International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Prostate Cancer Radiation Therapy and Risk of Thromboembolic Events

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Received Nov 2, 2016, and in revised form Jan 13, 2017. Accepted for publication Jan 21, 2017.

Summary

We investigated the risk of thromboembolic disease (TED) after radiation therapy (RT) with curative intent for prostate cancer in a cohort including 6232 men who received external beam RT (EBRT) and 3178 who underwent brachytherapy (BT). No significant associations

Purpose: To investigate the risk of thromboembolic disease (TED) after radiation therapy (RT) with curative intent for prostate cancer (PCa).

Patients and Methods: We identified all men who received RT as curative treatment (n = 9410) and grouped according to external beam RT (EBRT) or brachytherapy (BT). By comparing with an age- and county-matched comparison cohort of PCa-free men (n = 46,826), we investigated risk of TED after RT using Cox proportional hazard regression models. The model was adjusted for tumor characteristics, demographics, comorbidities, PCa treatments, and known risk factors of TED, such as recent surgery and disease progression.

Results: Between 2006 and 2013, 6232 men with PCa received EBRT, and 3178 underwent BT. A statistically significant association was found between EBRT and BT

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This work was supported by the Swedish Research Council (2012-5047) for Working Life, Health, and Welfare, the Swedish Cancer Society, the Cancer Society in Stockholm (141012).

Conflict of interest: none.

Acknowledgment—The authors thank Prof. Niklas Hammar for his continued support in supervising the analytical work of Dr Bosco. This project was made possible by the continuous work of the National PCa Register of Sweden (NPCR) steering group: Pär Stattin (chairman), Anders Widmark, Camilla Thellenberg Karlsson, Ove Andrén, Anna Bill Axelson, Ann-Sofi Fransson, Magnus Törnblom, Stefan Carlsson, Marie Hjälm Eriksson, David Robinson, Mats Andén, Jonas Hugosson, Ingela Franck Lissbrant, Maria Nyberg, Göran Ahlgren, René Blom, Lars Egevad, Calle Waller, Olof Akre, Per Fransson, Eva Johansson, and Fredrik Sandin, Karin Hellström.

Int J Radiation Oncol Biol Phys, Vol. 97, No. 5, pp. 1026–1031, 2017

http://dx.doi.org/10.1016/j.ijrobp.2017.01.218

were found between EBRT or BT and risk of deep venous thromboembolism or pulmonary embolism. Curative RT for prostate cancer using contemporary methodologies was thus not associated with an increased risk of TED.

and risk of pulmonary embolism in the crude analysis. However, upon adjusting for known TED risk factors these associations disappeared. No significant associations were found between BT or EBRT and deep venous thrombosis.

Conclusion: Curative RT for prostate cancer using contemporary methodologies was not associated with an increased risk of TED.

Introduction

Cancer increases the risk of embolic or thromboembolic diseases (TED) because tumor cells can activate the coagulation system (1). Previously we have shown that men with prostate cancer (PCa) are at higher risk of TED (2), and this risk was especially high for those who had undergone PCa-related surgeries while receiving androgen deprivation therapy (ADT) (3).

No large epidemiologic study has yet investigated the association between radiation therapy (RT) and risk of TED. It has been suggested that veins are less susceptible to radiation effects; however, there are several case reports of arterial thrombosis for patients who received RT for breast, lung, or uterine cancer (4-6). There is also a considerable body of experimental and epidemiologic evidence showing that RT causes damage to endothelial cells in the arteries via different mechanisms (7). For instance, the association between RT for breast cancer and higher risk of myocardial infarction and coronary heart disease is well established (8, 9). On the basis of this evidence, endothelial damage to veins is possible, and therefore quantifying the risk of TED after RT is of relevance.

In this study we investigated the association between curative RT given with contemporary standards for prostate cancer and risk of TED in a nationwide population-based cohort in Sweden.

