Letters

RESEARCH LETTER

Second Primary Cancers After Intensity-Modulated vs 3-Dimensional Conformal Radiation Therapy for Prostate Cancer

Intensity-modulated radiation therapy (IMRT) is commonly used for patients with prostate cancer because it allows dose escalation to the tumor while reducing radiation exposure to surrounding healthy tissues such as the bladder and rectum.[1,2] This reduction may be at the expense of increased radiation exposure to more distant tissues from scatter radiation, particularly the red bone marrow, compared with the exposure from 3-dimensional conformal radiotherapy (3D-CRT), the previous standard radiotherapy technique.[1] Simulation studies have suggested this reduced radiation exposure could double the risk of second primary cancers.[3] To date, however, no observational studies have directly compared second cancer rates after IMRT to 3D-CRT for prostate cancer.[4] We compared the risks of leukemia and myelodysplasia (of particular concern given the potentially higher bone marrow dose and because they can occur as early as 2 years after exposure[5]) and second solid cancers after IMRT vs 3D-CRT in a large cohort of prostate cancer patients.

Methods | We conducted a retrospective cohort study using SEER (Surveillance, Epidemiology, and End Results) Medicare data. The cohort included men diagnosed between 2002 and 2009 with nonmetastatic prostate cancer who were aged 66 through 84 years and who received IMRT or 3D-CRT, but no chemotherapy, within the first year after diagnosis and survived at least 2 years after treatment initiation. As previously reported,[6] SEER data were used to collect demographic, cancer, and death information. Medicare billing records were used to obtain information on cancer treatments and comorbidities. Eligible individuals were followed up from radiotherapy initiation until the earliest of second cancer diagnosis, death, 90th birthday, or December 31, 2011.

Relative risks (RRs) of second primary cancers after IMRT vs 3D-CRT were estimated by Poisson regression to simultaneously account for attained age, time since exposure, and calendar time. Person-years at risk were accumulated from RT initiation + 2 years (for hematopoietic tumors) or 5 years (for solid cancers), to account for minimal time intervals to develop radiation-related cancers,[5] up to study end. The analyses were stratified by attained age, time since diagnosis, and calendar year, and adjusted for tumor grade, race, Charlson comorbidity score, smoking history, receipt of chemotherapy (≥1 year after diagnosis), hormonal therapy, and brachytherapy. Sensitivity analyses excluding men diagnosed in 2002-2003 were conducted to account for possible treatment misclassification in the early period of IMRT use.

Table. Characteristics of the Study Population of 2-Year Prostate Cancer Survivors

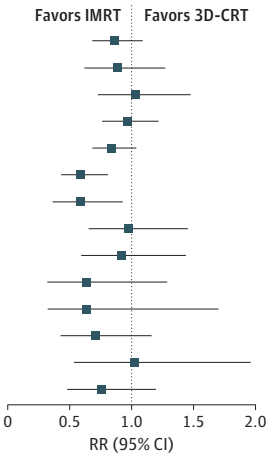
Characteristic	No. (%)	
	IMRT	3D-CRT
Patients, No.	27 904	11 124
Person-years since RT + 2 y, No.	80 149	53 654
Age at diagnosis, y		
65-69	6847 (24.5)	2922 (26.3)
70-74	10 415 (37.3)	4235 (38.1)
75-79	7933 (28.4)	3028 (27.2)
≥80	2709 (9.7)	939 (8.4)
Year at diagnosis		
2002-2003	3684 (13.2)	6840 (61.5)
2004-2005	7296 (26.2)	2808 (25.2)
2006-2007	9555 (34.2)	1147 (10.3)
2008-2009	7369 (26.4)	329 (3.0)
Tumor grade		
1 to 2	11 525 (41.3)	6083 (54.7)
3 to 4	16 379 (58.7)	5041 (45.3)
Charlson comorbidity score		
0	18 761 (67.2)	7668 (68.9)
1	6110 (21.9)	2472 (22.2)
≥2	3033 (10.9)	984 (8.9)
Tobacco use		
Never	20 347 (72.9)	8085 (72.7)
Ever	7557 (27.1)	3039 (27.3)
Race		
White	22 666 (81.2)	9237 (83.0)
Other	5238 (18.8)	1887 (17.0)
Status at end time		
Alive	23 571 (84.5)	7736 (69.5)
Dead	2642 (9.5)	2178 (19.6)
Second cancer	1691 (6.1)	1210 (10.9)

Abbreviations; IMRT, intensity-modulated radiation therapy; RT, radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy.

