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Risk of Second Cancers According to Radiation Therapy Technique and Modality in Prostate Cancer Survivors

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Abstract

Purpose—Radiation therapy (RT) techniques for prostate cancer are evolving rapidly, but the impact of these changes on risk of second cancers, which are an uncommon but serious consequence of RT, are uncertain. We conducted a comprehensive assessment of risks of second cancer according to RT technique (>10 MV vs 10 MV and 3-dimensional [3D] vs 2D RT) and modality (external beam RT, brachytherapy, and combined modes) in a large cohort of prostate cancer patients.

Methods and Materials—The cohort was constructed using the Surveillance Epidemiology and End Results-Medicare database. We included cases of prostate cancer diagnosed in patients 66 to 84 years of age from 1992 to 2004 and followed through 2009. We used Poisson regression analysis to compare rates of second cancer across RT groups with adjustment for age, follow-up, chemotherapy, hormone therapy, and comorbidities. Analyses of second solid cancers were based on the number of 5-year survivors ($n = 38,733$), and analyses of leukemia were based on number of 2-year survivors ($n = 52,515$) to account for the minimum latency period for radiation-related cancer.

Results—During an average of 4.4 years' follow-up among 5-year prostate cancer survivors (2DRT = 5.5 years; 3DRT = 3.9 years; and brachytherapy = 2.7 years), 2933 second solid cancers were diagnosed. There were no significant differences in second solid cancer rates overall between 3DRT and 2DRT patients (relative risk [RR] = 1.00, 95% confidence interval [CI]: 0.91-1.09), but second rectal cancer rates were significantly lower after 3DRT (RR = 0.59, 95% CI: 0.40-0.88). Rates of second solid cancers for higher- and lower-energy RT were similar overall (RR = 0.97,

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95% CI: 0.89-1.06), as were rates for site-specific cancers. There were significant reductions in colon cancer and leukemia rates in the first decade after brachytherapy compared to those after external beam RT.

Conclusions—Advanced treatment planning may have reduced rectal cancer risks in prostate cancer survivors by approximately 3 cases per 1000 after 15 years. Despite concerns about the neutron doses, we did not find evidence that higher energy therapy was associated with increased second cancer risks.

Introduction

Subsequent malignancies are an uncommon but serious and debilitating consequence of radiation therapy for the treatment of cancer (1). Among men who elect treatment for prostate cancer, nearly two-thirds of those who are older than 65 years of age receive some form of radiation therapy (RT), and one-third undergo surgery (2). There are a variety of RT techniques and modalities available, including external beam RT and brachytherapy or a combination of both. External beam RT with photons can be delivered with lower or higher energy photons and as 2-dimensional RT (2DRT), 3D conformal RT (3DRT), or intensity modulated RT (IMRT) and can also be delivered with protons.

Published reports examining the risks of subsequent malignancies after RT for prostate cancer have revealed mixed findings (3). Several registry-based studies have shown an increased risk of second malignancies with RT (all techniques and modalities) compared to surgery or no treatment (4-6). Other studies have found no evidence of an increase in second cancers after brachytherapy compared to surgery (7-9). However, no previous study has investigated whether 3DRT techniques or lower-energy RT treatments are associated with reductions in subsequent malignancies. By reducing the volume of normal tissue (ie rectum and bladder) exposed to the radiation beam, it is possible that 3DRT reduces the risks of second malignancies relative to older 2DRT techniques (10). Similarly, by reducing neutron scatter in the treatment room, it is possible that lower-energy (< 10 MV) radiation beams reduce the risks of second malignancies relative to higher-energy RT (>10 MV), which is used to improve radiation tissue penetration (11).

By definition, it is difficult to study the late effects of treatment for cancer in a timely manner, particularly for radiation-related second cancer risks, which can take 10 or more years to develop, yet 3DRT modalities of different energies and brachytherapy have now been used for more than a decade in large enough numbers of older men with prostate cancer to conduct a reliable evaluation. In this study, we comprehensively assessed risks of second malignancy according to RT technique and modality in a large cohort of prostate cancer patients, using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.

