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Bladder Cancer

External Beam Radiotherapy Increases the Risk of Bladder Cancer When Compared with Radical Prostatectomy in Patients Affected by Prostate Cancer: A Population-based Analysis

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Abstract

Background: Long-term survival can be achieved in patients affected by localized prostate cancer (PCa) treated with either radical prostatectomy (RP) or external beam radiotherapy (EBRT). However, development of a second primary tumor is still poorly investigated.
Objective: To investigate the impact of RP and EBRT on subsequent risk of developing bladder (BCa) and/or rectal cancer (RCa) among PCa survivors.
Design, setting, and participants: A total of 84 397 patients diagnosed with localized PCa, treated with RP or EBRT between 1988 and 2009, and older than 65 yr of age were identified in the Surveillance, Epidemiology, and End Results Medicare insurance program-linked database. Our primary objective was to investigate the effect of EBRT and RP on the second primary BCa and RCa incidence.
Outcome measurements and statistical analysis: Multivariable competing-risk regression analyses were performed to assess the risk of developing a second primary BCa or RCa.
Results and limitations: Of the 84 397 individuals included in the study, 33 252 (39%) were treated with RP and 51 145 (61%) with EBRT. Median follow-up was 69 months, and follow-up periods for patients who did not develop BCa, RCa, or pelvic cancer were 68, 69, and 68 mo, respectively. A total of 1660 individuals developed pelvic tumors (1236 BCa and 432 RCa). The 5- and 10-yr cumulative BCa incidence rates were 0.75% (95% confidence interval [CI]: 0.64–0.85%) and 1.63% (95% CI: 1.45–1.80%) versus 1.26% (95% CI: 1.15–1.37%) and 2.34% (95% CI: 2.16–2.53%) for patients treated with RP versus EBRT, respectively. The 5- and 10-yr cumulative RCa incidence rates were 0.32% (95% CI: 0.25–0.39%) and 0.73% (95% CI: 0.61–0.85%) versus 0.36% (95% CI: 0.30–0.41%)

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and 0.69% (95% CI: 0.60–0.79%) for patients treated with RP versus EBRT, respectively. On multivariable competing risk regression analyses, treatment with EBRT was independently associated with the risk of developing a second primary BCa (hazard ratio: 1.35, CI: 1.18–1.55; $p < 0.001$), but not RCa ($p = 0.4$). Limitations include lack of information regarding the dose of radiotherapy and the retrospective nature with the implicit risk of selection bias.

Conclusions: Patients treated with EBRT are at increased risk of developing a second primary BCa compared with those treated with RP. However, no differences were found considering RCa incidence in patients treated with RP or EBRT within the first 5 yr after primary therapy. These results need to be validated in a well-designed randomized prospective trial.

Patient summary: We retrospectively analyzed the risk of developing a second primary bladder or rectal cancer during follow-up for patients treated with radical prostatectomy or external beam radiotherapy for a localized prostate cancer. We found that those treated with external beam radiotherapy are at an increased risk of developing a second primary bladder cancer tumor.

1. Introduction

Radical prostatectomy (RP) and external beam radiotherapy (EBRT) are the standard of care options for active treatment of localized prostate cancer (PCa) [1]. Alternatively, active surveillance (AS) should be considered in very-low-risk PCa patients. While many studies focused on their oncological effects for PCa [2–6], their differential effect on the development of second primary cancers such as bladder (BCa) and rectal (RCa) cancers remains only partially investigated.

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program reported that multiple primary cancers account for approximately 17% of all incident cancers [7]. This rate can sensitively increase in oncological patients who harbor a low-risk primary cancer, expecting them to have long-term survival and the risk of a second primary tumor. Risk factors for the development of second malignancy include aging, lifestyle, and environmental and genetic factors [8–11]. Most of these factors are only partially modifiable, such as smoking cessation or healthy life style adoption.

Therapy of the first tumor might influence the risk of harboring a second tumor, and identifying such a factor would improve selection of patients among those who are at an increased risk of developing a potentially deadly second primary tumor. Therefore, we investigated the impact of primary PCa treatment on the subsequent risk of developing a second primary BCa or RCa in a large population-based cohort of clinically localized PCa.

2. Patients and methods

2.1. Data source and study population

The study relied on the SEER-Medicare insurance program-linked database [12]. The SEER registries cover approximately 28% of the US population with Medicare administrative data. Identification of the study cohort consisted of several steps. First, we identified patients diagnosed between 1988 and 2009 with histologically confirmed PCa without previous cancer diagnoses (International Classification of Diseases for Oncology [ICD-O] site code 61.9, histological code 8140) aged ≥66 yr. After PCa treatment, patients were followed up until 2012 to assess diagnosis of a second primary tumor. Only patients with nonregional and nonmetastatic disease at diagnosis (N0, M0) treated with RP or EBRT were considered. Additional exclusion criteria consisted of unknown race, unknown socioeconomic status, unknown biopsy Gleason score, unknown clinical T stage, and usage of adjuvant or salvage radiation therapy after RP. After calculation of the time lag between PCa and secondary tumor diagnosis, we excluded from the study cohort all patients with a time lag of ≤6 mo, with the assumption that these patients might have been diagnosed with PCa and another second primary pelvic tumor at the same time. Figure 1 reports the inclusion and exclusion criteria of the cohort. This resulted in a cohort of 84 397 individuals, from which we further identified 1660 records that contained a claim for a secondary pelvic cancer. Specifically, 1238 patients had a claim for BCa (ICD-O site code C67.0-C67.9, any histological code) and 432 records contained a claim for RCa (ICD-O site code C19.9 or C20.9, any histology code). This study was approved by the SEER program managers and the institutional review board.