Patients and Methods

Study population

We selected all men with PCa who received curative RT for prostate cancer between 1996 and 2013, as registered in Prostate Cancer data Base Sweden (PCBaSe) (n = 9410), which is described in detail elsewhere (Fig. 1) (10, 11). Briefly, PCBaSe Sweden was created by linking the National Prostate Cancer Register (NPCR) of Sweden with a number of other population-based registers via the use of the Swedish personal identity number. It also contains a control series of men free of PCa at the time of sampling. These men were matched by county of residence and birth year with an index case. For the present study we selected 46,826 men free of PCa. This comparison with a non-PCa cohort has been successfully applied previously in Prostate Cancer data Base Sweden when investigating the risk of TED, cardiovascular disease, or diabetes after ADT or surgery (2, 3, 12-14). Radiation therapy data were obtained from the NPCR, as well as from RetroRadioTherapy, a separate retrospective data collection at radiation units in Sweden. For this register data on treatment type, timing, total dose, and fractionation were retrieved directly from the verification/oncology information systems and local databases of the RT departments in Sweden. Men were followed up starting on the day of RT until the end of the study, death, immigration, or loss to follow-up. Prostate cancer–free men inherited an RT date according to their matched PCa men. The Research Ethics Board at Umea University approved this study (11).

The main outcomes were deep venous thrombosis (DVT) (International Classification of Diseases, 10th revision code: I80-82) and pulmonary embolism (PE) (International Classification of Diseases, 10th revision code: I26) as primary diagnoses in the National Inpatient Register and National Outpatient Register or Cause of Death Register. All 3 registers were used to avoid underestimation of severe cases of PE that may have only been captured as fatal in the Cause of Death Register (2).

The following information on potential confounders was also obtained. On the basis of information from the National Patient Register, comorbidities were measured using the Charlson comorbidity index (CCI), which assigns weights to a number of medical conditions. Each condition is assigned a score of 1, 2, 3, or 6, and the final CCI is given as the sum of these scores (15). Individuals were grouped into CCI categories for final scores of 0, 1, 2, or 3+. Information on age, serum prostate-specific antigen level, treatment at time of diagnosis, tumor grade, and stage, educational level, and history of TED was also used. Prostate cancer risk category was defined according to a modification of the National Comprehensive Cancer Network guideline (16): low risk: T1-2, Gleason score 2 to 6, and PSA <10 ng/mL; intermediate risk: T1-2, Gleason score 7, and/or PSA 10 to 20 ng/mL; high risk: T3 and/or Gleason score 8 to 10 and/or PSA 20 to 50 ng/mL; regionally metastatic/locally advanced: T4 and/or N1 and/or PSA 50 to 100 ng/mL in the absence of distant metastases (M0 or MX); and distant metastases: M1 and/or PSA >100 ng/mL. Information on surgeries was taken from the National Patient Register and included transurethral resection of the prostate (TURP), open or laparoscopic

