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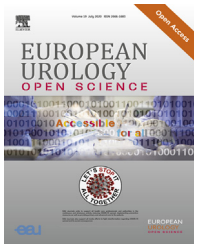

European Association of Urology

Prostate Cancer

Comparative Survival Outcomes of High-risk Prostate Cancer Treated with Radical Prostatectomy or Definitive Radiotherapy Regimens

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Abstract

Background: Observational data has indicated improved survival after radical prostatectomy (RP) compared with definitive radiotherapy (RT) in men with high-risk prostate cancer (PCa).
Objective: To compare PCa-specific mortality (PCSM) and overall mortality (OM) in men with high-risk PCa treated with RP or RT, providing information on target doses and fractionations.
Design, setting, and participants: This is an observational study from the Cancer Registry of Norway. Patients were diagnosed with high-risk PCa during 2006–2015, treated with RP ≤12 mo or RT ≤15 mo after diagnosis, and stratified according to RP or RT modality; external beam radiotherapy (EBRT; 70–<74, 74–<78, or 78 Gy), hypofractionated RT or EBRT combined with brachytherapy (BT-RT).
Outcome measurements and statistical analysis: Competing risk and Kaplan-Meier methods estimated PCSM and OM, respectively. Multivariable Cox regression models evaluated hazard ratios (HRs) for PCSM and OM.
Results and limitations: In total, 9254 patients were included (RP 47%, RT 53%). RT patients were older, had poorer performance status and more unfavorable disease characteristics. With a median follow-up time of seven and eight yrs, the overall 10-yr PCSM was 7.2% (95% confidence interval [CI] 6.4–8.0) and OM was 22.9% (95% CI 21.8–24.1). Compared with RP, EBRT 70–<74 Gy was associated with increased (HR 1.88, 95% CI 1.33–2.65, $p < 0.001$) and BT-RT with decreased (HR 0.49, 95% CI 0.24–0.96, $p = 0.039$) 10-yr PCSM. Patients treated with EBRT 70–78 Gy had higher adjusted 10-yr OM than those treated with RP.
Conclusions: In men with high-risk PCa, treatment with EBRT <74 Gy was associated with increased adjusted 10-yr PCSM and OM, and BT-RT with decreased 10-yr PCSM, compared with RP.

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Patient summary: In this study, we compared mortality after radical prostatectomy (RP) and radiotherapy (RT) in men with high-risk prostate cancer (PCa); the results suggest that men receiving lower-dose RT have higher, and patients receiving brachytherapy may have lower, risk of death from PCa than patients treated with prostatectomy.

1. Introduction

Men diagnosed with high-risk prostate cancer (PCa) have a substantial risk of death from PCa, even after curatively intended treatment [1]. In the primary setting, curative treatment options include radical prostatectomy (RP) with extended pelvic lymph node dissection, in selected patients followed by adjuvant radiotherapy (aRT), or definitive radiotherapy (RT) combined with long-term (neo-)adjuvant androgen deprivation therapy (ADT) [2,3].

Based on observational data, RP has been associated with increased survival compared with RT in men with high-risk PCa [4–11]. External beam RT (EBRT) combined with brachytherapy (BT-RT) has, however, indicated comparable results to RP [7,8,12], particularly in patients with Gleason score (GS) 9–10 tumors [13]. In observational studies, adjustments for pretreatment clinical parameters attenuate survival differences between treatment groups [4,6], but residual confounding, incomplete information on ADT, different surgical and RT techniques and application of multimodal therapy limit the interpretation and clinical application of such results [9]. Dose-escalated RT (≥74 Gy) and BT-RT have been associated with improved PCa-specific and overall survival compared with lower-dose RT in men with intermediate- to high-risk disease [14–18]. The majority of registry-based studies comparing the effectiveness of RP versus RT, however, do not include information on target doses and dose fractionation. In patients with locally and regionally advanced disease, RP followed by pelvic RT has been associated with increased disease-specific and overall survival compared with RP alone, with comparable results to the traditional treatment with combined RT and ADT [19,20]. Not until the completion of the ongoing SPCG-15 trial, randomized evidence will be available on survival outcomes in men with T3 tumors treated with RP +/− aRT compared with dose-escalated RT combined with ADT (NCT02102477). Further, even in patients with high-risk PCa, survival differences among curative treatment groups may become evident only after long-term follow-up [21].

With this background, the aim of this cohort study is to compare PCa-specific (PCSM) and overall (OM) mortality in men with high-risk PCa treated with RP or definitive RT regimens, providing information on RT techniques/modalities and adjusting for available clinical variables recorded in a population-based cancer registry.

