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ORIGINAL ARTICLE

Risk of prostate cancer death after radical radiotherapy with neoadjuvant and adjuvant therapy with bicalutamide or gonadotropin-releasing hormone agonists

Tiago M. Bonde[a], Hans Garmo[b], Pär Stattin[b], Per Nilsson[c], Adalsteinn Gunnlaugsson[c], Daniela Swanberg[d] and David Robinson[e]

[a]Department of Urology, Ryhov Hospital, Jönköping, Sweden; [b]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; [c]Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund University, Sweden; [d]Department of Surgery, Höglandssjukhuset, Eksjö, Sweden; [e]Department of Urology, Höglandssjukhuset, Eksjö, Sweden

ABSTRACT

Background: Oncological outcome after radical radiotherapy (RRT) combined with neoadjuvant and adjuvant androgen suppression therapy (AST) may differ according to type of AST. The aim of this nationwide register-based study was to investigate risk of prostate cancer (Pca) death after different neoadjuvant and adjuvant ASTs; (i) bicalutamide, (ii) gonadotropin-releasing hormone agonists (GnRH) or (iii) combined bicalutamide and GnRH (CAB), together with RRT.

Materials and Methods: Data for 6882 men diagnosed with high-risk Pca between 2007 and 2020 and treated with primary RRT was retrieved from Prostate Cancer data Base Sweden (PCBaSe) 5.0. Time to Pca death according to type of neoadjuvant and adjuvant AST was assessed by use of Kaplan–Meier plots and Cox proportional hazard models adjusted for putative confounders.

Results: Data were stratified by RRT type since the effect of AST in risk of Pca death differed according to type of RRT. Compared with the reference *RRT* combined with neoadjuvant CAB/adjuvant GnRH, risk of Pca death for men treated with CAB/bicalutamide and conventionally fractionated external beam radiotherapy (CF-EBRT) was hazard ratio (HR) 0.73 (95% CI: 0.50–1.04), hypofractionated EBRT (HF-EBRT), HR 1.35 (95% CI: 0.65–2.81) and EBRT with high dose rate brachytherapy (EBRT-HDRBT), HR 0.85 (95% CI: 0.37–1.95). Risk of Pca death for men treated with bicalutamide/bicalutamide and: (i) CF-EBRT was HR 2.35 (95% CI: 1.42–3.90), (ii) HF-EBRT, HR 0.70 (95% CI: 0.26–1.85), (iii) HF-EBRT, HR 4.07 (95% CI: 1.88–8.77) vs the reference.

Conclusion: In this observational study, risk of Pca death between men receiving different combinations of AST varied according to RRT type. No difference was found in risk of Pca death for men treated with bicalutamide or GnRH as adjuvant therapy to RRT following neoadjuvant CAB. Risk of Pca death was increased for men with monotherapy neo-/adjuvant bicalutamide in combination with CF-EBRT or EBRT-HDRBT.

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Prostate neoplasms; androgen antagonists; gonadotropin-releasing hormone; radiotherapy; prognosis; mortality

Background

In men with localized high-risk and locally advanced prostate cancer (Pca), the addition of neoadjuvant and adjuvant androgen suppression therapy (AST) to radical radiotherapy (RRT) improves biochemical progression-free survival, Pca-specific survival, and overall survival [1–4]. In most trials [4], AST was achieved by use of gonadotropin-releasing hormone agonists (GnRH). The antiandrogen bicalutamide is, however, sometimes preferred in clinical praxis in Scandinavia due to a lower incidence of cardiovascular events in comparison to GnRH [5–9]. It remains unclear if adjuvant bicalutamide is as effective as GnRH in the reduction of risk of Pca death.

Both European and Swedish guidelines recommend GnRH as neoadjuvant therapy before start of RRT. However, while European guidelines recommend adjuvant GnRH after RRT, the Swedish guidelines recommend adjuvant bicalutamide as first choice to all men with high-risk Pca [10,11]. The aim of our study was to compare risk of Pca death in men with high-risk Pca treated with RRT and different types of neoadjuvant and adjuvant AST.