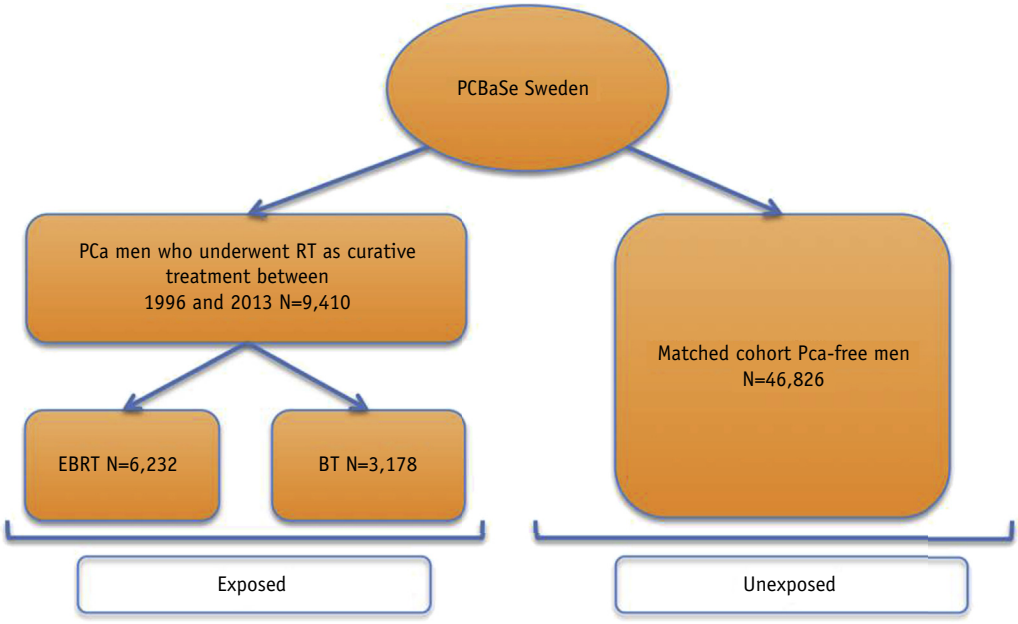

Fig. 1. Selection of study population from Prostate Cancer Database Sweden.

radical prostatectomy, pelvic lymph node dissection, and orchiectomy (3). Information on filled prescriptions of anti-androgens and gonadotropin-releasing hormone agonists was obtained from the National Prescribed Drug Register, in which all filled prescriptions have been registered since July 1, 2005. This allowed us to create a time-updated covariate for adjuvant and neoadjuvant ADT. Disease progression was defined by using the following proxy variables as time-dependent covariates: transurethral resection of the prostate indicating infravesical obstruction; palliative RT indicating a rise in serum PSA level or skeletal pain; and use of nephrostomy indicating overgrowth on the ureter. This is consistent with previously published work on the association between ADT and TED (13).

Statistical analysis

First we conducted univariate Cox proportional hazards models to evaluate the association between known clinical risk factors (ie, lymph node dissection, palliative RT, ADT due to disease progression, hydronephrostomy, non–prostate cancer related surgeries) and TED. This then confirmed the need to take these factors into account as time-updated covariates in our multivariate models. To further justify our choice for time-updated covariates related to PCa only, we performed a sensitivity analysis in which we censored for these events (eg, ADT for disease progression) or used delayed entry (eg, 1 year after lymph node dissection). The results were virtually the same as for the adjusted models (results not shown). Univariate and multivariate Cox proportional hazards models with age as a time-scale were then conducted to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of DVT and PE by types of RT (brachytherapy [BT] and external beam RT [EBRT]). The assumption of proportionality of the Cox model covariates was tested by plotting Schoenfeld residuals (17). The multivariate analyses were conducted stepwise, allowing us to identify the effect of each confounder: CCI, education, PCa risk categories, PCa-related surgeries, history of TED, disease progression markers, other surgeries, adjuvant and neoadjuvant ADT. Exposure to surgeries, neoadjuvant and adjuvant ADT, and markers of disease progression were incorporated as time-updated covariates. Because of the rather small sample size for BT, we only performed an additional stratified analysis by time since RT for EBRT: 0 to 6 months, 6 to 12 months, 1 to 2 years, and >2 years.

Data management was performed using SAS version 9.3 (SAS Institute, Cary, NC), and data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between 1996 and 2013, 9410 men received curative RT as registered in PCBaSe Sweden, out of which 6232 underwent EBRT and 3178 BT. The latter group consisted of patients receiving either high-dose-rate BT to the prostate (n = 2452), combined with EBRT in the majority of the patients, or low-dose-rate BT via implanted radioactive seeds (n = 726). There were a total of 144 TED events in the exposed groups (43 in the BT group and 101 in the EBRT group) and 483 in the comparison cohort. Baseline characteristics of the study cohort are presented in Table 1.

