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Article

Comparative Effectiveness of Different Radical Radiotherapy Treatment Regimens for Prostate Cancer: A Population-Based Cohort Study

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Abstract

Background: It is unclear which radiotherapy technique and dose fractionation scheme is most effective in decreasing the risk of prostate cancer death. **Methods:** We conducted a population-based cohort study among 15 164 men in the Prostate Cancer database Sweden (version 4.0) treated with primary radical radiotherapy for prostate cancer in Sweden from 1998 to 2016. We calculated hazard ratios with 95% confidence intervals (CIs) of the association between the following exposure groups and outcome: conventionally fractionated external beam radiotherapy (EBRT) to 78 Gy (39 × 2 Gy), EBRT combined with high dose-rate brachytherapy (HDR-BT) (25 × 2 Gy + 2 × 10 Gy), conventionally fractionated EBRT to 70 Gy (35 × 2 Gy), and moderately hypofractionated (M-HF) dose-escalated EBRT (29 × 2.5 Gy or 22 × 3 Gy). **Results:** Of the men, 7296 received conventionally fractionated EBRT to 78 Gy, 4657 EBRT combined with HDR-BT, 1672 conventionally fractionated EBRT to 70 Gy, and 1539 M-HF EBRT. Using EBRT to 78 Gy as the reference, the multivariable hazard ratios (95% CIs) of prostate cancer death was 0.64 (0.53 to 0.78) for EBRT combined with HDR-BT, 1.00 (0.80 to 1.27) for EBRT to 70 Gy, and 1.51 (0.99 to 2.32) for M-HF EBRT. The multivariable hazard ratios (95% CIs) for death from any cause were 0.79 (0.71 to 0.88), 0.99 (0.87 to 1.14), and 1.12 (0.88 to 1.42), respectively. The lower risk of prostate cancer death comparing EBRT combined with HDR-BT with conventionally fractionated EBRT to 78 Gy was more pronounced for men with high-risk or poorly differentiated tumors. **Conclusions:** In this study, EBRT combined with HDR-BT was the most effective radiotherapy treatment regimen, especially for poorly differentiated tumors. Randomized trials comparing EBRT combined with HDR-BT with dose-escalated EBRT should be a priority.

Radiotherapy is an established treatment for prostate cancer. It is, however, unclear which radiotherapy technique and dose fractionation scheme is most effective in decreasing the risk of prostate cancer death. Multiple randomized trials have reported lower risk of biochemical recurrence with dose escalation from 64–70 Gy to 74–80 Gy using conventionally fractionated (CF) (ie, 1.8–2.0 Gy per fraction) external beam radiotherapy (EBRT) (1–6). Several other trials have reported similar or noninferior risk (7–12), and one trial reported lower risk (13) of biochemical recurrence comparing moderately hypofractionated (M-HF) (ie, 2.4–3.4 Gy per fraction) with CF dose-escalated EBRT. Three additional trials have reported lower risk of biochemical recurrence for men with intermediate- or high-risk disease treated with EBRT combined with low dose-rate (LDR) or high dose-rate (HDR) brachytherapy vs EBRT alone (14–16). Based on these and other observations, standard of care includes CF dose-escalated EBRT, M-HF dose-escalated EBRT, or, for intermediate- or high-risk disease, EBRT combined with brachytherapy (BT). BT alone

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is also a treatment option, especially for low-risk disease. For men with intermediate or high-risk disease, neoadjuvant and/or adjuvant androgen deprivation therapy (ADT) is also part of current standard of care (17–21).

In this study, we used a population-based prostate cancer research database including 98% of all men diagnosed with prostate cancer in Sweden to compare the risk of prostate cancer death after treatment with four standard radical radiotherapy treatment regimens: CF EBRT to 78 Gy, EBRT combined with HDR-BT, CF EBRT to 70 Gy, and M-HF dose-escalated EBRT.

Methods

Data Sources

This study was conducted using the Prostate Cancer database Sweden (PCBaSe) version 4.0 (22). PCBaSe includes data from the National Prostate Cancer Register of Sweden (NPCR) and several other nationwide registries, including the National Patient Registry, the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), the Total Population Registry, and the Cause of Death Registry.

The NPCR includes 98% of Swedish men diagnosed with prostate cancer since 1998 (22). Data are available on mode of detection, date, age at diagnosis, clinical TNM classification, biopsy Gleason score and serum prostate-specific antigen (PSA) level (ng/ml) at diagnosis, and planned primary treatment within 6 months of diagnosis. Since 2007, data have been registered on the total number of diagnostic biopsy cores, the number of cores with cancer, the total cancer extent in all cores, and the prostate volume.

The National Patient Registry includes in-patient and, since 2001, out-patient discharge diagnoses according to International Classification of Disease (ICD) codes. The LISA database includes information on educational level, income, and marital status. The Total Population Registry includes data on deaths and migrations. The Cause of Death Registry contains underlying and contributory causes of death, with 86% agreement with cause of death determined by medical record review for prostate cancer (23).