2.2. Variable definition

Patient characteristics included age at PCa diagnosis, gender, race (Caucasian, African American, or other), comorbid conditions, as well as marital status (married, unmarried, or unknown), residence (rural, urban, or unknown), and hospital region (East Coast, South, Midwest, or West). The Charlson comorbidity index (CCI) was derived from the Medicare claims using previously validated algorithms [13]. Baseline comorbid conditions were recorded in all patients and were identified using unique ICD-9-CM diagnostic codes by the Medicare claims for the 12-mo interval preceding PCa diagnosis. RCa included rectosigmoid junction cancers. Moreover, given the well-known importance of smoking on the risk of BCa, Medicare claims were used in order to perform stratification according to the ever-smoker status. Comorbidities were identified by classifying inpatient and outpatient claims for the 12-mo interval preceding PCa diagnosis into 15 categories [13]. For each of the individuals included in the study cohort, we identified treatment modalities and stratified them according to RP and EBRT.

2.3. Outcomes and statistical analyses

The primary objective of the present study consisted of investigating the incidence of second primary pelvic tumors after treatment for PCa. The secondary objective was to investigate predictors of second primary pelvic tumors, BCa, or RCa prior to and after propensity match analyses. To evaluate our hypothesis, our analyses consisted of several steps. First, we evaluated differences between individuals treated with RP and those treated with EBRT. Descriptive statistics was performed focusing on

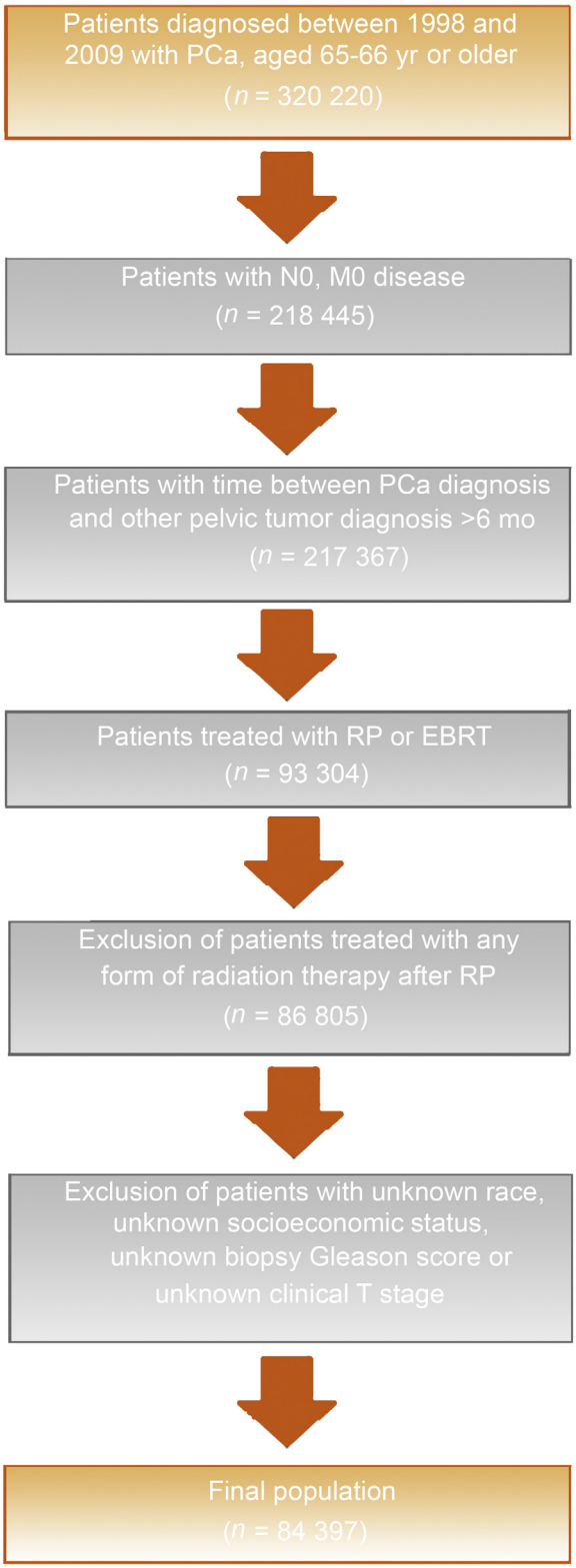

Fig. 1 – Flow diagram of the study population. EBRT = external beam radiotherapy; PCa = prostate cancer; RP = radical prostatectomy.