2. Patients and methods

2.1. Data sources

PCa cases were identified by the Cancer Registry of Norway (CRN), which supplied date of and age at diagnosis, as well as information on prior cancers. Clinically relevant data were obtained from the Norwegian Prostate Cancer Registry (NoPCR), a clinical registry with national coverage administered by the CRN. The following variables were extracted: Eastern Cooperative Oncology Group (ECOG) performance status (PS), prostate-specific antigen (PSA) level, TNM categories, GS and date of RP. The National Radiotherapy Database, also administered by the CRN, provided data on RT (treatment intention, target dose to the prostate and start date) [22]. Information on the date and cause of death was collected from the Cause of Death Registry. The study was approved by the Regional Committee for Medical and Health Research Ethics (2011/1746).

2.2. Patients

Eligible patients were diagnosed with PCa in Norway from 2006 to 2015 and classified with high risk disease according to the European Association of Urology (PSA >20 ng/ml or GS 8–10 or clinical (c)T category ≥2c) [2]. Complete information on clinical N category was not available. The following exclusion criteria were applied:

1 No cytological/histological verification of cancer, diagnosis based on cystoprostatectomy or morphology other than adenocarcinoma
2 Evidence of distant metastases or PSA >100 ng/ml
3 No curative treatment

Curative treatment was defined as RP performed ≤12 mo after diagnosis, with or without aRT initiated within 4 mo of RP [23], or RT ≥70 Gy started ≤15 mo after diagnosis. Performance of pelvic lymph node dissection, the use of pelvic lymph node–directed RT or (neo-)adjuvant ADT were not documented reliably in the registry. Long-term ADT (2–3 yrs) was, however, routine practice in high-risk RT patients in Norway during the study period. Patients receiving RT were stratified into the following subgroups: conventionally fractionated EBRT 70–<74 Gy or dose-escalated EBRT 74–<78 Gy or 78 Gy. We also identified patients who received ≥2.7 Gy/d × 25 (HYPO-RT) and high-dose-rate brachytherapy (BT) combined with EBRT (BT-RT) [24]. Patients who received other RT regimens were excluded (89 patients).

2.3. Statistical methods

Descriptive statistics were presented as means or medians for continuous variables, and as frequencies and percentages for categorical variables. For survival analyses, patients were followed from the date of primary treatment to the date of the event of interest (death from PCa or death from all causes), date of emigration or date of administrative

censoring, whichever came first. Based on complete information on vital status and cause of death, administrative censoring occurred on December 31, 2019 when analyzing OM and December 31, 2018 when analyzing PCSM.

The standard Kaplan-Meier method estimated OM, whereas PCSM was estimated using the Aalen-Johansen estimator, incorporating the competing risk of death from other causes. Differences in OM curves were tested using standard log-rank tests. Differences in PCSM curves were tested by estimating a univariable Fine-Gray regression model. Independent-sample *t* test and standard chi-square test were used for differences in clinical parameters among treatment groups.

As we were interested in estimating the effects of treatment on PCSM and OM, which could facilitate some causal interpretation, we estimated cause-specific hazard ratios (CSHRs) from multivariable Cox regressions. When estimating CSHRs for PCSM, this meant censoring all individuals on the date of death if they died of other causes. To better understand the effects of confounding, we first estimated univariable Cox regressions and compared the CSHR estimates with estimates from two multivariable models. The first multivariable model adjusted only for basic confounders such as age at diagnosis (<60, 60–69, 70–79, and 80+ yrs), cT category (T1–2 vs T3–4), PSA level (<10, 10–20, and >20 ng/ml), and GS (6–10). In the second model, we added diagnostic period (2006–2010 vs 2011–2015), health region (southeast, west, middle and north), prior cancer diagnosis (yes/no), and ECOG PS (0, 1, and ≥2). A p value of <0.05 was considered statistically significant. All analyses were done using SPSS v25.1 and Stata v16.1.

3. Results

In total, 9254 patients were eligible for the present study, of whom 4306 (47%) underwent RP and 4948 (53%) underwent RT (Table 1 and Supplementary Table 1). The use of RP increased during the study period, comprising 29% of all curatively treated high-risk patients in 2006 and 54% in 2015 (Supplementary Table 1). In total, 300 RP patients received aRT. The majority of patients who underwent RT received EBRT 74–<78 Gy (18%) or EBRT 78 Gy (18%). There

Table 1 – Characteristics of patients receiving primary curative treatment for high-risk prostate cancer in Norway during 2006–2015