For patients treated from 1998 to 2006, radiotherapy data (date of treatment start, number of fractions, and dose per fraction for EBRT and EBRT combined with HDR-BT) were gathered from an audit of radiotherapy (retrospective collection of data on radiotherapy [RetroRad]) from the Oncology Information Systems and local databases at 17 out of 18 radiotherapy units throughout Sweden. RetroRad does not contain information on any extra-prostatic targets. For patients treated from 2007 onward, radiotherapy data (date of treatment start, dose per fraction, total dose, use of intraprostatic markers, inclusion of seminal vesicles in the target, inclusion of regional lymph nodes in the target, use of HDR-BT, and use of proton boost) have been registered in the NPCR. Since 2007, data on intended duration of adjuvant ADT treatment has also been available ($<$6 months, 6–18 months, 18–30 months, $\geq$30 months).

Covariate and Outcome Data

The study participants were divided into four risk categories based on a modified version of the National Comprehensive Cancer Network guidelines: low risk (cT1–T2, PSA $<$10, and Gleason score $\leq$6), intermediate risk (cT1–T2, PSA 10 to $<$20 ng/ml, or Gleason score 7), high risk (cT3, PSA 20 to $<$50, or Gleason score $\geq$8), and regionally metastatic (cT4 or N1 or PSA 50 to $<$100). Comorbidity was categorized according to the Charlson Comorbidity Index (CCI) based on ICD in-patient discharge codes at least 10 years prior to the prostate cancer diagnosis. Education level was categorized as low ($\leq$9 school years), middle (10–12 school years), or high ($\geq$13 school years).

Prostate cancer death (primary outcome) was defined as prostate cancer (ICD10: C61) listed as the underlying cause of death. Death from any cause was a secondary outcome. Cause of death data was available until December 31, 2016.

The Uppsala Research Ethics Board approved the study (reg. no.: 2016–239).

Statistical Analyses

The study cohort included all men (n = 15 164) in the NPCR diagnosed with nonmetastatic (ie, M0/x) prostate cancer from 1998 to 2016 treated with CF EBRT to 78 Gy (39 $\times$ 2 Gy), EBRT combined with HDR-BT (25 $\times$ 2 Gy + 2 $\times$ 10 Gy), CF EBRT to 70 Gy (35 $\times$ 2 Gy), or M-HF dose-escalated EBRT (29 $\times$ 2.5 Gy or 22 $\times$ 3 Gy). Follow-up started at the date of prostate cancer diagnosis and ended at the date of prostate cancer death, emigration, death from other causes, or end of follow-up (December 31, 2016), whichever occurred first. We used Cox regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The regression models were stratified by year of diagnosis (1998–2000, 2001–2003, 2004–2006, 2007–2009, 2010–2012, 2013–2016). CF EBRT to 78 Gy was used as the reference category in all analyses. The multivariable models were stepwise adjusted for age, cT, PSA at diagnosis, number of cores with cancer, mode of detection, Gleason score, educational level, and CCI. The main analysis was restricted to men with low-risk, intermediate-risk, or high-risk disease (ie, we excluded men with regionally metastatic disease). We also ran analyses stratified by risk category (ie, low-risk, intermediate-risk, high-risk, or regionally metastatic disease), given the large differences by risk category in prognosis, treatment recommendations, and observed treatment patterns. We used chained equations resulting in five datasets with imputed values for missing data (24). The imputation model including all variables is presented in Table 1 with the addition of survival time. We used predictive mean matching for missing continuous variables and ordinal regression for categorical variables. The analyses were performed on each imputed dataset and summarized using combined estimates applying Rubin's rules. All imputations were performed in the R-package "mice" (25).

The comparison of CF EBRT to 70 Gy vs 78 Gy was restricted to men diagnosed with prostate cancer before 2007, because only 90 men were treated with CF EBRT to 70 Gy after 2006 (Table 1 and Figure 1). The comparison between M-HF EBRT and CF EBRT to 78 Gy was restricted to men diagnosed in 2007 or later, because no men were treated with M-HF EBRT before 2007 (Table 1).