frequencies and proportions. Median ranges and interquartile ranges (IQRs) were reported for continuous variables. Second, we performed a competing risk regression analysis adjusting for the risk of overall mortality during the follow-up investigating the risk to develop a second primary BCa or RCa. All multivariable models were adjusted for age, year of surgery, race, marital status, CCI, smoking status, Gleason biopsy, Clinical stage, region of origin, and socioeconomic status. A landmark analysis (Supplementary Fig. 1 and Supplementary Tables 1–3) was performed excluding patients with follow-up <6 mo or those with secondary tumor diagnosis within the first 6 mo after treatment. All statistical tests were two sided with a level of significance was set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.3.0; http://www.r-project.org/).

3. Results

3.1. Baseline characteristics

Of the 84 397 individuals included in the study, 33 252 (39%) were treated with RP and 51 145 (61%) with EBRT. A total of 15 233 individuals (18%) were followed for >10 yr. A total of 1660 individuals developed pelvic tumors (1238 BCa and 432 RCa). Median follow-up periods for patients who did not develop BCa, RCa, or pelvic cancer were 68 (IQR: 37–106), 69 (IQR: 37–106), and 68 (IQR: 37–106) mo, respectively. Table 1 depicts the baseline characteristics of the individuals included in the study.

Specifically, RP patients were younger (69 vs 74 yr; $p < 0.001$) and more likely to be Caucasian (85% vs 81%; $p < 0.001$). Married individuals were more likely to be treated with RP when compared with nonmarried individuals (82% vs 71%; $p < 0.001$). Conversely, individuals with a CCI of 2 or ≥3 were more likely to undergo EBRT (19% and 10%, respectively; $p < 0.001$). Differences were also observed considering smoking status, area of origin, and socioeconomic status (all $p < 0.01$). Patients treated with RP were more likely to have clinical stages T3 or T4 (T3 5.4% and T4 5.2%, respectively) compared with patients treated with EBRT (3.0% and 1.9%, respectively; $p < 0.001$). Conversely, RP patients were more likely to harbor lower biopsy Gleason scores of 8–10 compared with EBRT patients (16% vs 24%; $p < 0.001$). Table 2 depicts the pathological characteristics of RCa and BCa diagnosed in patients previously treated with RP or EBRT for PCa. Patients treated with RP were more likely to show advanced clinical T3 or T4 RCa stages compared with those treated with EBRT (41% vs 40%; $p = 0.02$). Conversely, no differences in pathological stage were found between RP and EBRT in patients who developed BCa during the follow-up ($p = 0.07$).

3.2. Cumulative incidence

Cumulative incidence–derived 5-yr probabilities to develop a pelvic cancer, BCa, or RCa in the overall population were 1.42% (95% confidence interval [CI]: 1.33–1.51%), 1.06% (95% CI: 0.98–1.14%), and 0.37% (95% CI: 0.32–0.41%), respectively. Cumulative incidence–derived 10-yr rates for developing BCa and BCa, BCa alone, and RCa alone were 2.76% (95% CI: 2.61–2.91%), 2.04% (95%CI: 1.91–2.17%), and 0.74% (95% CI: 0.66–0.81%, Fig. 2), respectively. After stratification per primary treatment, the 5- and 10-yr cumulative BCa incidence rates were 0.75% (95% CI: 0.64–0.85%) and

Table 1 – Descriptive characteristics of our study cohort, composed of 84 397 patients diagnosed with prostate cancer between 1988 and 2009 and treated with either RP or primary EBRT

Variables	RP (n = 33 252, 39%)	EBRT (n = 51 145, 61%)	p value
Age at surgery (yr), median (IQR)	69 (67–72)	74 (70–77)	<0.001
Race			<0.001
Caucasian	28 360 (85%)	41 381 (81%)	
Afro-American	2388 (7.2%)	6019 (12%)	
Other	2504 (7.5%)	3475 (7.3%)	
Marital status			<0.001
Married	27 228 (82%)	36 413 (71%)	
Unmarried			
Unknown	4720 (14%)	10 366 (20%)	
CCI	1304 (3.9%)	4366 (8.5%)	<0.001
0	22 222(67%)	26 230 (51%)	
1	7807 (23%)	14 751 (29%)	
2	1894 (6%)	5343 (10%)	
≥3	1329 (4%)	4821 (9.4%)	
Smoking	10 337 (31%)	16 376 (32%)	<0.001
Gleason biopsy			<0.001
6	6232 (19%)	10 620 (21%)	
7	21 656 (65%)	28 430 (56%)	
8–10	5364 (16%)	12 095 (24%)	
Clinical T stage			<0.001
cT1	13 350 (40%)	21 874 (43%)	
cT2	16 407 (49%)	26 773 (52%)	
cT3	1782 (5.4%)	1548 (3.0%)	
cT4	1713 (5.2%)	950 (2%)	
Area			<0.001
Rural	4802 (14%)	8155 (16%)	
Urban	28 450 (86%)	42 990 (84%)	
Region			<0.001
Midwest	5738 (17%)	11 482 (22%)	
Northeast	3662 (11%)	11 518 (22%)	
South	4858 (15%)	8801 (17%)	
West	18 994 (57%)	19 344 (38%)	
SES, high	15 738 (47%)	25 811 (50%)	<0.001
Second primary cancer	601 (1.8%)	1059 (2.1%)	<0.001

CCI = Charlson comorbidity index; EBRT = external beam radiotherapy; IQR = interquartile range; RP = radical prostatectomy; SES = socioeconomic status. Comorbidities are presented according to comorbid condition groupings of the Deyo adaptation of the CCI.