Treatment group	RP	Def-RT	EBRT 70–<74 Gy	EBRT 74–<78 Gy	EBRT 78 Gy	HYPO-RT	BT-RT	All
Number of patients	4306	4948	606	1651	1692	565	434	9254
Diagnostic period								
2006–2010	1443 (34)	2393 (48)	514 (85)	579 (30)	849 (50)	181 (32)	270 (62)	3836 (42)
2011–2015	2863 (66)	2555 (52)	92 (15)	1072 (65)	843 (50)	384 (68)	164 (38)	5418 (59)
Health region								
Southeast	2611 (61)	2644 (53)	485 (80)	1578 (96)	148 (9)	14 (3)	419 (97)	5255 (57)
West	534 (12)	872 (18)	56 (9)	19 (1)	243 (14)	548 (97)	6 (1)	1406 (15)
Middle	766 (18)	954 (19)	34 (6)	10 (<1)	907 (54)	0	3 (<1)	1720 (19)
North	380 (9)	459 (9)	25 (4)	38 (2)	390 (23)	0	6 (1)	839 (9)
Unknown	15 (<1)	19 (<1)	6 (1)	6 (<1)	4 (<1)	3 (<1)	0	34 (<1)
Age group (yrs), mean	64	69	68	70	69	68	67	66
<60	1197 (28)	542 (11)	84 (14)	135 (8)	177 (11)	70 (12)	76 (18)	1739 (19)
60–<70	2615 (61)	2282 (46)	305 (50)	718 (44)	775 (46)	257 (46)	227 (52)	4897 (53)
70–<80	492 (11)	2049 (41)	211 (35)	762 (46)	719 (43)	226 (40)	131 (30)	2541 (28)
80+	2 (<1)	75 (2)	6 (1)	36 (2)	21 (1)	12 (2)	0	77 (<1)
ECOG PS								
0	3259 (76)	3250 (66)	423 (70)	965 (58)	1114 (66)	421 (75)	327 (75)	6509 (70)
1	304 (7)	853 (17)	90 (15)	319 (19)	322 (19)	68 (12)	54 (12)	1157 (13)
≥2	52 (1)	212 (4)	35 (6)	94 (6)	64 (4)	8 (1)	11 (3)	264 (3)
Missing	691 (16)	633 (13)	58 (10)	273 (17)	192 (11)	68 (12)	42 (10)	1324 (14)
Prior cancer								
No	4062 (94)	4514 (91)	560 (92)	1497 (91)	1539 (91)	510 (90)	408 (94)	8576 (93)
Yes	244 (6)	434 (9)	46 (8)	154 (9)	153 (9)	55 (10)	26 (6)	678 (7)
PSA (ng/ml), median	10	15	17	15	15	20	14	12
<10	2183 (51)	1407 (28)	167 (28)	495 (30)	482 (29)	113 (20)	150 (35)	3590 (39)
10–20	1019 (24)	1434 (29)	154 (25)	467 (28)	532 (31)	154 (27)	127 (29)	2453 (27)
>20	772 (18)	1779 (36)	241 (40)	529 (32)	630 (37)	251 (44)	128 (30)	2551 (28)
Missing	332 (8)	4620 (93)	44 (7)	160 (10)	48 (3)	47 (8)	29 (7)	660 (7)
Gleason score								
6	539 (13)	440 (9)	88 (15)	101 (6)	172 (10)	45 (8)	34 (8)	979 (11)
7a	1064 (25)	1009 (20)	138 (23)	286 (17)	373 (22)	99 (18)	113 (26)	2073 (22)
7b	639 (15)	880 (18)	104 (17)	266 (16)	317 (19)	107 (19)	86 (20)	1519 (16)
8	1417 (33)	1572 (32)	179 (30)	630 (38)	443 (26)	183 (32)	137 (32)	2989 (32)
9–10	567 (13)	977 (20)	76 (13)	350 (21)	367 (22)	126 (22)	58 (13)	1544 (17)
Missing	80 (2)	70 (1)	21 (4)	18 (1)	20 (1)	5 (<1)	6 (1)	150 (2)
cT category								
1–2	2673 (62)	2025 (41)	267 (44)	631 (38)	712 (42)	245 (43)	170 (39)	4698 (51)
3a	919 (21)	1617 (33)	175 (29)	521 (32)	538 (32)	196 (35)	187 (43)	2536 (27)
3b	238 (6)	518 (11)	34 (6)	206 (13)	212 (13)	51 (9)	15 (4)	756 (8)
3x	175 (4)	417 (8)	94 (16)	119 (7)	147 (9)	22 (4)	35 (8)	592 (6)
4	17 (<1)	60 (1)	6 (1)	25 (2)	25 (2)	2 (<1)	2 (<1)	77 (<1)
Missing	284 (7)	311 (6)	30 (5)	149 (9)	58 (3)	49 (9)	25 (6)	595 (6)

BT-RT = brachytherapy combined with EBRT; cT category = clinical tumor category; Def-RT = definitive radiotherapy; EBRT = external beam radiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; HYPO-RT = hypofractionated radiotherapy; PSA = prostate specific antigen; RP = radical prostatectomy.