Methods and Materials

The SEER-Medicare database was used to define the cohort, treatment, and outcomes in the study. The SEER-Medicare program links SEER cancer registry data to longitudinal health care claims for Medicare enrollees in the United States (12). Medicare claims are based on

physician documentation of medical diagnoses and procedures in billing records and can be used to define details of cancer treatments and other medical conditions (13). For the current study, we defined the initial cohort of prostate cancer patients from the SEER registries and then linked the cohort to Medicare claims data to refine eligibility and to define RT, surgery, hormone therapy, and comorbidities.

Prostate cancer survivors were included if their disease was diagnosed between 1992 and 2004, they were between 66 and 84 years of age at diagnosis, and they had Part A and B Medicare coverage for the period of 9 months subsequent to diagnosis and no Health Maintenance Organization coverage during that period (Fig. 1). Patients with metastatic prostate cancer were excluded. The exclusion was based on SEER historic stage A for patient cases diagnosed after 1994. Before 1994, this staging variable was not available, and therefore we excluded patients who did not have surgery or RT in the 9-month period after diagnosis as they were highly likely to have had metastatic cancer.

Receipt of RT was defined as any single claim for RT between the prostate cancer diagnosis and before the study exit date. The International Classification of Diseases-9 procedure codes and Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System codes used to define treatments are shown in Appendix EA (available online at www.redjournal.com). Patients were divided into 3 treatment groups based on the RT modality received in the first 12 months after diagnosis: external beam only, brachytherapy, or combined brachytherapy and external beam RT (14). External beam RT patients were subdivided into a higher-energy (>10 MV) or lower-energy (<10 MV) and 3DRT or 2DRT group (15). Patients who received IMRT or proton therapy (n = 33,299) were excluded because these treatments could only be identified in Medicare from 2002 onward (eg IMRT), or the sample size was too small (eg proton therapy), and follow-up time would be inadequate to evaluate most radiation-related cancers. Patients who did not receive any RT within the first year of prostate cancer diagnosis were also excluded (n=94,906). The full description of the sequential exclusions is shown in Figure 1.

Potential confounders included in all analyses were chemotherapy, hormone therapy, comorbidities, race, and cancer grade. Receipt of chemotherapy and hormone therapy in the first year after prostate cancer diagnosis was defined as any claim for those treatments during that time period (see Appendix E for CPT codes; available online at www.redjournal.com). Comorbidities were identified by classifying all available inpatient and outpatient Medicare claims in the year preceding prostate cancer diagnosis into 46 categories using the Charlson comorbidity index (16).

Patients were followed from 5 years after their prostate cancer diagnosis until diagnosis of a second solid malignant cancer or from 2 years after diagnosis until diagnosis of a second leukemia, death, or end of cancer registry follow-up (December 31, 2009) as radiation-related cancers are unlikely to occur earlier (17). The second malignances were ascertained using the SEER cancer registry records. The SEER rules for classifying multiple primary cancers depend on the cancer site of origin, date of diagnosis, histology, tumor behavior, and laterality of paired organs (18). In general, any metachronous cancer (occurring 2 or more months after initial diagnosis) is considered a second cancer unless the medical record states

that the tumor is recurrent or metastatic. Notable exceptions to this rule are second adenocarcinomas of the prostate, which are not reported as second cancers.

Statistical methods

We used Poisson regression analysis to compare second cancer rates across RT groups with the person-years table stratified by attained age (70, 75, 80, 85, and 90 years) and follow-up time (5-10 years and 11-17 years for solid cancers and 2-9 and 10-17 years for leukemia) to control for differences in age and follow-up time between treatment groups. Outcomes of interest included all solid cancers as well as individual cancer sites that were selected a priori because they received the highest doses or had previously been associated with increased RT risk (bladder, rectum, leukemia, colon, pancreas, and lung cancer) (4-6). For analyses of solid cancers, we excluded the first 5 years of follow-up, and for leukemia, we excluded the first 2 years of follow-up based on the previously observed minimum latency period for radiation-related cancers (17). We estimated the cumulative risk of incident cancers accounting for competing risks (19).