1.63% (95% CI: 1.45–1.82%) versus 1.26% (95% CI: 1.15–1.37%) and 2.34% (95% CI: 2.16–2.53%) for patients treated with RP versus EBRT, respectively ($p < 0.001$). The 5- and 10-yr cumulative RCa incidence rates were 0.32% (95% CI: 0.25–0.39%) and 0.73% (95% CI: 0.61–0.85%) versus 0.36% (95% CI: 0.30–0.41%) and 0.69% (95% CI: 0.60–0.79%) for patients treated with RP versus EBRT, respectively ($p = 0.4$).

Table 2 – Rectum and bladder cancer characteristics of patients included in the study

Variables	RP N = 601	EBRT N = 1059	p value
Rectum cancer			0.02
Tx/unknown	14 (8.0%)	41 (16%)	
Ta/Tis	19 (11%)	14 (5%)	
T1	43 (25%)	49 (19%)	
T2	27 (15%)	50 (19%)	
T3/T4	72 (41%)	103 (40%)	
Bladder cancer			0.07
Tx/unknown	15 (3.5%)	32 (4.0%)	
Ta	223 (52%)	460 (57%)	
Tis	22 (5.1%)	30 (3.7%)	
T1	94 (22%)	145 (18%)	
T2	57 (13%)	104 (13%)	
T3/T4	17 (4.0%)	39 (5.3%)	

EBRT = external beam radiotherapy; RP = radical prostatectomy.

Figure 3 shows the 3- and 5-year cumulative incidence temporal trends of BCa and RCa, BCa alone, and RCa alone, stratified according to primary therapy. The 3- and 5-y cumulative BCa incidence rates ranged, respectively, from 0.41% (95% CI: 0.05–0.77%) and 0.98% (95% CI: 0.43–1.53%) between 1988 and 1990 to 0.42% (95% CI: 0.34–0.49%) and 0.75% (95% CI: 0.64–0.85%) between 2006 and 2008 for patients treated with RP, and from 0.59% (95% CI: 0.36–0.81%) and 1.05% (95% CI: 0.75–1.36%) between 1991 and 1993 to 0.70% (95% CI: 0.52–0.89%) and 1.18% (95% CI: 0.62–1.86%) between 2006 and 2008 for patients treated with EBRT. The 3- and 5-yr cumulative RCa incidence rates ranged, respectively, from 0.16% (95% CI: 0–0.39%) and 0.49% (95% CI: 0.10–0.88%) between 1988 and 1990 to 0.15% (95% CI: 0.04–0.26%) between 2006 and 2008 for patients treated with RP, and from 0.33% (95% CI: 0.16–0.450%) and 0.52% (95% CI: 0.30–0.73%) between 1991 and 1993 to 0.16% (95% CI: 0.08–0.24) between 2006 and 2008 for patients treated with EBRT.