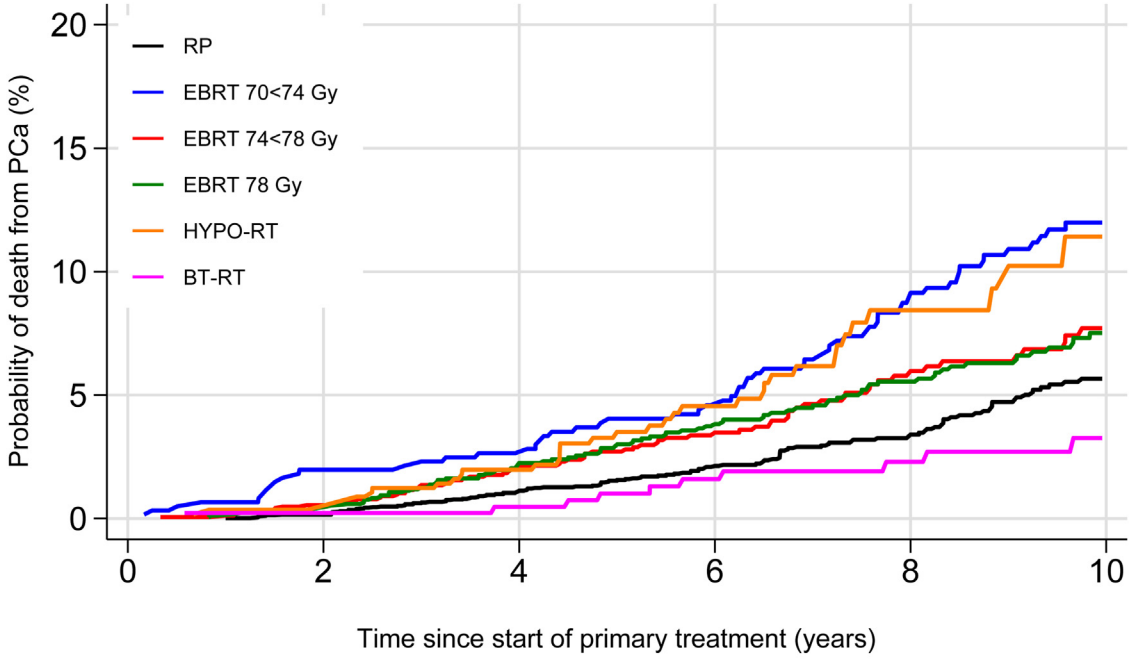
Table 2 – Five-year and 10-yr prostate cancer–specific mortality (PCSM) and overall mortality (OM) in men with high-risk prostate cancer according to primary treatment

Treatment	5-yr PCSM	10-yr PCSM
RP	1.5 (1.2–2.0)	5.7 (4.6–6.9)
EBRT 70–<74 Gy	4.0 (2.7–5.9)	12.0 (9.4–15.0)
EBRT 74–<78 Gy	2.7 (2.0–3.6)	7.7 (5.9–9.8)
EBRT 78 Gy	2.9 (2.1–3.8)	7.5 (6.0–9.3)
HYPO-RT	3.5 (2.2–5.4)	11.4 (7.5–16.3)
BT-RT	1.0 (0.3–2.5)	3.3 (1.6–5.8)
Total	2.3 (2.0–2.6)	7.2 (6.4–8.0)
	5-yr OM	10-yr OM
RP	5.2 (4.6–5.9)	15.5 (14.0–17.1)
EBRT 70–<74 Gy	11.9 (9.5–14.7)	32.4 (28.5–36.6)
EBRT 74–<78 Gy	11.3 (9.8–12.9)	30.9 (27.7–34.3)
EBRT 78 Gy	10.6 (9.2–12.3)	28.6 (26.0–31.4)
HYPO-RT	11.1 (8.7–14.0)	28.6 (23.4–34.6)
BT-RT	5.4 (3.6–8.1)	15.4 (11.9–19.8)
Total	8.1 (7.5–8.7)	22.9 (21.8–24.1)

BT-RT = brachytherapy combined with EBRT; EBRT = external beam radiotherapy; HYPO-RT = hypofractionated radiotherapy; OM = overall mortality; PCSM = prostate cancer–specific mortality; RP = radical prostatectomy.

were significant regional differences according to RT modalities applied (Table 1).