Results | The cohort included 39 028 patients with a median follow-up of 5.2 years (range, 2.0-10.0 years) (**Table**). A total of 2901 men developed second cancers: 1691 (6.1%) in the IMRT group and 1210 (10.9%) in the 3D-CRT group. There was no difference in the risk of leukemia or myelodysplasia after IMRT vs 3D-CRT (**Figure**). Risks of colon cancer (RR, 0.59; 95% CI, 0.43-0.81) and rectal cancer (RR, 0.58; 95% CI, 0.36-0.93) were significantly lower after IMRT. The risks of other solid cancers and lymphomas did not differ significantly between IMRT and 3D-CRT. Receipt of chemotherapy, brachytherapy, hormonal therapy, or surgery did not confound or significantly modify the results. In sensitivity analyses, the results did not differ meaningfully from the main analyses.

Figure. Cases, Crude Incidence Rates, and Adjusted Relative Risks of Second Primary Cancers Associated With Intensity-Modulated vs 3D-Conformal Radiation Therapy for Nonmetastatic Prostate Cancer

Source	IMRT No. of Cases	IMRT Incidence Rate	3D-CRT No. of Cases	3D-CRT Incidence Rate	RR (95% CI) for IMRT vs 3D-CRT
All leukemia and myelodysplasia[a]	135	168	108	201	0.86 (0.68-1.09)
Non-CLL leukemia	49	61	37	69	0.89 (0.62-1.28)
Myelodysplasia	63	79	43	80	1.03 (0.72-1.48)
Lymphoma[a]	130	162	91	170	0.97 (0.76-1.22)
All solid cancers[b]	318	1015	440	1392	0.84 (0.68-1.04)
Colon	25	80	47	149	0.59 (0.43-0.81)
Rectum	<11		13	41	0.58 (0.36-0.93)
Urinary bladder	66	211	80	253	0.97 (0.65-1.46)
Other urinary organs and tracts	20	64	25	79	0.92 (0.59-1.44)
Pancreas	<11		16	51	0.63 (0.30-1.29)
Stomach	<11		15	47	0.63 (0.24-1.70)
Other digestive organs	15	48	24	76	0.71 (0.43-1.16)
Lung and bronchus	94	300	110	348	1.02 (0.53-1.96)
Head and neck	31	99	46	146	0.76 (0.48-1.20)



Relative risks (RRs) are adjusted for attained age (as a continuous variable, in years), tumor grade (well/moderately differentiated vs poorly/not differentiated), race (white vs other), receipt of chemotherapy more than 1 year after prostate cancer diagnosis (for hematopoietic tumors only), receipt of hormonal therapy (for solid cancers only), receipt of brachytherapy (for solid cancers only), Charlson comorbidity score (0, 1, or ≥2; for solid cancers only), and ever smoking (for solid cancers only). Receipt of chemotherapy, hormonal therapy, and brachytherapy are coded as time-dependent binary covariates (ie, individuals are considered nonexposed until the date of first claim of treatment, and exposed afterward). Numbers of cases fewer than 11 are not displayed in accordance with SEER-Medicare's requirements for protection of personal health information. IMRT indicates intensity-modulated radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; IR, incidence rate (per 100 000 person-years); and CLL, B-cell chronic lymphocytic leukemia. 95% Confidence intervals are based on the Wald test.

[a] In 2-year survivors.

[b] In 5-year survivors.