Results

After exclusions, there were 38,733 5-year prostate cancer survivors who were eligible for the analysis of second solid cancers, and 52,515 2-year survivors who were eligible for the analysis of leukemia (Fig. 1). Descriptive statistics were broadly similar for both groups of survivors (Table 1 and Appendix EB; available online at www.redjournal.com), and hence, here we describe the 5-year survivors. In the eligible 5-year survivors, 23,542 (61%) received external beam RT, 22% received brachytherapy, and 17% received combined brachytherapy and RT. Of the external beam RT patients, 69% underwent 3DRT, and 60% received higher-energy RT. During the exposure period (1992-2004), the use of brachytherapy and combined therapy increased as did 3DRT and higher-energy therapy, which meant that average follow-up was slightly shorter for those newer treatments. Approximately 25% of patients had poorly differentiated or undifferentiated disease in all groups, except for the brachytherapy patients, in whom it was only 10%. The proportion of patients with 2 or more comorbidities was reasonably consistent across RT groups (range: 14%-17%), as was receipt of chemotherapy in the first year (2%-3%). Lower-energy and 2DRT patients were less likely to undergo hormone therapy than the other RT patients. During an average of approximately 3 to 4 years of follow-up among the 5-year survivors, 2933 second solid cancers were diagnosed, including 681 lung, 572 bladder, 384 colon, and 144 rectal cancers; and during an average of 5 to 6 years of follow-up in the 2-year survivors, there were 213 cases of leukemia and 156 cases of myelodysplastic syndrome (MDS).

There were no significant differences in second solid cancer rates overall between the 3DRT and 2DRT patients (relative risk [RR] = 1.00, 95% confidence interval [CI]: 0.91-1.09). The risk of a second rectal cancer was, however, significantly lower in the 3DRT patients than in those receiving conventional RT (RR = 0.59, 95% CI: 0.40-0.88) (Table 2). Second solid cancer rates for higher- and lower-energy RT were similar overall (RR = 0.97, 95% CI: 0.89-1.06) for site-specific second solid cancers and leukemia (Table 2).

When we compared all brachytherapy to all external beam RT patients there were lower rates of second solid cancers overall (RR = 0.92, 95% CI: 0.83-1.02), and significantly lower rates of second colon cancer (RR = 0.52, 95% CI: 0.37-0.73) and leukemia (RR = 0.60, 95% CI: 0.40-0.89) (Table 3). Combined therapy patients had a significantly reduced risk of colon cancer (RR = 0.72, 95% CI: 0.53-0.99) but not all second solid cancers (0.98 95% CI: 0.86-1.09), possibly due to an apparent increased risk of bladder cancer (RR = 1.25, 95% CI: 1.00-1.56). Risks of leukemia were lower but not significantly so (RR = 0.68, 95% CI: 0.45-1.02). In analyses restricted to 10-year survivors, these reductions in risk were not apparent, but the number of events were currently limited, and confidence intervals were wide (Table 4).

The cumulative incidence of any second solid cancers (both spontaneous and possibly radiation-related, with adjustment for competing cases of death) was 8% by 10 years after prostate cancer diagnosis and 15% by 15 years after diagnosis in the RT patients overall. For rectal cancers, the cumulative incidence by 15 years was 0.9% after 2DRT compared to 0.6% in the 3DRT patients, a difference of 3 per 1000 cancers over 10 years of follow-up (5-15 years).

Discussion

This large-scale study provides a comprehensive assessment of the risk of second cancers following prostate cancer according to technique and modality and is the first study to investigate whether higher-energy RT increases risks of second cancer. We found no evidence that higher-energy RT was associated with increased risks of second malignancies. However, 3DRT was associated with a 40% lower risk of rectal cancer than 2DRT, which is consistent with the aim of the treatment planning to avoid rectal toxicity. The reductions in colon cancer and leukemia in the first decade after brachytherapy are possibly consistent with lower doses compared to external beam RT. However, longer follow-up is needed to confirm if they persist.