For the comparison between EBRT combined with HDR-BT and CF EBRT to 78 Gy, we conducted three sensitivity analyses. The first one restricted the analyses to men with prostate volume less than 50 cm^3 and cT1–T2, because large prostate volume and seminal vesicle involvement (ie, cT3b) is a relative contraindication for HDR-BT and data on cT3 subclass is not available in PCBaSe. The second one was restricted to men with Gleason 9–10 tumors given recent findings of strong treatment effects for EBRT combined with BT for these men (26). The third one was restricted to men aged 60–75 years and with a CCI of

Table 1. Baseline characteristics among 15 164 men diagnosed with prostate cancer from 1998 to 2016 in Prostate Cancer data Base Sweden 4.0 treated with radical radiotherapy stratified by radiotherapy technique and dose fractionation scheme

Characteristic	Conventionally fractionated EBRT*		Moderately hypofractionated EBRT		Conventionally fractionated EBRT combined with HDR-BT
	35 × 2.0 Gy	39 × 2.0 Gy	29 × 2.5 Gy	22 × 3 Gy	25 × 2 Gy + 2 × 10 Gy
Number	1672	7296	1100	439	4657
Follow-up time, median (IQR), y	12 (9–15)	6 (3–8)	3 (2–5)	3 (1–4)	8 (5–12)
Age at diagnosis, No. (%), y					
≤60	242 (14.5)	884 (12.1)	115 (10.5)	17 (3.9)	1008 (21.6)
61–65	376 (22.5)	1510 (20.7)	209 (19.0)	71 (16.2)	1274 (27.4)
66–70	553 (33.1)	2317 (31.8)	350 (31.8)	144 (32.8)	1464 (31.4)
71–75	453 (27.1)	1952 (26.8)	301 (27.4)	144 (32.8)	811 (17.4)
≥76	48 (2.9)	633 (8.7)	125 (11.4)	63 (14.4)	100 (2.1)
Year of diagnosis, No. (%)					
1998–2003	1271 (76.0)	493 (6.8)	0 (0.0)	0 (0.0)	1219 (26.2)
2004–2006	311 (18.6)	1029 (14.1)	0 (0.0)	0 (0.0)	768 (16.5)
2007–2009	39 (2.3)	1609 (22.1)	104 (9.5)	51 (11.6)	948 (20.4)
2010–2011	25 (1.5)	1280 (17.5)	239 (21.7)	41 (9.3)	678 (14.6)
2012–2014	24 (1.4)	1680 (23.0)	509 (46.3)	196 (44.6)	712 (15.3)
2015–2016	2 (0.1)	1205 (16.5)	248 (22.5)	151 (34.4)	332 (7.1)
T-class, No. (%)					
T1a	16 (1.0)	41 (0.6)	4 (0.4)	3 (0.7)	7 (0.2)
T1b	37 (2.2)	72 (1.0)	15 (1.4)	4 (0.9)	16 (0.3)
T1c	553 (33.1)	2831 (38.8)	396 (36.0)	139 (31.7)	1534 (32.9)
T2	683 (40.8)	2864 (39.3)	450 (40.9)	178 (40.5)	1940 (41.7)
T3	358 (21.4)	1398 (19.2)	215 (19.5)	110 (25.1)	1110 (23.8)
T4	9 (0.5)	21 (0.3)	5 (0.5)	3 (0.7)	8 (0.2)
Missing	16 (1.0)	69 (0.9)	15 (1.4)	2 (0.5)	42 (0.9)
N-class, No. (%)					
N0	740 (44.3)	2726 (37.4)	689 (62.6)	188 (42.8)	1907 (40.9)
N1	18 (1.1)	166 (2.3)	45 (4.1)	9 (2.1)	53 (1.1)
NX	906 (54.2)	4391 (60.2)	363 (33.0)	242 (55.1)	2657 (57.1)
Missing	8 (0.5)	13 (0.2)	3 (0.3)	0 (0.0)	40 (0.9)
M-class, No. (%)					
M0	1087 (65.0)	5548 (76.0)	963 (87.5)	406 (92.5)	3186 (68.4)
MX	575 (34.4)	1730 (23.7)	133 (12.1)	33 (7.5)	1442 (31.0)
Missing	10 (0.6)	18 (0.2)	4 (0.4)	0 (0.0)	29 (0.6)
Gleason score, No. (%)					
2–6	827 (49.5)	1767 (24.2)	132 (12.0)	51 (11.6)	1290 (27.7)
3 + 4	227 (13.6)	2271 (31.1)	342 (31.1)	143 (32.6)	1265 (27.2)
4 + 3	144 (8.6)	1475 (20.2)	294 (26.7)	88 (20.0)	789 (16.9)
8	119 (7.1)	921 (12.6)	162 (14.7)	70 (15.9)	579 (12.4)
9–10	74 (4.4)	760 (10.4)	160 (14.5)	81 (18.5)	421 (9.0)
Missing	281 (16.8)	102 (1.4)	10 (0.9)	6 (1.4)	313 (6.7)
PSA, ng/ml					
Median (Q1–Q3)	10.1 (7–19)	11 (6.7–20)	9.8 (6.3–20)	13 (7.6–27)	10 (6.4–19)
Missing, No. (%)	3 (0.2)	19 (0.3)	6 (0.5)	4 (0.9)	20 (0.4)
Proportion positive cores					
Median (Q1–Q3)	0.5 (0.33–0.7)	0.5 (0.3–0.75)	0.5 (0.3–0.8)	0.5 (0.38–0.88)	0.5 (0.33–0.75)
Missing, No. (%)	605 (36.2)	462 (6.3)	32 (2.9)	14 (3.2)	755 (16.2)
Prostate volume (ml)					
Median (Q1–Q3)	39 (29–50)	38 (29–50)	40 (30–54)	40 (30–56)	33 (26–42)
Missing, No. (%)	1595 (95.4)	2020 (27.7)	72 (6.5)	30 (6.8)	2247 (48.2)
PSA density, ng/ml2					
Median (Q1–Q3)	0.36 (0.2–0.75)	0.27 (0.17–0.49)	0.24 (0.15–0.49)	0.32 (0.18–0.65)	0.28 (0.18–0.52)
Missing, No. (%)	1595 (95.4)	2032 (27.9)	73 (6.6)	33 (7.5)	2251 (48.3)
Mode of detection, No. (%)					
Screening	459 (27.5)	3449 (47.3)	555 (50.5)	223 (50.8)	2160 (46.4)
LUTS3	322 (19.3)	2339 (32.1)	355 (32.3)	145 (33.0)	973 (20.9)
Other symptoms	627 (37.5)	1309 (17.9)	158 (14.4)	67 (15.3)	1068 (22.9)
Missing	264 (15.8)	199 (2.7)	32 (2.9)	4 (0.9)	456 (9.8)