Univariate analyses for the association between known TED risk factors and PE and DVT are presented in Table 2,

Table 1 Baseline characteristics of PCBaSe

Characteristic	BT		EBRT		PCa-free men	
	n	%	n	%	n	%
Total no. of men	3178	100	6232	100	46,826	100
Age (y)						
<60	490	15.4	566	9.1	5299	11.3
60-64	772	24.3	1179	18.9	9678	20.7
65-74	1747	55.0	3827	61.4	27,706	59.2
75+	169	5.3	660	10.6	4143	8.8
CCI						
0	2574	81.0	4632	74.3	35,975	76.8
1	382	12.0	935	15.0	5751	12.3
2	158	5.0	436	7.0	2944	6.3
3+	64	2.0	229	3.7	2156	4.6
Stage group						
No PCa	0	0.0	0	0.0	46,826	100.0
Low risk	864	27.2	900	14.4	0	
Intermediate risk	1059	33.3	2387	38.3	0	
High risk	1106	34.8	2503	40.2	0	
Regionally metastatic	126	4.0	391	6.3	0	
Missing data	23	0.7	51	0.8	0	
Prior DVT						
0	3171	99.8	6190	99.3	46,529	99.4
1	7	0.2	38	0.6	140	0.3
2+	0	0.0	4	0.1	157	0.3
Prior PE				0.0		
0	3151	99.2	6157	98.8	46,497	99.3
1	26	0.8	65	1.0	146	0.3
2+	1	0.0	10	0.2	183	0.4
Neoadjuvant ADT						
No ADT	1029	32.4	2463	39.5	46,826	100.0
AA	200	6.3	309	5.0	0	
GnRH	1949	61.3	3460	55.5	0	
Educational level						
Low	869	27.3	2279	36.6	16,861	36.0
Middle	1333	41.9	2525	40.5	18,684	39.9
High	959	30.2	1388	22.3	10,652	22.7
Missing	17	0.5	40	0.6	629	1.3
Follow-up time (y), mean (SD)	5.1 (2.1)		4.6 (2.1)		4.7 (2.2)	

Abbreviations: AA = anti-androgens; ADT = androgen deprivation therapy; BT = brachytherapy; CCI = Charlson comorbidity index; DVT = deep venous thrombosis; GnRH = gonadotropin-releasing hormone agonist; PCa = prostate cancer; PCBaSe = Prostate Cancer data Base Sweden; PE = pulmonary embolism.

Adjuvant ADT: BR group (AA = 222, GnRH = 134); EBRT group (AA = 484, GnRH = 678).

confirming the need for time-updated covariates in the multivariate analyses.

There was a positive association between EBRT and BT and the risk of PE, although after adjusting for CCI, PCa risk category, PCa-related surgeries, previous TED, disease progression markers, other surgeries, education, adjuvant ADT, and neoadjuvant ADT it was no longer statistically significant (HR 1.05, 95% CI 0.61-1.79; and HR 0.97, 95% CI 0.29-1.44, respectively) (Table 3). In the stratified analysis, the highest HR was observed for the first period (0-6 months); however, after adjustment for the named covariates it remained not statistically significant (data not shown). No associations between EBRT or BT and the risk of DVT were found. Residual plots for all covariates versus time at risk showed the residuals centered around zero, indicating no violation of the hazards proportionality assumption.

Discussion

The present study shows that in a cohort of Swedish men with PCa, curative RT for prostate cancer was not associated with an increased risk of TED. Our analyses compare men with PCa receiving RT with matched men from the general population, so that our results cannot entirely disentangle the effects of RT and the tumor itself on development of TED. The observed lack of an association

Table 2 Univariate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of DVT and PE according to known clinical risk factors for TED

TED known risk factors	No. of events		Univariate			
			PE		DVT	
	BT	EBRT	HR	95% CI	HR	95% CI
PCa men						
Lymph node dissection (LND within last 12 mo vs no LND within last 12 mo)	759	1166	2.03	0.82-4.99	3.44	0.80-14.76
Palliative RT	25	90	1.68	0.23-12.06	17.72	4.16-75.47
AA due to disease progression vs no AA	181	665	1.09	0.50-2.58	2.64	0.92-7.56
GnRH due to disease progression	183	537	2.46	1.30-4.65	9.41	3.83-23.06
Hydronephrostomy	4	24	7.56	1.03-55.44	NA*	NA
Non-PCa related surgeries†	427	863	7.83†	4.88-12.56	5.04†	1.86-13.62

Abbreviations: EBRT = external beam radiation therapy; LND = lymph node dissection; NA = nonapplicable; TED = thromboembolic disease. Other abbreviations as in Table 1.