As far as we are aware, there have not been any previous studies that have evaluated second cancer risks after higher-energy external beam RT. There are concerns that the neutron dose from RT higher than 10 MV would increase second cancer risks, especially given the higher but uncertain radiobiological effectiveness of neutrons (11). It is reassuring that higher-energy RT was not associated with increased second cancer risks given the prevalence of use in prostate cancer patients over the last 2 decades. Our study cannot rule out small increases in risk that could be clinically significant, however, and continued follow-up and replication of our findings are needed. In addition higher energies are also used in IMRT, and modeling studies have suggested that this may increase second cancer risks (20). Neutron doses are estimated to be even higher for higher-energy IMRT than 3DRT, and this will require further investigation once sufficient follow-up time has accrued, as IMRT became widely used only in the last decade.

Basic 2DRT, which is not in common use today for prostate cancer, involves RT delivery with noncustomized shielding blocks and without formal definition of the tumor target volume or organs at risk delineated by computed tomography. In contrast, 3DRT uses

customized blocks to shape radiation beams to a tumor volume while minimizing dose to nearby normal organs. 3DRT methods allow a smaller volume of normal tissues to be irradiated. It is reassuring that our results suggest a reduced risk of second rectal cancer from 3DRT as rectal dose should be reduced by this technique. However, the SEER-Medicare data cannot be used to directly determine that tissue volume was reduced, and in earlier periods, the patients may have received less conformal treatment planning, which could have biased our comparison toward the null. Our results are consistent with and extend prior randomized evidence suggesting that 3DRT causes less rectal toxicity than 2DRT, likely through a similar mechanism of normal tissue sparing (21, 22). Only 1 previous study has evaluated 3DRT and 2DRT techniques for prostate cancer, and that study also found a lower second cancer risk after 3DRT, but the authors did not conduct a formal comparison with 2DRT (10). The single-institution cohort was small (2120 matched pairs of surgery and RT patients) with only 315 second cancers after an average follow-up of 7 years.

A previous comparison of brachytherapy with external beam therapy in SEER also found that the second cancer risks were lower initially but converged 10 years after diagnosis (7). Although organ doses were lower for brachytherapy, the exposure was protracted rather than fractionated, which could affect cancer risks (17). Two other smaller studies (1888 and 1310 patients) with average follow-up periods of 7 to 8 years did not find any evidence of increased second cancer risks after brachytherapy compared to surgery (8, 9). Longer follow-up is needed to clarify the magnitude of the second cancer risks after brachytherapy. Zefelsky et al (9) estimated an actuarial 10-year second cancer risk (excluding skin cancer) of 12% after brachytherapy and Hinnen et al (8) estimated a cumulative 10-year incidence (adjusted for competing causes of death) of 14%. In our population, the cumulative incidence was 15% for the 10-year period (5-15 years) for all types of RT combined. It should be noted that these cumulative risks are for both spontaneous and possible radiation-related cancers and that comparisons are complicated because the age of the populations studied, the adjustments for competing risk and exclusion periods, and the follow up periods varied.

The advantage of our study, compared to previous studies that relied on SEER records alone, is that linkage with Medicare gave us more treatment details, especially pertaining to RT technique, and also more complete information on chemotherapy and hormone therapies, which are potential confounders for some of these second cancers. Compared to single-institution studies, SEER-Medicare database has the advantage of much larger patient numbers and longer, more complete follow-up and outcome ascertainment. Finally, because we restricted our analysis to patients who received RT rather than a comparison to surgery or non-RT prostate cancer patients this should have reduced biases due to treatment selection factors. However, we did not have details of radiation fields, dose, or other potential confounders such as smoking. IMRT and proton therapy have been recorded only since 2002 but were likely used for a small number of patients before that date, which will have resulted in some misclassification in our external beam technique categories. Second cancers may have been underestimated, especially with increasing follow-up time as SEER is not able to follow patients if they move out of the cancer registry area. We found 226 solid cancer deaths after external beam RT and 61 after brachytherapy and combined therapy from Medicare records that were not reported as incident cancers, which was

approximately 8% and 7% of the total cancers, respectively. This suggests that the migration rates appeared to be similar and although absolute second cancer risks may be slightly underestimated the relative risks should not have been affected by migration.