(continued)

Table 1. (continued)

Characteristic	Conventionally fractionated EBRT*		Moderately hypofractionated EBRT		Conventionally fractionated EBRT combined with HDR-BT
	35 × 2.0 Gy	39 × 2.0 Gy	29 × 2.5 Gy	22 × 3 Gy	25 × 2 Gy + 2 × 10 Gy
Risk category, No. (%)					
Low risk	402 (24.0)	785 (10.8)	82 (7.5)	16 (3.6)	599 (12.9)
Intermediate risk	383 (22.9)	2816 (38.6)	424 (38.5)	154 (35.1)	1495 (32.1)
High risk	501 (30.0)	2941 (40.3)	459 (41.7)	202 (46.0)	1960 (42.1)
Regionally metastatic	80 (4.8)	523 (7.2)	99 (9.0)	52 (11.8)	245 (5.3)
Missing	306 (18.3)	231 (3.2)	36 (3.3)	15 (3.4)	358 (7.7)
Adjuvant ADT, No. (%)*					
No	15 (16.7)	2640 (45.7)	261 (23.7)	145 (33.0)	650 (24.3)
<6 months	34 (37.8)	2028 (35.1)	529 (48.1)	60 (13.7)	1335 (50.0)
6–18 months	10 (11.1)	314 (5.4)	60 (5.5)	32 (7.3)	105 (3.9)
18–30 months	15 (16.7)	655 (11.3)	219 (19.9)	199 (45.3)	461 (17.3)
≥30 months	16 (17.8)	137 (2.4)	31 (2.8)	3 (0.7)	119 (4.5)
Radiotherapy to regional lymph nodes, No. (%)†					
Yes	11 (12.2)	938 (16.2)	242 (22.0)	100 (22.8)	488 (18.3)
No	71 (78.9)	4627 (80.1)	843 (76.6)	335 (76.3)	1976 (74.0)
Missing	8 (8.9)	209 (3.6)	15 (1.4)	4 (0.9)	206 (7.7)
Education level, No. (%)					
Low	320 (19.1)	1568 (21.5)	346 (31.5)	85 (19.4)	1394 (29.9)
Middle	585 (35.0)	3019 (41.4)	470 (42.7)	180 (41.0)	1927 (41.4)
High	756 (45.2)	2675 (36.7)	268 (24.4)	168 (38.3)	1318 (28.3)
Missing	11 (0.7)	34 (0.5)	16 (1.5)	6 (1.4)	18 (0.4)
Charlson Comorbidity Index, No. (%)					
0	1244 (74.4)	5162 (70.8)	732 (66.5)	306 (69.7)	3656 (78.5)
1	233 (13.9)	1164 (16.0)	169 (15.4)	69 (15.7)	586 (12.6)
2	141 (8.4)	630 (8.6)	117 (10.6)	46 (10.5)	292 (6.3)
≥3	54 (3.2)	340 (4.7)	82 (7.5)	18 (4.1)	123 (2.6)
Time from diagnosis to treatment, No. (%)					
<3 mo	175 (10.5)	357 (4.9)	11 (1.0)	18 (4.1)	75 (1.6)
3–6 mo	873 (52.2)	4129 (56.6)	385 (35.0)	277 (63.1)	1332 (28.6)
6–12 mo	588 (35.2)	2648 (36.3)	640 (58.2)	137 (31.2)	2774 (59.6)
1–2 y	36 (2.2)	162 (2.2)	64 (5.8)	7 (1.6)	476 (10.2)
Cause of death, No. (%)					
Alive	871 (52.1)	6252 (85.7)	1024 (93.1)	409 (93.2)	3820 (82.0)
Dead from prostate cancer	284 (17.0)	346 (4.7)	27 (2.5)	9 (2.1)	255 (5.5)
Dead from other causes	517 (30.9)	698 (9.6)	49 (4.5)	21 (4.8)	582 (12.5)

*Data available for patients diagnosed 2007 onward. Patients with no information on duration of ADT treatment were considered not treated. ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; HDR-BT = high dose-rate brachytherapy; IQR = Interquartile range; LUTS = lower urinary tract symptoms; PSA = prostate-specific antigen.
†Data available for patients diagnosed 2007 onward.