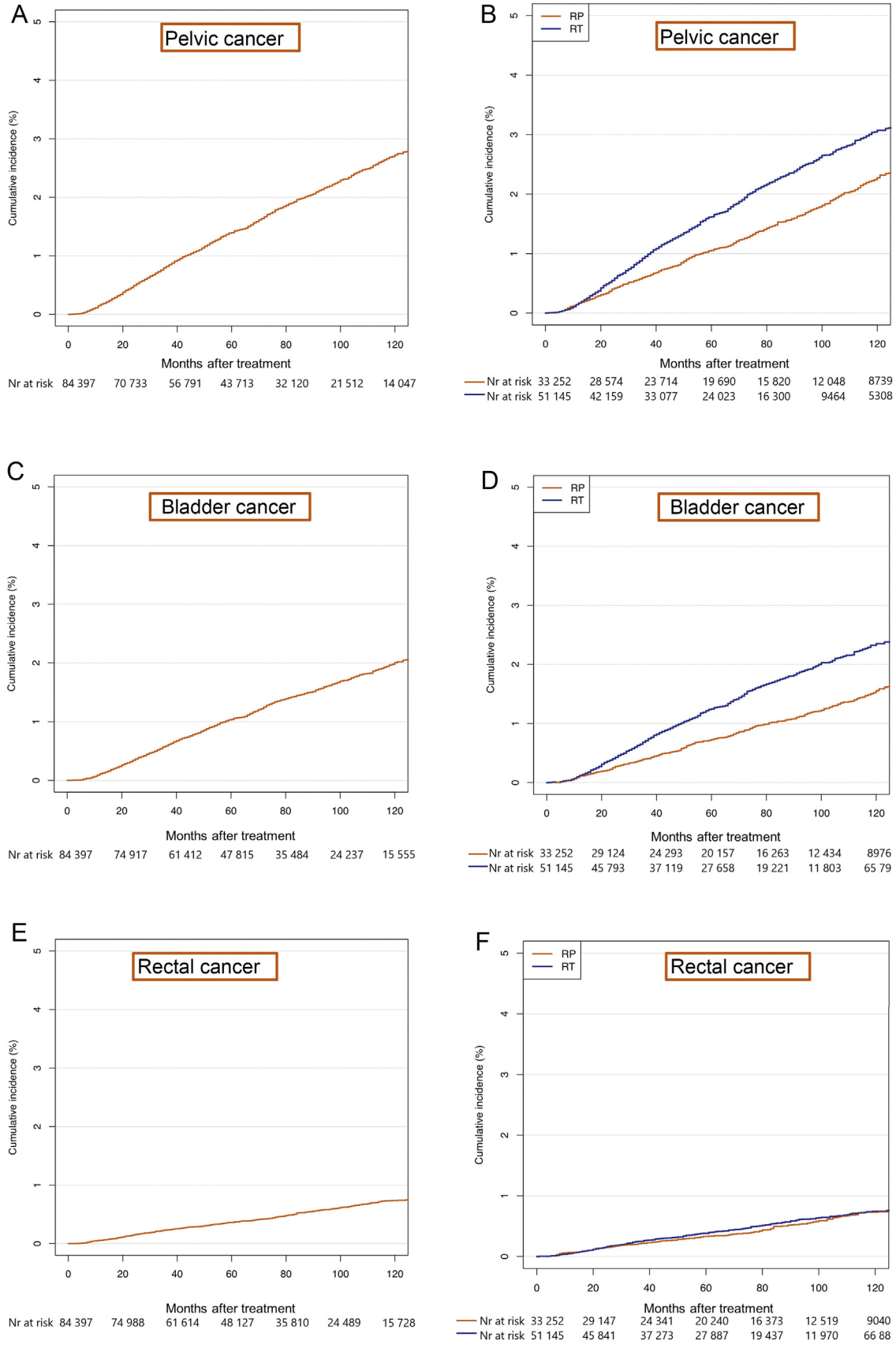

Fig. 2 – Cumulative incidence assessing (A) the risk of pelvic cancer in the overall population and (B) stratified by treatment, and (C) the risk of bladder cancer in the overall population and (D) stratified by treatment, and (E) cumulative incidence of rectal cancer in the overall population and (F) stratified by treatment. Nr = number; RP = radical prostatectomy; RT = radiotherapy.