Compared with RP patients, men treated with RT were older and had higher ECOG PS, PSA levels, GSs (RT: 52% GS 8–10 vs RP: 46%), and cT categories (RT: 53% cT3–4 vs RP: 31%; Table 1). Comparing RP and BT-RT patients, similar differences emerged. Within the RT subgroups, BT-RT patients were younger and had lower ECOG scores than the average RT patient, and patients who received EBRT 74–<78 Gy and HYPO-RT had the highest GSs (Table 1).



Numbers at risk

RP	4305	4281	3429	2248	1248	599
EBRT 70<74 Gy	606	588	546	492	416	229
EBRT 74<78 Gy	1651	1625	1224	796	401	192
EBRT 78 Gy	1692	1666	1319	1004	681	324
HYPO-RT	565	560	471	302	116	44
BT-RT	434	429	385	302	228	121

Fig. 1 – Prostate cancer–specific mortality according to treatment modality in men with high-risk prostate cancer. BT-RT = external beam radiotherapy combined with brachytherapy; EBRT = external beam radiotherapy; HYPO-RT = hypofractionated radiotherapy; PCa = prostate cancer; RP = radical prostatectomy.

The median follow-up time was seven yrs for the evaluation of PCSM and eight yrs for OM. For all patients, the 5- and 10-yr PCSM rates were 2.3% (95% confidence interval [CI] 2.0–2.6) and 7.2% (95% CI 6.4–8.0), and OM 8.1% (95% CI 7.5–8.7) and 22.9% (95% CI 21.8–24.1), respectively (Table 2). Patients treated with RP and BT-RT had the lowest, and those treated with EBRT 70–<74 Gy had the highest 10-yr PCSM rates (Table 2 and Fig. 1). Unadjusted 10-yr PCSM was significantly higher in patients receiving EBRT 70–<78 Gy and HYPO-RT than in patients treated with RP (Supplementary Table 2 and Fig. 1). When restricting the analysis to patients with GS 8–10 disease, the risk of PCa death was higher after RP than after BT-RT (Supplementary Fig. 1). BT-RT was not superior to RP in subanalyses of patients with localized or locally advanced disease, and only EBRT 70–<74 Gy was inferior to RP in patients with cT3–4 tumors (Supplementary Fig. 2A and 2B).

When adjusted for clinical covariates, including age and tumor risk factors (GS, PSA, and cT category), EBRT 70–<74 Gy was associated with higher 10-yr PCSM than RP (hazard ratio [HR] 1.88, 95% CI 1.33–2.65, $p < 0.001$; Table 3). Using RP as a reference, the risk of PCa death was reduced by half in the BT-RT group (HR 0.49, 95% CI 0.24–0.96, $p = 0.039$). Inclusion of diagnostic period, health region, prior cancer diagnosis and ECOG PS in the analysis did not alter these results (Table 3). No differences in adjusted HR for PCa death emerged according to treatment at 5 yrs follow-up (Supplementary Table 3). There was no significant difference in 10-yr PCSM between RP patients treated with or without aRT (Supplementary Table 4).

Table 3 – Adjusted Cox regression of 10-yr prostate cancer–specific (PCSM) and overall (OM) mortality in men with high-risk prostate cancer

	PCSM				OM			
	Model 1		Model 2		Model 1		Model 2	
	HR	*p* value	HR	*p* value	HR	*p* value	HR	*p* value
Treatment								
RP	1		1		1		1	
EBRT 70–<74 Gy	1.88	0.000	1.54	0.023	1.75	0.000	1.56	0.000
EBRT 74–<78 Gy	1.09	0.627	0.95	0.795	1.55	0.000	1.40	0.001
EBRT 78 Gy	1.08	0.615	1.10	0.617	1.50	0.000	1.50	0.000
HYPO-RT	1.24	0.340	1.04	0.882	1.32	0.023	1.14	0.377
BT-RT	0.49	0.039	0.43	0.019	0.87	0.372	0.81	0.173
Age (yrs)								
<60	1		1		1		1	
60–69	0.93	0.598	0.86	0.316	1.40	0.000	1.33	0.002
70–79	1.06	0.704	1.05	0.777	2.20	0.000	2.00	0.000
80+	1.16	0.798	1.01	0.993	2.60	0.000	1.96	0.023
Gleason score								
6	1		1		1		1	
7a	2.46	0.007	2.46	0.008	1.56	0.001	1.52	0.001
7b	4.71	0.000	4.71	0.000	1.82	0.000	1.79	0.000
8	5.13	0.000	4.94	0.000	1.93	0.000	1.85	0.000
9–10	13.66	0.000	13.97	0.000	2.78	0.000	2.75	0.000
PSA (ng/ml)								
<10	1		1		1		1	
10–20	1.20	0.188	1.21	0.189	1.30	0.000	1.31	0.000
>20	1.48	0.004	1.53	0.003	1.53	0.000	1.49	0.000
cT category								
T1–2	1		1		1		1	
T3–4	1.35	0.007	1.40	0.004	1.08	0.200	1.13	0.048
Diagnostic period								
2006–2010			1				1	
2011–2015			0.68	0.008			0.96	0.593
Health region								
Southeast			1				1	
West			0.99	0.956			1.06	0.609
Middle			0.83	0.340			0.82	0.062
North			0.88	0.552			0.91	0.394
Prior cancer								
No			1				1	
Yes			1.15	0.502			1.66	0.000
ECOG PS								
0			1				1	
1			1.04	0.786			1.52	0.000
≥2			0.81	0.491			1.86	0.000