0–1 at the time of diagnosis, because men treated with combination therapy generally are younger and healthier than men treated with EBRT alone. For the comparison between EBRT combined with HDR-BT and CF EBRT to 78 Gy, as well as for the comparison between M-HF EBRT and CF EBRT to 78 Gy, we conducted a sensitivity analysis adjusting for duration of adjuvant ADT treatment and radiotherapy to regional lymph nodes. This last sensitivity analysis was restricted to men diagnosed with prostate cancer in 2007 or later because data on adjuvant ADT and radiotherapy to regional lymph nodes were not available before then.

All statistical tests were two-sided. *P* values less than .05 were considered statistically significant.

Results

Baseline characteristics of the study cohort are available in Table 1. Of the men, 7296 received conventionally fractionated EBRT to 78 Gy, 4657 EBRT combined with HDR-BT, 1672 conventionally fractionated EBRT to 70 Gy, and 1539 M-HF EBRT. There was a shift toward higher total doses among men treated with CF EBRT during the study period (Table 1 and Figure 1). EBRT combined with HDR-BT was used during the whole study period but decreased during the latter part. The use of M-HF EBRT started in 2007 and increased over time. Men treated with EBRT combined with HDR-BT were generally younger and had fewer comorbidities compared with men treated with either CF or M-HF EBRT, whereas a larger proportion of men treated with M-HF EBRT received neoadjuvant and/or adjuvant ADT and radiotherapy to regional lymph nodes compared with men treated with either CF EBRT or EBRT combined with HDR-BT (Table 1).

Among men diagnosed from 1998 to 2016, 4657 were treated with EBRT combined with HDR-BT and 7296 with CF EBRT to 78 Gy. EBRT combined with HDR-BT was associated with a 36% reduced risk of prostate cancer death in both the unadjusted (HR = 0.64, 95% CI = 0.53 to 0.77) and fully adjusted model (HR = 0.64, 95% CI = 0.53 to 0.78) (Table 2). When stratified by risk category, the multivariable hazard ratio was 1.15 (95% CI = 0.24