Conclusions

Radiation therapy techniques and modalities for prostate cancer patients are evolving. Our study suggests that 3DRT may have reduced rectal cancer risks in prostate cancer survivors by approximately 3 cases per 1000 after 15 years. Brachytherapy may also reduce second cancer risks compared to external beam therapy, but longer follow-up is still needed to confirm these findings. Despite concerns about neutron doses, higher energy RT does not appear to increase the second cancer risks, which is reassuring. Neutron doses from higher-energy IMRT are estimated to be several times greater than from 3DRT, however, and studying the late effects from this and proton therapy remains a high priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary

We assessed the risk for second cancer according to radiation therapy (RT) modality and technique in 40,000 prostate cancer survivors. In the first study to assess development of second cancers after higher-energy (>10MV) radiation therapy, we found no evidence of increased risks compared to lower-energy radiation. This should reduce concerns about related neutron doses. Rectal cancer rates were significantly lower after 3-dimensional RT than after 2DRT. The 40% risk reduction was equivalent to 3 fewer rectal cancers per 1000 patients by 15 years.

Fig. 1. Selection criteria for analysis of second solid cancer and leukemia after prostate cancer radiation therapy in the Surveillance, Epidemiology, and End Results-Medicare database.

Table 1
Descriptive information for 5-year prostate cancer survivors by treatment received (N = 38,733)

Characteristic	External beam only						Brachytherapy only		External beam plus brachytherapy	
	Overall		Low energy		High energy		2D		3D	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total no. of patients	23,542 (100)	9437 (100)	14,105 (100)	7306 (100)	16,236 (100)	8513 (100)	6678 (100)			
Mean follow-up (yrs)	9.4	9.8	9.1	10.5	8.9	7.7	8.5			
Age at diagnosis (yrs)										
<70	5220 (22)	2067 (22)	3153 (22)	1700 (23)	3520 (22)	2565 (30)	1923 (29)			
70-74	9533 (40)	3819 (40)	5714 (41)	3022 (41)	6511 (40)	3522 (41)	2753 (41)			
75-79	7084 (30)	2863 (30)	4221 (30)	2122 (29)	4962 (31)	2001 (24)	1673 (25)			
80+	1705 (7)	688 (7)	1017 (7)	462 (6)	1243 (8)	425 (5)	329 (5)			
Calendar year of diagnosis										
1992	2347 (10)	1455 (15)	892 (6)	1685 (23)	662 (4)	37 (0)	157 (2)			
1993	2059 (9)	1195 (13)	864 (6)	1330 (18)	729 (4)	25 (0)	133 (2)			
1994	1701 (7)	911 (10)	790 (6)	945 (13)	756 (5)	13 (0)	102 (20)			
1995	1640 (7)	711 (8)	929 (7)	791 (11)	849 (5)	96 (1)	77 (1)			
1996	1480 (6)	622 (7)	858 (6)	613 (8)	867 (5)	171 (2)	165 (2)			
1997	1460 (6)	552 (6)	908 (6)	570 (8)	890 (5)	280 (3)	299 (4)			
1998	1390 (6)	522 (6)	868 (6)	363 (5)	1027 (6)	340 (4)	362 (5)			
1999	1536 (7)	525 (6)	1011 (7)	217 (3)	1319 (8)	446 (5)	451 (7)			
2000	2772 (12)	883 (9)	1889 (13)	278 (4)	2494 (15)	1160 (14)	1277 (19)			
2001	2599 (11)	783 (8)	1816 (13)	201 (3)	2398 (15)	1295 (15)	1244 (19)			
2002	2131 (9)	587 (6)	1544 (11)	127 (2)	2004 (12)	1586 (19)	1114 (17)			
2003	1495 (6)	443 (5)	1052 (7)	108 (1)	1387 (9)	1493 (18)	748 (11)			
2004	932 (4)	248 (3)	684 (5)	78 (1)	854 (5)	1571 (18)	549 (8)			
Race										
White	19,930 (85)	8276 (88)	11,654 (83)	6377 (87)	13,553 (83)	7602 (89)	5762 (86)			
Other (Black, Asian, Hispanic, NA, Native, other)	3612 (15)	1161 (12)	2451 (17)	929 (13)	2683 (17)	911 (11)	916 (14)			
Grade										

