
	60–64	51/3, 416	1.57	0.62–3.96	0.34	1.54	0.61–3.87	0.36
	65–69	67/3, 691	2.17	1.14–4.14	0.019	2.21	1.16–4.23	0.016
	70–74	60/1, 933	2.37	1.38–4.05	0.0017	2.36	1.38–4.04	0.0017
	75–79	35/631	0.70	0.34–1.47	0.35	0.70	0.33–1.45	0.34
	80–84	31/203	0.47	0.23–0.96	0.038	0.48	0.23–0.97	0.041
	85+	21/78	0.50	0.2–1.27	0.15	0.50	0.20–1.27	0.15
Stage IV	45–49	14/93	5.91	1.65–21.22	0.0064	5.85	1.63–21.04	0.0068
	50–54	66/336	3.84	2.23–6.6	< 0.0001	3.84	2.24–6.61	< 0.0001
	55–59	78/596	5.18	3.12–8.62	< 0.0001	5.19	3.11–8.66	< 0.0001
	60–64	140/852	2.83	1.99–4.02	< 0.0001	2.84	2.00–4.03	< 0.0001
	65–69	164/962	2.83	2.05–3.91	< 0.0001	2.83	2.05–3.92	< 0.0001
	70–74	144/649	1.66	1.18–2.32	0.0032	1.66	1.19–2.33	0.003
	75–79	131/460	0.88	0.63–1.25	0.48	0.88	0.62–1.24	0.47

80–84	137/308	1.15	0.82–1.61	0.42	1.21	0.86–1.71	0.28
85+	125/263	0.80	0.55–1.17	0.25	0.80	0.55–1.16	0.24

[a]unadjusted.
[b]adjusted grade (continuous).
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

related mortality after RP than after RT [14]. Moreover, another meta-analysis including 19 studies also indicated that overall and prostate cancer-specific mortality for patients treated with RT is higher than that for patients treated with RP [5]. However, a large-sample observational study suggested that the difference in prognosis after RT and RP was quite small [7]. In line with this result, Hamdy and his colleagues also reported that prostate cancer-specific mortality was low irrespective of the treatment assigned after a median of 10 years [6]. Similar results were observed in patients older than 65 [15]. Two other studies supported no difference between the choice of RT and RP [16, 17].

Through stratified analysis rather than adjustment, we found that as the age and cancer process are altered, the best treatment for patients changes. A large-sample cohort study showed similar results after a 13-year follow-up [18]. However, because their cohorts consisted of patients from 65 to 80 years old, divided into three categories, no significant trend of HRs with age was shown. Moreover, the conclusion was drawn by three additional studies that younger men and those with intermediate- or high-risk localized PCa might have a greater benefit from RP [19–21]. These elucidations are consistent with our results. Our result is different but does not conflict with previous studies. Age and TNM stage were adjusted for in previous studies, but few stratified analyses were performed. Thus, the trend by age and TNM stage for HRs for RT versus RP is likely to be covered. Meanwhile, due to differences in the age composition and progression of PCa, different cohorts may lead to different results. Our results may demonstrate why previous studies drew different conclusions.

As a retrospective study, straightforward comparisons of survival between different treatments would be biased by confounders. In this work, we have taken several measures to reduce the bias. First, we established strict inclusion and exclusion criteria for participants. Second, stratified analyses were performed rather than adjustment. To eliminate potential confounders, available baseline characteristics such as grade and BMI were included in the model. Third, two independent PCa cohorts were employed to confirm the results. The significant interaction between TNM stage/age and treatment in survival in two cohorts indicated that there were associations between them.

The results changed little when other factors were included in the models. Thus, potential confounders may result in little bias. To further validate the findings, rigorous and long-term randomized controlled trials are needed before clinical use.

The limitations of our study include the following three aspects. First, our results were obtained from public databases rather than independent cohorts. Second, the cohorts from the two databases were heterogeneous to some extent, and the sample size of PLCO was relatively small. This made the results from the two databases not completely consistent. Third, because of restricted available information on subjects in the SEER database, we only adjusted for age, grade and TNM stage.

In summary, this study highlights a difference in the prognosis of PCa patients between RT and RP based on stratified analysis by TNM stage and age. Thus, the choice between these two treatments should be guided by TNM stage and age. These findings may facilitate counseling regarding the prognostic effect of RT and RP.

AUTHOR CONTRIBUTIONS

G.M., L.-W.Q., and Q.Y. conceived and directed the project. G.M. applied for the data from SEER and PLCO. Y.F., and F.W. analysis the data and wrote the manuscript. X.Y. edited the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

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SUPPLEMENTARY MATERIALS

Supplementary Table

Supplementary Table 1. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) of prostate cancer (PCa) deaths for men received both prostatectomy and radiotherapy versus only prostatectomy or radiotherapy in PLCO.

PLCO	No. of patients (deaths/total)	HR[a]	95% CI[a]	p^a	HR[b]	95% CI[b]	p^b
Both prostatectomy and radiotherapy Verse prostatectomy	301/3, 105	1.23	0.75–2.00	0.42	1.13	0.67–1.90	0.64
Both prostatectomy and radiotherapy Verse radiotherapy	510/3, 579	0.82	0.50–1.33	0.41	0.83	0.50–1.38	0.47

[a]unadjusted.
[b]adjusted age at diagnosis (5-year groups), TNM stage (continuous), grade (continuous), smoke (categorical), education levels (continuous), race (categorical), body mass index (continuous), aspirin does (continuous), diabetes (categorical) and family history (categorical).
Abbreviation: PLCO, the Prostate, Lung, Colorectal, and Ovarian.