Discussion | In this large cohort of prostate cancer patients, IMRT was not associated with an early elevated risk of leukemia or myelodysplasia. There was some preliminary evidence of reduced risks of colon and rectal cancers compared with 3D-CRT, which is potentially consistent with lower radiation doses from IMRT to these organs.[1,3] No association of RT modality with lung cancer risk was observed, suggesting that residual confounding by smoking is unlikely to account for the inverse associations observed for colon and rectal cancers. The study had sufficient follow-up to evaluate early incidence of leukemia and myelodysplasia, which might occur as soon as 2 years after radiation exposure, but was currently limited to evaluate the risks of solid cancers, which usually occur 5 to 10 years after radiation exposure.[5] Further follow-up is needed to continue to monitor the potential impact of IMRT on second cancer risks.

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COMMENT & RESPONSE

Aspirin and Cancer Risk

To the Editor We read with interest the recent article by Cao et al,[1] which examined the association between long-term aspirin use and cancer risk. The authors imply that besides the Cancer Prevention Study II, no prior studies have examined these associations. Indeed, the finding of Cao et al[1] of inverse associations for total cancer risk restricted to men echoes findings from several prior observational studies[2-4] and a randomized trial.[5] In 2007, data from the Iowa Women's Health Study suggested some benefit of aspirin use for total cancer risk.[2] However, in the Vitamins and Lifestyle cohort, we found that long-term use of adult-strength aspirin was inversely associated with total cancer incidence among men (HR, 0.89; 95% CI, 0.80-0.99) but not women (*P* for interaction = .01).[3] We also examined associations of aspirin use with risk of individual cancers. This analysis is the only one to examine interaction by sex for shared cancer sites aside from the colorectum. Different from Cao et al,[1] we reported reductions in risk of these cancers for men (HR, 0.84; 95% CI, 0.71-0.99) but not women (HR, 1.18; 95% CI, 0.93-1.49; *P* for interaction < .01).[3] The results of this analysis suggested that aside from associations with reduced colorectal cancer incidence, which were apparent in both sexes, use of aspirin for cancer prevention at other cancer sites shared between the sexes conferred little benefit to women.[3]

These data are further supported by our analysis in the Women's Health Initiative observational study and clinical trials cohort of postmenopausal women. With barely fewer women than total participants in the analysis by Cao et al,[1] this study is the single largest prospective study in women to examine these associations to date.[4] In it, we observed no overall cancer benefit in women who used aspirin regularly and again concluded little chemopreventive benefit to women beside that for colorectal cancer.[4] These data also support findings from the Women's Health Study randomized trial,[5] which reported no overall cancer benefit with low-dose aspirin given every second day, and reductions in risk only for colorectal cancers. We believe that Cao et al[1] not only failed to acknowledge a wealth of literature on a well-researched topic (≥2 more studies are not cited in this Letter) but also failed to note, with respect to their own findings, that there is ample prior evidence to hypothesize that women may not benefit from a global reduction in cancer incidence with regular, long-term aspirin use.

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To the Editor We read with interest the recent study of Cao et al[1] examining the benefits of aspirin use over a range of doses and by subgroups. This study adds to the growing body of compelling evidence supporting long-term, low-dose aspirin chemoprevention for colorectal cancer. With respect to the authors' concluding statement that cost-effectiveness analyses are warranted, we would add that several cost-effectiveness studies have been performed on this topic. In their Markov analyses, Pence et al[2] concluded that aspirin with colonoscopy was more cost-effective at $12 950 per life-year saved than colonoscopy alone. In another study, Hassan et al[3] observed that the cost-effectiveness of aspirin adjunct to colonoscopy was dependent on the risk of aspirin-related upper gastrointestinal bleeding and hemorrhagic stroke. In this model, the cost-effective benefit of aspirin with colonoscopy was lost when the efficacy of colonoscopy in preventing proximal colorectal cancer was increased from 56% to 73%.[3]

Although these studies, in addition to other cost-effectiveness analyses not summarized here, varied in model assumptions, interventions, and inputs, they collectively demonstrate that aspirin adjunct to colonoscopy can be a cost-effective strategy. To the best of our knowledge, no cost-