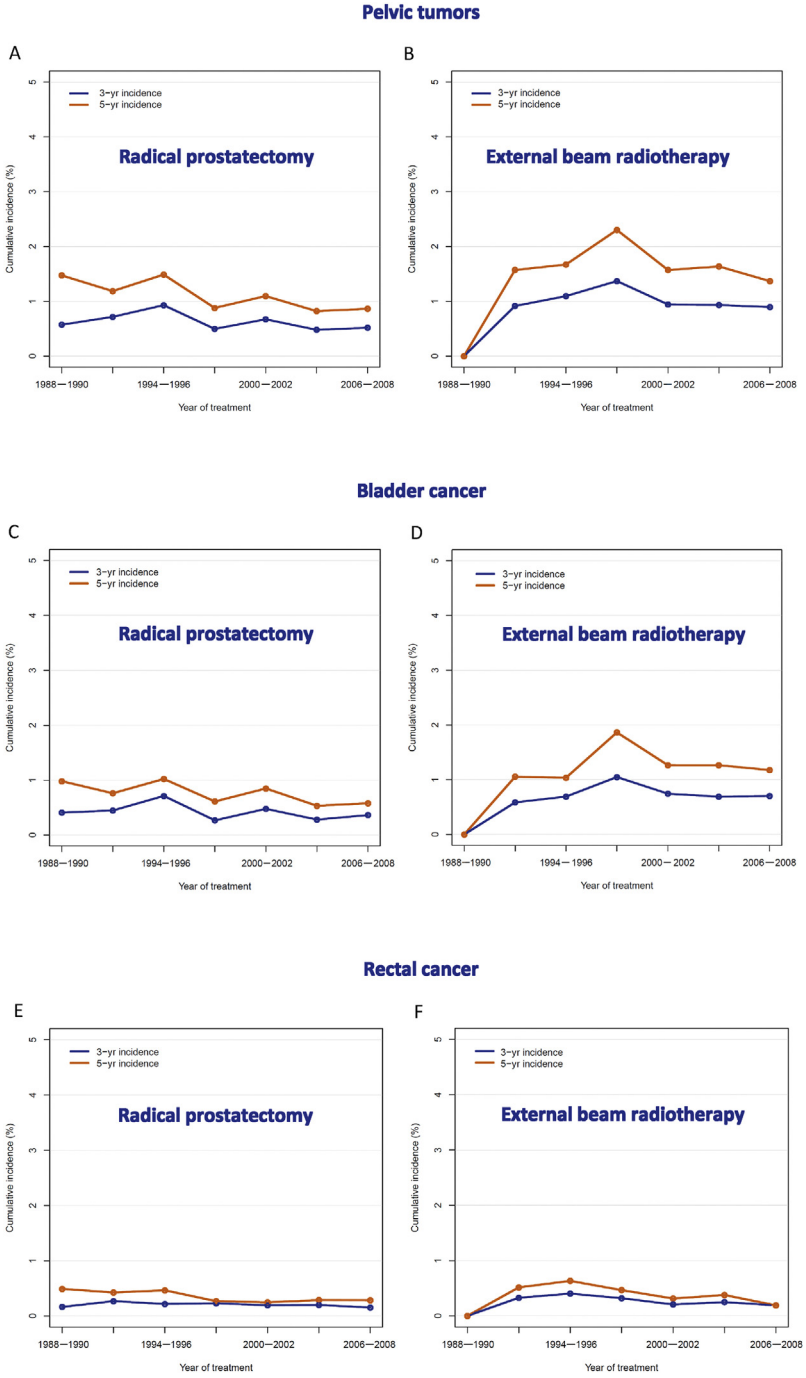

Fig. 3 – Three-year and 5-yr Incidences of pelvic tumor in patients treated with (A) radical prostatectomy and (B) external beam radiotherapy (B); 3- and 5-yr incidences of bladder cancer in patients treated with (C) radical prostatectomy and (B) external beam radiotherapy; and 3- and 5-yr incidences of rectal cancer in patients treated with (E) radical prostatectomy and (F) external beam radiotherapy.

3.3. *Predictors of pelvic tumors*

Table 3 shows multivariable competing risk regression analyses predicting BCa, RCa, and pelvic cancers. In multivariable competing risk regression analyses, patients treated with EBRT were more likely to develop a second primary pelvic cancer (hazard ratio [HR]: 1.27, CI: 1.13–1.43; $p < 0.001$) and a second primary BCa (HR: 1.35, CI: 1.18–1.55; $p < 0.001$), but not RCa ($p = 0.4$). Similar results were shown in the landmark analyses (Supplementary Table 3) reporting a multivariable competing risk analysis including only patients with at least 6 mo of follow-up, excluding patients with follow-up <6 mo or those with secondary tumor diagnosis within the first 6 mo after treatment.

3.4. *Impact of primary PCa treatment on secondary tumor*

Figure 4 illustrates the cumulative risk of BCa, RCa, and pelvic cancers in the overall population, and after stratification according to age and smoking status. At multivariable

Table 3 – Multivariable competing-risk regression analyses predicting the risk of developing bladder cancer, rectal cancer, or pelvic cancers after adjusting for the risk of overall mortality during follow-up

	Multivariable assessing BCa		Multivariable assessing rectal cancer		Multivariable assessing pelvic cancers	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at surgery (yr)	1.02 (1.01–1.03)	0.01	1.01 (0.99–1.03)	0.6	1.01 (1.01–1.03)	<0.01
Year of surgery	0.97 (0.95–0.98)	<0.001	0.94 (0.92–0.96)	<0.001	0.96 (0.95–0.97)	<0.001
Race						
Caucasian	Ref	Ref	Ref	Ref	Ref	Ref
Afro-American	0.63 (0.49–0.80)	<0.001	0.97 (0.70–1.36)	0.9	0.71 (0.58–0.86)	<0.001
Other	0.53 (0.39–0.71)	<0.001	1.60 (1.14–2.24)	<0.01	0.78 (0.62–0.97)	0.02
Marital status						
Married	Ref	Ref	Ref	Ref	Ref	Ref
Unmarried	0.80 (0.68–0.94)	<0.01	0.91 (0.70–1.18)	0.5	0.83 (0.73–0.95)	<0.01
Unknown	0.99(0.78–1.25)	0.9	0.48 (0.27–0.85)	0.01	0.87 (0.70–1.08)	0.2
CCI						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	0.97 (0.85–1.11)	0.7	0.96 (0.76–1.20)	0.7	0.97 (0.87–1.09)	0.6
2	0.98 (0.80–1.21)	0.9	0.67 (0.44–1.02)	0.06	0.91 (0.76–1.10)	0.3
≥3	0.98 (0.77–1.25)	0.9	1.01 (0.67–1.53)	0.9	0.99 (0.80–1.22)	0.9
Smoking	1.91 (1.70–2.14)	<0.001	1.44 (1.18–1.76)	<0.001	1.76 (1.60–1.95)	<0.001
Gleason biopsy						
6	Ref	Ref	Ref	Ref	Ref	Ref
7	1.21 (1.01–1.44)	0.03	0.86 (0.65–1.13)	0.3	1.10 (0.95–1.27)	0.2
8–10	1.19 (0.97–1.47)	0.09	1.05 (0.77–1.44)	0.8	1.15 (0.97–1.37)	0.1
Clinical stage						
cT1	Ref	Ref	Ref	Ref	Ref	Ref
cT2	0.96 (0.84–1.09)	0.5	0.88 (0.71–1.09)	0.2	0.94 (0.84–1.05)	0.2
cT3	1.01 (0.76–1.33)	0.9	0.62 (0.36–1.08)	0.09	0.91 (0.71–1.16)	0.4
cT4	1.08 (0.82–1.41)	0.6	1.22 (0.82–1.81)	0.3	1.13 (0.91–1.42)	0.3
Area						
Rural	Ref	Ref	Ref	Ref	Ref	Ref
Urban	1.07 (0.91–1.26)	0.4	0.95 (0.73–1.24)	0.7	1.04 (0.90–1.19)	0.6
Region						
Midwest	Ref	Ref	Ref	Ref	Ref	Ref
Northeast	1.12 (0.94–1.34)	0.2	0.92 (0.69–1.24)	0.6	1.06 (0.91–1.23)	0.4
South	0.96 (0.78–1.16)	0.7	0.80 (0.55–1.17)	0.2	0.91 (0.76–1.10)	0.3
West	0.90 (0.78–1.05)	0.2	0.65 (0.51–0.83)	<0.001	0.83 (0.73–0.94)	<0.01
SES						
Low	Ref	Ref	Ref	Ref	Ref	Ref
High	1.00 (0.89–1.12)	0.9	1.20 (0.98–1.46)	0.08	1.05 (0.95–1.17)	0.3
Therapy						
RP	Ref	Ref	Ref	Ref	Ref	Ref
EBRT	1.35 (1.18–1.55)	<0.001	1.10 (0.88–1.38)	0.4	1.27 (1.13–1.43)	<0.001