Materials and methods

Setting

The National Prostate Cancer Register of Sweden (NPCR) [12] contains data on cancer characteristics (local clinical T stage, N stage, M stage, Gleason Score, proportion of positive core biopsies, prostate-specific antigen at date of diagnosis—PSA, type of RRT, type and duration of neoadjuvant and adjuvant AST) and given primary treatments for 98% of all Pca cases in Sweden since 1998 [13]. Data on RRT treatments from 2007 onwards are reported in NPCR and includes: intention

CONTACT Tiago M. Bonde tiagobonde.miranda@gmail.com Department of Urology, Ryhov Hospital, Jönköping, Sweden
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of treatment, radiation technique, start- and end-date of RRT, number of fractions and dose per fraction, total dose, use of intraprostatic markers for external beam radiotherapy and intended type and duration of neoadjuvant and adjuvant AST.

Prostate Cancer data Base Sweden (PCBaSe) 5 [14,15] was created by linking NPCR with national health care registries and demographic databases including [12], the Swedish National Patient Registry [16], the Cause of Death Registry [17,18], the Prescribed Drug Registry [19] and the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) [20].

Comorbidity was assessed through use of in-patient discharge diagnostic codes available in The National Patient Registry [21]. Data on civil status and educational level was retrieved from LISA.

Data on use of AST were retrieved from NPCR where intended type and duration of AST is registered. Together with data on filled prescriptions from the Prescribed Drug Registry and defined daily dose (DDD) for bicalutamide, GnRH and CAB, we could determine the degree of misclassification relative to AST-use. An analysis based on intention to treat followed by determination of grade of misclassification of AST was preferred in order to avoid immortal time bias [22].

Study population

Men were included in the study if they (i) were diagnosed with high-risk localized Pca according to National Comprehensive Cancer Network guidelines [23] (PSA $>$ 20 ng/mL or Gleason score $>$ 7 or local clinical T stage T3 and N0/NX and M0 on bone scintigraphy) between 2007 (when registration of hormone treatment in NPCR started) and 2020, (ii) received primary radical conventionally fractionated ($\approx$ 2.0 Gy/fraction, total dose $\geq$ 74 Gy) external beam radiotherapy (CF-EBRT), radical hypofractionated ($\geq$ 2.40 Gy/fraction) external beam radiotherapy (HF-EBRT), or radical external beam radiotherapy combined with high-dose rate brachytherapy (EBRT-HDRBT) administered within one year from date of Pca diagnosis, (iii) were registered in NPCR as users of neoadjuvant and adjuvant hormonal therapy with bicalutamide (ATC code: L02BB03), GnRH (L02AE01-5) or both in case of combined androgen blockade (CAB). No additional data were available in NPCR regarding the selection of men for different combinations of AST.

The event of interest was Pca death (ICD: C61) as recorded in the Cause of Death Registry. Follow-up started at date of initiation of RRT and ended at date of Pca death, date of other death, or December 2020 when the studied ended, whichever came first.

Statistical analysis

Likelihood ratio tests (crude and adjusted) were used to test the null-hypothesis of no interaction between neo-/adjuvant treatments (CAB/bicalutamide, CAB/GnRH, CAB/CAB, GnRH/bicalutamide, GnRH/GnRH and bicalutamide/bicalutamide) and type of RRT, with Pca death as event. The model was adjusted for age at start of RRT, local clinical T stage, N stage, Gleason score, PSA at diagnosis, percentage of positive cores at biopsy, year of RRT, duration of adjuvant treatment, Charlson Comorbidity Index (CCI), educational level, and civil status.

In a further analysis, stratified by type of RRT, univariable Cox models were used to determine hazard ratios (HR) for risk of Pca death for men receiving different combinations of neo-/adjuvant treatments. Multivariable analyses were performed including Pca characteristics and socioeconomical variables.

A misclassification analysis was performed by determining the proportion of intended neo-/adjuvant time (as registered on NPCR) covered by filled prescriptions for bicalutamide, GnRH and CAB on Prescribed Drug Registry.

The neoadjuvant period started 3 months before initiation of RRT and lasted 6 months. The adjuvant period started 3 months after the initiation of RRT and lasted up to 6 months, 6 to 18 months or more than 18 months.

Data from a preliminary analysis on risk of Pca death for men under different types of AST showed wide confidence intervals. Moreover, a separate analysis revealed misclassification of bicalutamide among adjuvant CAB-users. Therefore, and given the similar biological effect of GnRH and CAB, both groups were merged in the main analysis. The groups [(CAB/GnRH) (CAB/CAB) (GnRH/GnRH)] were merged into *merged CAB/GnRH* (mCAB/GnRH) and the groups [(CAB/bicalutamide) and (GnRH/bicalutamide)] into *merged CAB/bicalutamide* (mCAB/bicalutamide). The group bicalutamide/bicalutamide remained unaltered.