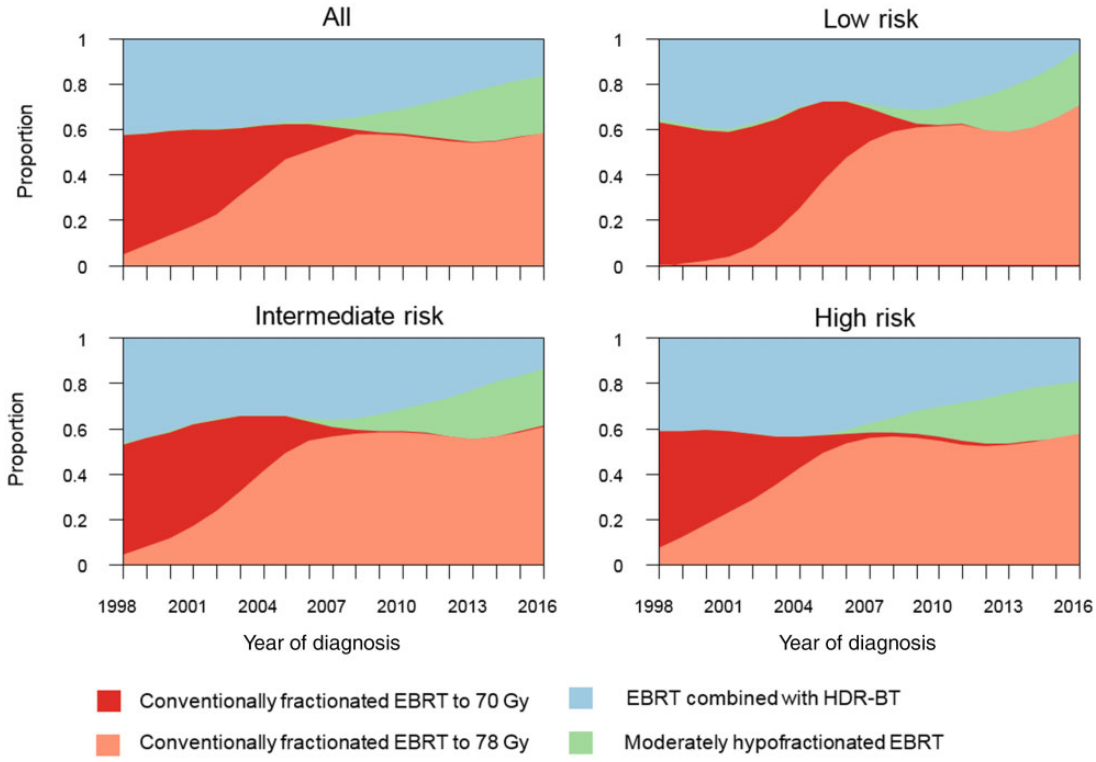

Figure 1. Temporal trends in radiotherapy treatment practice overall and by risk category. EBRT = external beam radiotherapy; HDR-BT = high dose-rate brachytherapy.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between different radiotherapy treatment regimens and risk of prostate cancer death overall and stratified by risk category

Treatment	Total (low- to high-risk)	Low risk	Intermediate risk	High risk	Regionally metastatic
Conventionally fractionated EBRT combined with HDR-BT vs conventionally fractionated EBRT to 78 Gy, events (N)	544 (11 095)	27 (1448)	138 (4564)	379 (5083)	57 (858)
Crude model, HR (95% CI)	0.64 (0.53 to 0.77)	0.81 (0.18 to 3.70)	0.69 (0.48 to 1.00)	0.63 (0.51 to 0.78)	0.52 (0.28 to 0.96)
Adjusted model, HR (95% CI)*	0.64 (0.53 to 0.78)	1.15 (0.24 to 5.59)	0.75 (0.50 to 1.12)	0.59 (0.47 to 0.74)	0.54 (0.27 to 1.09)
Conventionally fractionated EBRT to 70 vs 78 Gy, events (N)†	422 (2929)	39 (625)	119 (1009)	264 (1296)	52 (175)
Crude model, HR (95% CI)	0.86 (0.69 to 1.07)	0.52 (0.09 to 3.18)	1.12 (0.72 to 1.75)	1.13 (0.85 to 1.51)	1.68 (0.95 to 2.97)
Adjusted model, HR (95% CI)*	1.00 (0.80 to 1.27)	0.49 (0.06 to 3.77)	1.01 (0.64 to 1.58)	1.05 (0.78 to 1.42)	1.98 (1.06 to 3.70)
Moderately hypofractionated EBRT vs conventionally fractionated EBRT to 78 Gy, events (N)‡	164 (6651)	3 (749)	35 (2975)	126 (2927)	23 (662)
Crude model, HR (95% CI)	1.69 (1.11 to 2.56)	NA	1.15 (0.40 to 3.30)	1.65 (1.03 to 2.64)	1.22 (0.43 to 3.47)
Adjusted model, HR (95% CI)*	1.51 (0.99 to 2.32)	NA	1.14 (0.33 to 3.89)	1.71 (1.04 to 2.80)	1.04 (0.00 to ∞)

*The adjusted model includes age (categorical: ≤60, 61–65, 66–70, 71–75, ≥76), cT (categorical: T1a, T1b, T1c, T2, T3, T4), prostate-specific antigen (continues), proportion of positive cores (continues), mode of detection (categorical: screening, lower urinary tract symptoms, other symptoms), Gleason score (categorical: 2–6, 3 + 4, 4 + 3, 8, 9–10), education level (categorical: low, middle, high), and Charlson Comorbidity Index (categorical: 0, 1, 2, ≥3). EBRT = external beam radiotherapy; HDR-BT = high dose-rate brachytherapy.
†Restricted to men diagnosed with prostate cancer in 2006 or earlier.
‡Restricted to men diagnosed with prostate cancer in 2007 or later.

to 5.59) for low-risk, 0.75 (95% CI = 0.50 to 1.12) for intermediate-risk, and 0.59 (95% CI = 0.47 to 0.74) for high-risk tumors. The results remained in sensitivity analyses restricted to men with a prostate volume less than 50 cm^3 and cT1–cT2 (Supplementary Table 1, available online), restricted to men aged 60–75 years and with a CCI of 0–1 (Supplementary Table 1, available online), and with additional adjustment for neoadjuvant and/or adjuvant ADT and radiotherapy to regional lymph nodes (Supplementary Table 2, available online). In the sensitivity analysis restricted to men with Gleason 9–10 cancer, the decrease in risk was more pronounced (fully adjusted HR = 0.32, 95% CI = 0.12 to 0.87) (Supplementary Table 1, available online).