BCa = bladder cancer; CCI = Charlson comorbidity index; CI = confidence interval; EBRT = external beam radiotherapy; HR = hazard ratio; RP = radical prostatectomy; SES = socioeconomic status.

analyses, patients treated with EBRT were associated with an increased risk of developing pelvic cancers (HR: 1.27, CI: 1.13–1.43) and BCa (HR: 1.35, CI: 1.18–1.55). Interestingly, these results regarding BCa prediction were confirmed in all the subgroups when stratified according to smoking status. On the contrary, patients >80 yr of age had no difference in developing a second tumor after the primary treatment. Regarding RCa, no difference was recorded at multivariable analyses in any group.

4. Discussion

We found that 2% of PCa patients developed a second primary pelvic cancer (BCa or RCa) within 5.8 yr after treatment with RP or EBRT. More than half of those diagnosed with RCa were found to harbor advanced disease (pT2–T4), while only 18% of those diagnosed with BCa were found to harbor pT2–T4 disease. We found that patients treated with EBRT for PCa were at an increased risk of developing pelvic cancers, specifically BCa, when compared with patients treated with RP.

While our findings confirmed previous results [8–11], in contrast with previous studies, we considered only patients with localized PCa treated with either RP or EBRT. These specific selection criteria were chosen for several reasons. First, EBRT and RP represent the current standard of treatment for localized PCa by the current guidelines [1,14] and are the most common strategies adopted among patients with clinically localized PCa. Second, previous literature suggested a potential role of radiations in the risk of developing a second primary cancer among PCa and other cancer survivors, although scarce data exist evaluating EBRT alone [11]. In this sense, brachytherapy has yet only a limited use in the urological community, as its contemporary usage