Characteristic	External beam only						Brachytherapy only		External beam plus brachytherapy		
	Overall	Low energy	High energy	2D		3D		N (%)	N (%)	N (%)	N (%)
				N (%)	N (%)	N (%)	N (%)				
Well/moderately differentiated	17,784 (76)	7245 (77)	10,539 (75)	5741 (79)	12,043 (74)			7644 (90)		4553 (68)	
Poorly/undifferentiated	5758 (24)	2192 (23)	3566 (25)	1565 (21)	4193 (26)			869 (10)		2125 (32)	
Prior plus Charlson comorbidity index											
0	13,549 (58)	5586 (59)	7963 (56)	4377 (60)	9172 (56)			5099 (60)		3942 (59)	
1	6215 (26)	2453 (26)	3762 (27)	1871 (26)	4344 (27)			2194 (26)		1721 (26)	
2+	3778 (16)	1398 (15)	2380 (17)	1058 (14)	2720 (17)			1220 (14)		1015 (15)	
Received chemotherapy within the first year of diagnosis											
No	23,079 (98)	9246 (98)	13,833 (98)	7162 (98)	15,917 (98)			8262 (97)		6489 (97)	
Yes	463 (2)	191 (2)	272 (2)	144 (2)	319 (2)			251 (3)		189 (3)	
Received hormone therapy within the first year of diagnosis											
No	13,616 (58)	5994 (64)	7622 (54)	5498 (75)	8118 (50)			4622 (54)		2390 (36)	
Yes	9926 (42)	3443 (36)	6483 (46)	1808 (25)	8118 (50)			3891 (46)		4288 (64)	
Status at the end of the study											
Alive	14,536 (62)	5197 (55)	9339 (66)	3274 (45)	11,262 (69)			7382 (87)		5316 (80)	
Deceased	6477 (28)	3122 (33)	3355 (24)	3031 (41)	3446 (21)			605 (7)		840 (13)	
Developed second cancer	2529 (11)	1118 (12)	1411 (10)	1001 (14)	1528 (9)			526 (6)		522 (8)	

RR and 95% CI of second cancers after EBRT among prostate cancer survivors undergoing higher versus lower energy and 3D versus 2D**Table 2**

Cancer type	2D		3D vs 2D		Low energy		High energy vs low energy	
	N	N	RR (95% CI)		N	N	RR (95% CI)	
All solid cancers *	806	1259	1.00 (0.91-1.09)		913	1152	0.97 (0.89-1.06)	
Bladder	153	244	1.08 (0.87-1.32)		184	213	0.92 (0.76-1.12)	
Colon	124	176	0.90 (0.71-1.15)		132	168	0.98 (0.78-1.24)	
Lung	171	314	1.16 (0.95-1.40)		218	267	0.92 (0.77-1.10)	
Pancreas	37	61	1.00 (0.65-1.51)		39	59	1.13 (0.75-1.70)	
Rectum	55	51	0.59 (0.40-0.88)		52	54	0.81 (0.55-1.19)	
Stomach	25	40	1.00 (0.60-1.67)		30	35	0.84 (0.52-1.38)	
All leukemia types †	53	102	1.02 (0.72-1.43)		65	90	1.00 (0.73-1.38)	
ALL	1	3	1.96 (0.19-19.63)		1	3	2.48 (0.26-24.04)	
AML	30	56	1.03 (0.65-1.62)		35	51	1.06 (0.69-1.64)	
CML	9	18	1.01 (0.44-2.31)		13	14	0.77 (0.36-1.64)	
Other	13	25	0.93 (0.46-1.85)		16	22	0.97 (0.51-1.86)	
MDS ‡	34	70	0.78 (0.51-1.18)		43	61	0.87 (0.59-1.29)	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CI = confidence interval; CML = chronic myeloid leukemia; EBRT = external beam radiation therapy; MDS = myelodysplastic syndrome; RR = relative risk.

Poisson regression models were adjusted for age attained, latency, race, grade, comorbidities, and receipt of chemotherapy or hormone therapy within the first year.

* Solid cancer analyses included 5-year prostate cancer survivors (N=23,542).

† Leukemia analyses included 2-year prostate cancer survivors (N=29,534).

‡ MDS incidence was available only from 2001 onward.