* No events.

† PCa-free men included for this variable (no. of events = 5106).

between RT and TED when comparing with the general population can be explained by one of the following reasons: (*1*) RT is truly not associated with risk of TED; or (*2*) men receiving RT are heavily selected according to their TED risk factors so that a potential increased risk of TED from RT is at most as big as the risk reduction due to the selection. However, because cancer itself is a risk factor for TED, this indicates that the second explanation is unlikely.

To the best of our knowledge, no large study to date has investigated the association between RT for prostate cancer and TED. Experimental data show that RT can induce changes in artery walls, sinusoids, and capillaries (7). The different layers of the wall vessels can suffer several alterations after radiation exposure, such as endothelial cell damage, neointima lipid deposit, necrosis, fibrosis rupture, and thrombosis (7, 18). Moreover, EBRT to the pelvis has been found to increase the risk of bleeding in men who were on an anticoagulant scheme before receiving RT (19). Less evidence has been found for large veins (20), except for hepatic and large intestine veins, which RT frequently affects. Little is known regarding the biological mechanisms for this lesser impact of RT in large veins, although it has been suggested that large veins that do get affected by RT were probably invaded by the neoplasm before RT (20). Our results suggest that large veins from the pelvic area of patients who received RT for PCa do not seem to suffer enough alterations that can lead to a short-term thromboembolic event. However most of the reported RT changes in the arteries and heart seem to happen several years after receiving RT, and our mean follow-up time was 5 years, so that the present study may not be sensitive for long-term events.

Men who undergo radical prostatectomy are at a slightly increased risk of TEDs (2). Moreover, results from a recent observational showed that ADT also increases the risk of TED (13). In our analysis we included adjuvant and neoadjuvant ADT as potential confounders; however, this adjustment did not alter the final point estimates for the association.

A major strength of our study is the use of comprehensive data in PCBaSe Sweden, a large nationwide population-based register from which information on complete follow-up, PCa treatment, PCa stage, surgeries, disease progression, ADT, comorbidities, and socioeconomic status can be retrieved, which allowed us to adjust for known TED risk factors. Additionally, the use of a PCa-free, age- and residence-matched comparison cohort allowed for accurate risk estimation. The availability of data regarding delivered RT doses for this large cohort is another strength of this study. It allowed us to confirm that the selected patients had received radiation doses with curative potential to the prostate.

Detailed information on irradiated volumes was lacking, which excluded the possibility of examining dose−volume effects on TED. Even though we had data on type and dosage of EBRT, it was not possible to divide this further into subtypes owing to the low number of TED events. However, it is unlikely that we have missed strong

Table 3 Multivariate analysis HRs and 95% CIs for risk of DVT and PE

Analysis	DVT		PE	
	HR	95% CI	HR	95% CI
No RT	1.00	Reference	1.00	Reference
Unadjusted				
BT	0.60	0.26-1.36	1.47	1.05-2.07
EBRT	1.09	0.68-1.74	1.73	1.35-2.2
Adjusted*				
BT	0.34	0.08-1.11	0.97	0.29-1.44
EBRT	0.44	0.14-1.4	1.05	0.61-1.79

Abbreviations as in Tables 1 and 2.

* Charlson comorbidity index, PCa risk category, PCa-related surgeries, previous thromboembolic events, TED known risk factors as determined in Table 2, education, adjuvant ADT, and neoadjuvant ADT.

associations because none of our findings suggested any indication of a positive trend. Additional limitations include lack of information on lifestyle factors and residual confounding, which could not be accounted for (21, 22). However, adjustment for CCI and history of TED served as proxies for lifestyle and health status at initiation of RT.

Conclusion

Our data indicate that curative RT for PCa is not associated with the risk of developing PE or DVT.

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