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between different radiotherapy treatment regimens and risk of death from any cause overall and stratified by risk category

Treatment	Total (low- to high-risk)	Low-risk	Intermediate-risk	High-risk	Regionally metastatic
Conventionally fractionated EBRT combined with HDR-BT vs conventionally fractionated EBRT to 78 Gy, events (N)	1751 (11 095)	225 (1448)	616 (4564)	948 (5083)	130 (858)
Crude model, HR (95% CI)	0.71 (0.64 to 0.79)	0.94 (0.64 to 1.37)	0.70 (0.59 to 0.83)	0.71 (0.62 to 0.81)	0.84 (0.58 to 1.23)
Adjusted model, HR (95% CI)*	0.79 (0.71 to 0.88)	0.99 (0.68 to 1.45)	0.81 (0.67 to 0.97)	0.75 (0.65 to 0.87)	0.94 (0.61 to 1.44)
Conventionally fractionated EBRT to 70 vs 78 Gy, events (N)†	1240 (2929)	225 (625)	425 (1009)	590 (1296)	78 (175)
Crude model, HR (95% CI)	0.99 (0.87 to 1.13)	1.10 (0.72 to 1.69)	1.09 (0.87 to 1.37)	1.06 (0.87 to 1.29)	1.52 (0.96 to 2.41)
Adjusted model, HR (95% CI)*	0.99 (0.87 to 1.14)	0.87 (0.56 to 1.36)	0.93 (0.73 to 1.17)	1.01 (0.83 to 1.23)	1.62 (0.87 to 3.01)
Moderately hypofractionated EBRT vs conventionally fractionated EBRT to 78 Gy, events (N)‡	552 (6651)	45 (749)	204 (2975)	304 (2927)	63 (662)
Crude model, HR (95% CI)	1.17 (0.92 to 1.48)	1.85 (0.73 to 4.68)	0.96 (0.63 to 1.46)	1.16 (0.85 to 1.58)	1.52 (0.85 to 2.71)
Adjusted model, HR (95% CI)*	1.12 (0.88 to 1.42)	1.76 (0.65 to 4.82)	0.91 (0.59 to 1.39)	1.19 (0.86 to 1.63)	1.71 (0.91 to 3.20)

*The adjusted model includes age (categorical: ≤60, 61–65, 66–70, 71–75, ≥76), cT (categorical: T1a, T1b, T1c, T2, T3, T4), prostate-specific antigen (continues), proportion of positive cores (continues), mode of detection (categorical: screening, lower urinary tract symptoms, other symptoms), Gleason score (categorical: 2–6, 3+4, 4+3, 8, 9–10), education level (categorical: low, middle, high), and Charlson Comorbidity Index (categorical: 0, 1, 2, 3+). EBRT = external beam radiotherapy; HDR-BT = high dose-rate brachytherapy.
†Restricted to men diagnosed with prostate cancer in 2006 or earlier.
‡Restricted to men diagnosed with prostate cancer in 2007 or later.

There was also a decrease in risk of death from any cause (fully adjusted HR = 0.79, 95% CI = 0.71 to 0.88) (Table 3).

Among men diagnosed from 1998 to 2006, 1582 were treated with CF EBRT to 70 Gy and 1522 to 78 Gy. There was no statistically significant difference in the risk of prostate cancer death between the two groups in the unadjusted (HR = 0.86, 95% CI = 0.69 to 1.07) or fully adjusted model (HR = 1.00, 95% CI = 0.80 to 1.27) (Table 2). There was also no association with death from any cause (fully adjusted HR = 0.99, 95% CI = 0.87 to 1.14) (Table 3).

Among men diagnosed from 2007 to 2016, 1539 men were treated with M-HF EBRT and 5774 with CF EBRT to 78 Gy. In the unadjusted model, there was a statistically significant difference in risk of prostate cancer death in favor of CF EBRT (HR = 1.69, 95% CI = 1.11 to 2.56), which was attenuated in the fully adjusted model (HR = 1.51, 95% CI = 0.99 to 2.32) (Table 2). The increased risk was confined to high-risk men (HR = 1.71, 95% CI = 1.04 to 2.80); the hazard ratio was 1.14 (95% CI = 0.33 to 3.89) for intermediate-risk men and could not be estimated for low-risk men because there were too few events (n = 3). The results did not differ materially between the 3 Gy to 66 Gy and 2.5 Gy to 72.5 Gy subgroups (Supplementary Table 3, available online), or in sensitivity analysis additionally adjusting for neoadjuvant and/or adjuvant ADT and radiotherapy to regional lymph nodes (Supplementary Table 3, available online). There was no association with death from any cause (fully adjusted HR = 1.12, 95% CI = 0.88 to 1.42) (Table 3).