BT-RT = brachytherapy combined with EBRT; cT category = clinical tumor category; EBRT = external beam radiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; HYPO-RT = hypofractionated radiotherapy; OM = overall mortality, PCSM = prostate cancer–specific mortality, PSA = prostate-specific antigen; RP = radical prostatectomy.

Similar to PCSM, the 10-yr OM rates were lowest in the RP and BT-RT groups, and highest among patients treated with EBRT 70–<74 Gy (Table 2, Supplementary Table 2 and Fig. 2). Adjusted for covariates, patients receiving EBRT 70–78 Gy had an increased risk of overall death after 5 and 10 yrs compared with RP patients (Table 3 and Supplementary Table 3). Increasing age, ECOG PS and prior cancer, along with increasing GS, PSA levels, and locally advanced disease, increased the risk of overall death (Table 3).

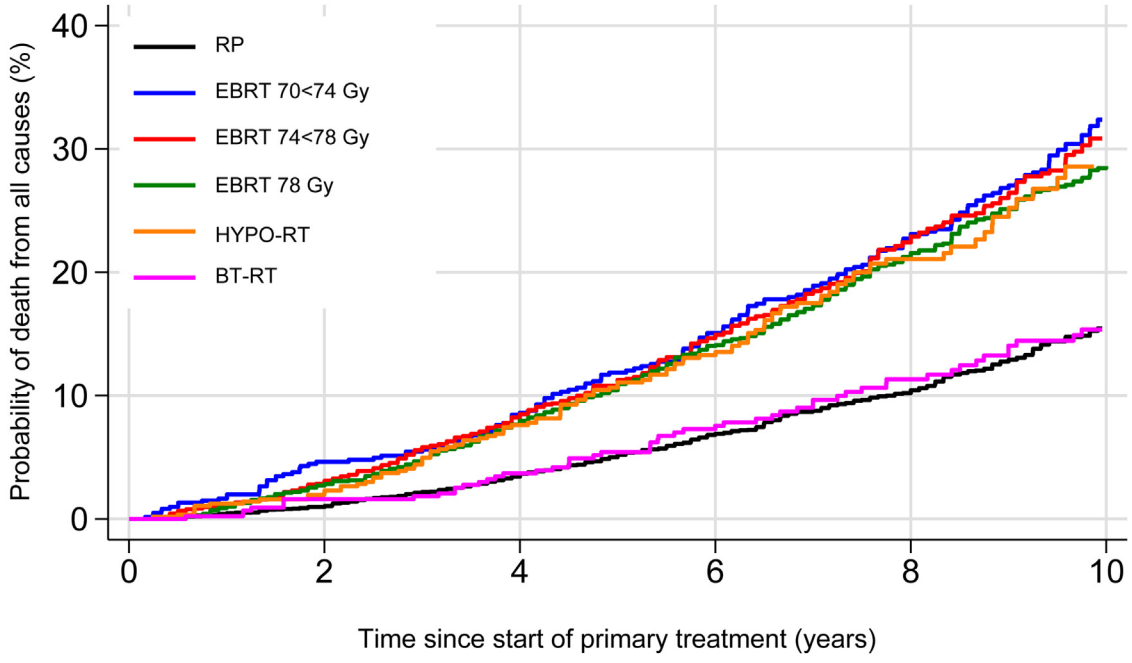
4. Discussion

In this population-based historical prospective cohort study, comprising patients with high-risk PCa only, primary treatment with EBRT 70–<74 Gy was associated with increased 10-yr PCSM and EBRT 70–78 Gy with increased 10-yr OM, compared with RP. The risk of death due to PCa was lowest in men treated with BT-RT. The survival differences emerged beyond 5 yrs of follow-up.