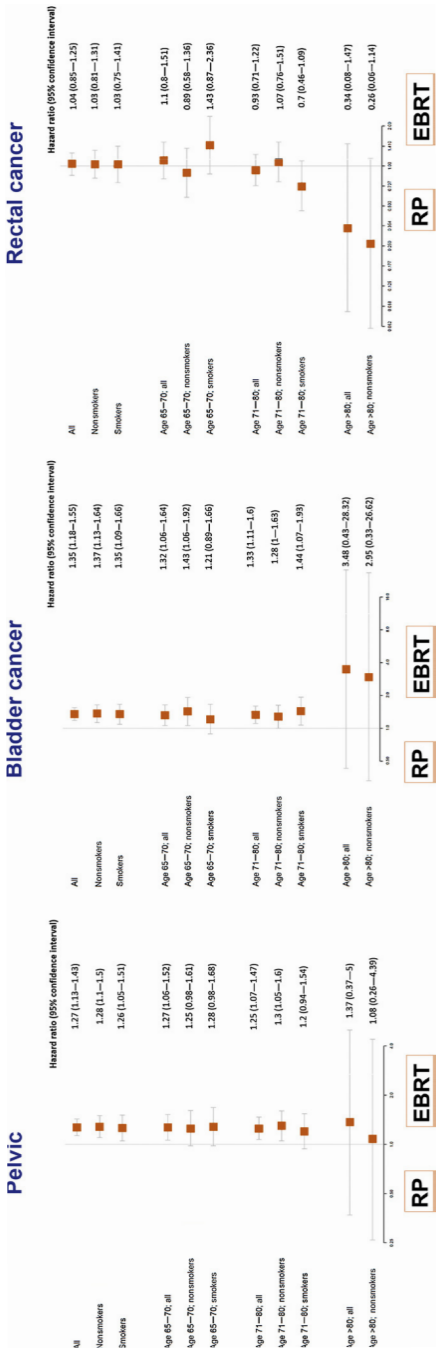

Fig. 4 – Estimated probability of developing a secondary tumor after prostate cancer treatment with radical prostatectomy or external beam radiotherapy in the overall population, and after stratification according to age and smoking status. The risk was assessed considering pelvic, bladder, and rectal cancers. EBRT = external beam radiotherapy; RP = radical prostatectomy.

in localized PCa patients is limited to 1.6% of all patients with clinically localized PCa [15]. Finally, while usage of AS is growing, it is estimated that still only 32% of patients potentially eligible for AS receives this treatment strategy [16]. Moreover, no clear definition of AS schemes across the SEER database has been adopted and AS patients are grouped together with watchful waiting patients, thus not allowing one to really understand the impact of these differential management strategies on the risk of developing a second primary cancer.

Davis et al. [8] using the SEER database found that PCa survivors had a lower risk when compared with the general US population to develop another cancer. Specifically, they found a decreased risk of developing leukemia and cancers of the oral cavity, pharynx, esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, lung, bronchus, and larynx. However, they found an increased risk of developing bladder, kidney, endocrine, and soft tissue cancers. Specifically, patients treated with EBRT were found to be at an increased risk of developing BCa and RCa during the follow-up period. In this regard, authors considered all patients with a diagnosis of PCa within the SEER database. This approach is, in our opinion, of certain interest in understanding the epidemiology of second primary cancer among PCa survivors. However, it does not consider the type of primary treatment in the context of localized PCa where these patients benefit from longer survivorship and therefore an increased risk of second primary tumors compared with primary nonlocalized PCa.

We confirmed in localized PCa patients that the treatment with EBRT was associated with a higher chance of developing a second primary BCa compared with the treatment with RP. These results were confirmed in multivariable competing risk analyses accounting for the effects of all the available confounders. Active smoking status was linked to an increased risk of developing both BCa and RCa. This is not surprising given the large and growing body of evidence unraveling the detrimental effect of smoking on the risk of developing BCa [17,18] and RCa [19]. Our data certainly support the importance of counseling patients for quitting smoking and support the PCa diagnoses as a teachable moment.

Considering temporal trends, similar rates of RCa and BCa were observed for patients treated with RP and EBRT across the entire study period. These results seem to suggest that technological advancements were not sufficient to reduce the risk of second primary pelvic tumor in the studied period. Intensity-modulated radiation therapy and charged particle therapy have been suggested to have the potential to reduce the risk of developing second primary tumors by reducing the amount of tissue exposed to high doses of radiation, in contrast to older techniques where a large volume of tissue were exposed to high doses of radiation with the consequent risk of morbidities and second primary cancers [20,21].

Strengths of this study include the use of a large, population-based database, which allows for the generalization of the results across the USA and the analyses of patients treated with EBRT or RP. This study reconciles with

previous findings, confirming the effect of EBRT on the risk of developing a second primary BCa. Our results focusing on patients affected by clinically localized PCa support the theory that radiation therapy might increase the risk of second primary BCa by 72% at 5 yr, and this aspect should therefore be taken in consideration, especially for patients who may potentially harbor long-term survivorship after PCa treatment and those who are anyway at an increased risk of BCa such as smokers.

Our study is not devoid of limitations. First, our findings were developed using administrative data, namely SEER-Medicare. In consequence, inclusion of a select cohort composed of Medicare beneficiaries aged 66 yr or older might limit the validity of long-term observations. This might have influenced our findings that might be different for patients aged 65 yr or younger. This might have influenced the selection of treatment where, as in our series, patients were more likely to be treated with EBRT compared with RP. Second, lack of information regarding the dose of radiotherapy prevented us from adjusting our analyses for the potential effect of these confounders. Moreover, improvements in EBRT technique have occurred over the years and patients treated in contemporary setting might experience different risks of harboring BCa. Third, several unmeasured parameters such as life style factors and comorbidities might alter our findings. To partially address this limitation, a multivariable competing risk analysis was performed. Last but not least, the retrospective nature of the study needs to be considered where it might present a risk of misclassification of the treatment received.

5. Conclusions

We found that patients treated with EBRT have a statistically significantly increased (by 72%) risk of developing a second primary BCa within 5 yr of therapy for PCa when compared with patients treated with RP. This information should be discussed during the counseling of clinically localized PCa patients during the decision making regarding RP versus EBRT. Further studies reporting the outcomes of contemporary patients treated with EBRT, especially well-designed randomized prospective trials, are urgently required to confirm our findings.

Author contributions: Marco Moschini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.034.

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