RR and 95% CI of second cancers in prostate cancer patients undergoing BR or combined BR plus EBRT compared to EBRT alone**Table 3**

Cancer types	EBRT		BR		BR vs EBRT		EBRT + BR		EBRT + BR vs EBRT	
	N	N	N	N	RR (95% CI)	RR (95% CI)	N	N	RR (95% CI)	RR (95% CI)
All solid cancers [‡]	2065	429			0.92 (0.83-1.02)		439		0.98 (0.88-1.09)	
Bladder	397	71			0.80 (0.62-1.04)		104		1.25 (1.00-1.56)	
Colon	300	37			0.52 (0.37-0.73)		47		0.72 (0.53-0.99)	
Lung	485	104			0.95 (0.77-1.18)		92		0.86 (0.69-1.08)	
Pancreas	98	21			0.95 (0.59-1.53)		16		0.71 (0.42-1.22)	
Rectum	106	20			0.88 (0.55-1.44)		18		0.80 (0.48-1.33)	
Stomach	65	11			0.79 (0.42-1.52)		21		1.53 (0.93-2.54)	
All leukemia types [†]	155	30			0.60 (0.40-0.89)		28		0.68 (0.45-1.02)	
ALL	4	0					2		1.93 (0.34-10.95)	
AML	86	15			0.53 (0.31-0.92)		14		0.62 (0.35-1.10)	
CML	27	2			0.22 (0.05-0.91)		6		0.84 (0.34-2.07)	
Other	38	13			1.10 (0.58-2.09)		6		0.57 (0.24-1.35)	
MDS [*]	104	30			0.67 (0.45-1.02)		22		0.69 (0.43-1.10)	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BR = brachytherapy; CI = confidence interval; CML = chronic myeloid leukemia; EBRT = external beam radiation therapy; RR = relative risk. Other abbreviations as in table 2.

Poisson regression models were adjusted for age attained, latency, race, grade, comorbidities, and receipt of chemotherapy or hormone therapy within the first year.

^{*} MDS incidence was available only from 2001 onward.

[†] Leukemia analyses included 2-year prostate cancer survivors (N=52,515).

[‡] Solid cancer analyses included 5-year prostate cancer survivors (N=38,733).

Table 4
RR and 95% CI of second cancers in prostate cancer patients undergoing BR or
combined BR plus EBRT compared to EBRT by follow-up time

Cancer type	5-10 y		11-17 y	
	N	RR (95% CI)	N	RR (95% CI)
All solid cancers *				
EBRT	1740	1.00 (ref.)	325	1.00 (ref.)
BR vs EBRT	408	0.91 (0.82-1.02)	21	1.14 (0.65-2.00)
EBRT + BR vs EBRT	398	0.96 (0.86-1.07)	41	1.28 (0.81-2.01)
Bladder				
EBRT	324	1.00 (ref.)	73	1.00 (ref.)
BR vs EBRT	67	0.80 (0.62-1.05)	4	0.98 (0.27-3.56)
EBRT + BR vs EBRT	88	1.16 (0.91-1.47)	16	2.23 (0.97-5.11)
Colon				
EBRT	259	1.00 (ref.)	41	1.00 (ref.)
BR vs EBRT	34	0.48 (0.34-0.69)	3	1.23 (0.25-6.00)
EBRT + BR vs EBRT	44	0.73 (0.53-1.00)	3	0.75 (0.16-3.50)
	2-9 y		10-17 y	
	N	RR (95% CI)	N	RR (95% CI)
All leukemia types †				
EBRT	129	1.00 (ref.)	26	1.00 (ref.)
BR vs EBRT	27	0.58 (0.38-0.89)	3	1.29 (0.24-6.93)
EBRT + BR vs EBRT	28	0.76 (0.50-1.14)	0	

Abbreviations: BR = brachytherapy; CI = confidence interval; EBRT = external beam radiation therapy; RR = relative risk. Poisson regression models were adjusted for age attained, latency, race, grade, comorbidities, and receipt of chemotherapy or hormone therapy within the first year.

* Solid cancer analyses included 5-year prostate cancer survivors (N=38,733).

† Leukemia analyses included 2-year prostate cancer survivors (N=52,515).