Definitions of high-risk PCa comprise heterogeneous subgroups of patients with multiple combinations of prognostic clinical parameters (PSA, GS, and cT category) influencing selection and outcomes of treatment. In this study, the proportion of patients with extraprostatic tumors ranged from 32% in the RP group to 56% in the BT-RT group (the majority having cT3a tumors in both groups). Crude survival rates according to treatment are therefore of limited value in comparative effectiveness studies, even in patients within the same risk category. Although the availability is limited in public registries, adjustments for clinical covariates impact the associations between curative treatment modality and mortality, in most cases by attenuating survival differences, and more so when analyzing PCSM compared with OM.

In the absence of randomized evidence, registry-based studies have previously demonstrated survival benefits with RP over RT in patients with high-risk PCa. However, in the current study, providing details on RT modalities, the increase in adjusted HR for PCa death with RT compared with RP was limited to patients receiving EBRT doses 70–<74 Gy. Similarly, dose-escalated RT (≥74 Gy) has been associated with lower 10-yr PCSM and OM in high-risk patients than with lower RT doses [14–16]. Our findings of reduced PCSM in men treated with BT-RT compared with those treated with RP, are in agreement with the conclusion of a recent systematic review by Greenberger et al [7]. Moreover, in line with our findings, Kishan et al [13] demonstrated significantly better PCSM with BT-RT than with EBRT and RP in patients with GS 9–10 tumors. In the present study, a survival benefit with BT-RT compared with RP in men with locally advanced disease approached the level of significance (p = 0.059).

There was no difference in OM between the RP and BT-RT groups, and we can only speculate whether unrecognized



Numbers at risk						
RP	4299	4254	4021	2727	1588	823
EBRT 70<74 Gy	605	576	550	471	401	261
EBRT 74<78 Gy	1650	1600	1395	952	494	246
EBRT 78 Gy	1692	1646	1479	1093	746	433
HYPO-RT	565	553	514	354	193	66
BT-RT	434	427	408	333	244	169

Fig. 2 – Overall mortality according to treatment modality in men with high-risk prostate cancer. BT-RT = external beam radiotherapy combined with brachytherapy; EBRT = external beam radiotherapy; HYPO-RT = hypofractionated radiotherapy; RP = radical prostatectomy.

residual confounding by comorbidity not covered by ECOG performance status affects RT patients more than RP patients. This may also contribute to the increased risk of all-cause death in patients receiving EBRT compared with those treated with RP.

With adjustments for pretreatment clinical factors, RP followed by aRT was not associated with a reduction in PCSM compared with RP alone in this dataset; however, patients with more aggressive tumors, based on pathological examination of the RP specimen, would have been more likely to receive aRT in the study period. Excluding the aRT patients from analysis did not significantly alter the treatment-related HRs for 10-yr PCSM (data not shown).

Our findings justify already well-established trends and contemporary guidelines defining RP, dose-escalated EBRT ($\geq$74 Gy), and BT-RT with long-term ADT as valid curative treatment options for men with high-risk PCa [2]. Whether modernly hypofractionated, in particular ultrafractionated, RT is non-inferior to curative treatment modalities in relation to 10-yr PCSM, is so far unknown [25]. Although results are significant in large cohorts, during counselling of individual patients, any survival benefit of a treatment in a population must be balanced against the risk of toxicity and altered health-related quality of life [8].

Besides the limitations related to use of registry data for the purpose of comparing treatments, there are other limitations to this study. First, regarding patient characteristics, we did not have detailed information on comorbidity and socioeconomic status, nor did we have complete data of clinical N category. The performance of pelvic lymph node dissection or pelvic lymph node–directed RT was not documented reliably in this study, although neither procedure has been proved to increase survival in PCa patients [26]. Considering long-term (neo-)adjuvant ADT reducing disease-specific mortality and OM in RT patients with a high risk of recurrence [7,15,19,27], complete information on ADT was unavailable. Further, no information on disease progression and second-line PCa treatments was available in the CRN. Finally, residual confounding in the treatment groups, even with adjustments for all parameters available in the registry, and the potential excess registration of death from PCa in old patients, must be acknowledged [28].

5. Conclusions

This population-based cohort study including men with high-risk PCa demonstrates increased PCSM and OM with nonescalated dose RT ($<$74 Gy) and suggests decreased PCSM with BT-RT compared with RP.

To obtain high-level comparative evidence on mortality outcomes in patients with high-risk PCa undergoing contemporary multimodal curative therapies, including RP and BT-RT, studies documenting details of RP and RT techniques, (neo-)adjuvant systemic treatments and long-term follow-up are called for.