Discussion

In this study, men treated with EBRT combined with HDR-BT had a 36% lower risk of prostate cancer death compared with those treated with CF EBRT to 78 Gy, and the risk reduction was more pronounced (68% lower risk) for Gleason 9–10 tumors. Randomized trial data on the efficacy of EBRT combined with BT are scarce. There are no randomized trials that have compared EBRT combined with HDR-BT with CF dose-escalated EBRT and that have used prostate cancer death as the primary outcome. Three trials have shown improved biochemical-free survival in men treated with EBRT combined with BT vs EBRT alone. In two trials (14,15), EBRT combined with BT [in one trial LDR-BT (14) and the other trial HDR-BT (15)] was compared with nondose-escalated EBRT (14,15), a suboptimal comparison group. The third trial, ASCENDE-RT, compared CF dose-escalated EBRT with EBRT combined with LDR-BT (16), which is a different treatment regimen from those evaluated in this study. Several observational studies have reported improved outcomes in men with high-risk tumors treated with EBRT combined with either HDR- or LDR-BT compared with EBRT alone (26–30). A recent cohort study comparing EBRT combined with BT, EBRT alone, and radical prostatectomy for men with Gleason 9–10 tumors also demonstrated superior prostate cancer survival for EBRT combined with BT (26). Observational data are, however, prone to selection bias and confounding by indication (31), because men treated with combination therapy generally are younger and healthier than men treated with EBRT alone and large prostate volume, obstructive symptoms, and seminal vesicle involvement are relative contraindications for BT. However, to create the substantially decreased risk that we observed (HR = 0.64), such bias would have to be very strong. This appears unlikely given that adjusting for known strong prognostic factors did not affect the risk estimate at all and because the association remained in sensitivity analysis restricted to men with a prostate volume less than 50 cm^3 and cT1–T2 and in sensitivity analysis restricted to men aged 60–75 years and with a CCI of 0–1. It is biologically plausible that EBRT combined with HDR-BT could lower the risk of prostate cancer death compared with CF EBRT to 78 Gy. If the biologically effective dose concept is valid for such high fractionation doses as 10 Gy, the biologically effective dose for EBRT (25 × 2 Gy) combined with HDR-BT (2 × 10 Gy) is, presuming an α:β ratio anywhere from 1 to 5 (the α:β ratio is estimated to be around 1.5 or even lower) (32,33), substantially higher than for CF EBRT to 78 Gy.

With one exception (6), randomized trials assessing the benefit of dose-escalation using CF EBRT have failed to show, both individually (1–6) and in meta-analysis (34), improved prostate cancer–specific or overall survival despite clear evidence of lower risk of biochemical recurrence. The largest observational study to date reported a 16–18% lower risk of death from any cause among men with intermediate- or high-risk disease treated with CF EBRT to no less than 75.6–90 Gy vs 68.4 to less than 75.6 Gy (35). This strong survival benefit is difficult to explain given the null findings for prostate cancer and overall death in randomized trials and in our study. Our null finding may have several explanations. It is possible that when dose escalation was introduced in Sweden, it was primarily given to men with adverse cancer characteristics that we were unable to fully control for. It is, however, also possible that dose escalation from 70 to 78 Gy lowers the risk of biochemical recurrence but not prostate cancer death. The biologically effective dose delivered with 78 vs 70 Gy may, for example, kill more indolent cancer cells (that cause biochemical recurrence) but may still be too low to kill all lethal cancer cells (that cause prostate cancer death). To conclusively address this issue, an updated meta-analysis of randomized trials using individual-level data, as well as additional data from observational studies, is needed.

Hypofractionation is an attractive treatment option for prostate cancer given its presumably low α:β ratio. Several randomized trials have reported comparable or noninferior efficacy, typically measured as 5-year biochemical and clinical failure free time, with M-HF compared with CF dose-escalated EBRT (7–12), and a recent trial reported a 4% lower 8-year PSA failure rate for M-HF (13). In light of these results, our finding of a nonstatistically significant 51% increased risk of prostate cancer death comparing M-HF with CF dose-escalated EBRT is difficult to explain and should be interpreted with utmost caution. Both residual bias and chance are likely explanations for the results. Indeed, the follow-up time was rather short and the number of events rather few for the comparison of M-HF to CF dose-escalated EBRT.

Our observational study design has strengths and weaknesses. The primary limitation is selection bias and confounding by indication, as discussed above. Although we had high-quality data on most known treatment selection factors, we lacked data on some potentially important factors. For example, we lacked detailed data on local tumor growth (eg, extent of extracapsular extension) and obstructive symptoms, which can affect choice of radiotherapy technique. Also, EBRT combined with HDR-BT, as well as M-HF EBRT, is not delivered at all radiotherapy units in Sweden, and it is possible that these regional differences have introduced bias. Also, we lacked data on side effects that are of major relevance for radiotherapy. Reliable data on side effects after the treatment regimens compared in this study have already been well documented (1,4,5,7–9,11–13,15). Major strengths of our real-world data include its population-based design, large number of patients, detailed clinical data, long and virtually complete follow-up, and the use of prostate cancer death as the endpoint.

In conclusion, we observed a 36% lower risk of prostate cancer death comparing EBRT combined with HDR-BT with CF dose-escalated EBRT. In light of these and previous findings from observational studies, coupled with the paucity of data from randomized trials, we suggest that randomized trials comparing EBRT combined with HDR-BT with dose-escalated EBRT should be a priority.

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