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

Study concept and design: Aas, Fosså, Myklebust.
Acquisition of data: Aas, Myklebust.
Analysis and interpretation of data: Aas, Berge, Fosså, Myklebust.
Drafting of the manuscript: Aas, Fosså, Myklebust.
Critical revision of the manuscript for important intellectual content: Aas, Berge, Fosså, Myklebust.
Statistical analysis: Aas, Myklebust.
Obtaining funding: Aas, Fosså.
Administrative, technical, or material support: Aas, Myklebust.
Supervision: Aas, Fosså, Myklebust.
Other: None.

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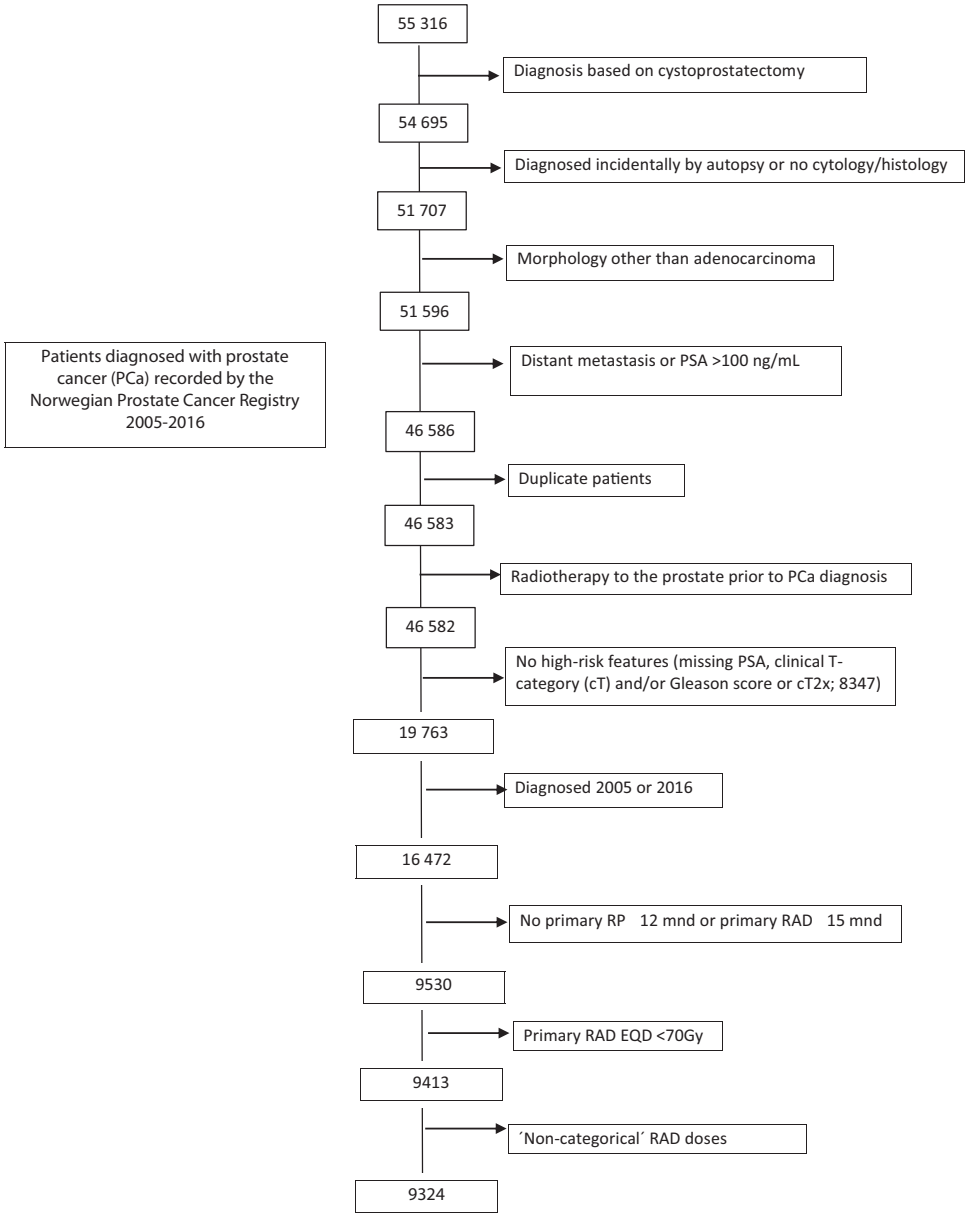
***Data sharing*:** The data that support the findings of this study are available from the Cancer Registry of Norway. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the Cancer Registry of Norway.

CRediT authorship contribution statement

Kirsti Aas: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Viktor Berge:** Writing - review & editing. **Tor Åge Myklebust:** Methodology, Formal analysis, Investigation, Writing - review & editing, Visualization. **Sophie Dorothea Fosså:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - review & editing.

Appendix A. Patient selection



Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2021.01.011.

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