The Research Ethics Authority in Uppsala approved of this study (Diary number: 2022 – 02079-02).

Results

Baseline characteristics for 6 882 men with high-risk Pca according to type of RRT are presented in Table 1. Median follow-up was 4 years for men treated with CF-EBRT (quartile 1 [Q1]: 2.3, quartile 3 [Q3]: 9.9), 3 years for men treated with HF-EBRT (Q1: 1.1, Q3: 5.4) and 5 years for men treated with EBRT-HDRBT (Q1: 2.2, Q3: 7.5).

There were 3 335 (48%) men who received CF-EBRT, 1 884 (27%) who received HF-EBRT and 1 663 (24%) EBRT-HDRBT. Within each RRT group, treatment with CAB as neoadjuvant and bicalutamide as adjuvant therapy was the most common combination.

Men in EBRT-HDRBT group were younger (median age 68 years) and had lower comorbidity (CCI 0: 82%) than men in CF-EBRT (71 years, CCI 0: 75%) and HF-EBRT groups (72 years, CCI 0: 74%).

Men receiving EBRT-HDRBT had lower median PSA at diagnosis, lower proportion of positive biopsies and lower percentage of positive biopsy cores than men in the CF-EBRT and HF-EBRT groups (Table 1). There was no difference in the proportion of different local clinical T stage or Gleason scores between men treated with EBRT-HDRBT, CF-EBRT or HF-EBRT.

Table 1. Characteristics for men in Prostate Cancer data Base Sweden 5,0 with localized high-risk prostate cancer treated with radical radiotherapy and neoadjuvant and adjuvant hormonal therapy according to type of radical radiotherapy.

	CF-EBRT ($n = 3\ 335$)		HF-EBRT ($n = 1\ 884$)		EBRT-HDRBT ($n = 1\ 663$)		Total ($n = 6\ 882$)	
Age, *n* (%)								
≤ 65 years	731	(22)	343	(18)	533	(32)	1607	(23)
66–70 years	888	(27)	412	(22)	519	(31)	1819	(26)
71–75 years	1056	(32)	590	(31)	462	(28)	2108	(31)
> 75 years	660	(20)	539	(29)	149	(9)	1348	(20)
Median age (IQR)	71 (Q1:66, Q3:75)	–	72 (Q1:67, Q3:76)	–	68 (Q1:64, Q3:72)	–		
Year of diagnosis, *n* (%)								
2007–2010	716	(22)	169	(9)	344	(21)	1229	(18)
2011–2013	691	(21)	365	(19)	417	(25)	1473	(21)
2014–2015	666	(20)	349	(19)	322	(19)	1337	(19)
2016–2017	825	(25)	415	(22)	325	(20)	1565	(23)
2018–2020	437	(13)	586	(31)	255	(15)	1278	(19)
Local clinical T stage, *n* (%)								
T1	794	(24)	473	(25)	386	(23)	1653	(24)
T2	1304	(39)	775	(41)	647	(39)	2726	(40)
T3	1237	(37)	636	(34)	630	(38)	2503	(36)
N stage, *n* (%)								
N0	2473	(74)	1329	(71)	1120	(67)	4922	(72)
NX	862	(26)	555	(30)	543	(33)	1960	(29)
Gleason grade group, *n* (%)								
Gleason score ≤ 6	114	(3)	47	(3)	60	(4)	221	(3)
Gleason score = 7 (3 + 4)	504	(15)	273	(15)	245	(15)	1022	(15)
Gleason score = 7 (4 + 3)	595	(18)	323	(17)	255	(15)	1173	(17)
Gleason score = 8	924	(28)	526	(28)	501	(30)	1951	(28)
Gleason score = 9 or 10	1198	(36)	715	(38)	602	(36)	2515	(37)
Percentage of positive cores, *n* (%)								
0–25	380	(11)	214	(11)	177	(11)	771	(11)
26–50	890	(27)	400	(21)	488	(29)	1778	(26)
51–75	591	(18)	320	(17)	314	(19)	1225	(18)
76–100	1262	(38)	750	(40)	579	(35)	2591	(38)
Missing	212	(6)	200	(11)	105	(6)	517	(8)
PSA ng/mL	19.0		21.0		15.0		–	
Median (Q1-Q3)	(9.0–34.0)		(9.5–38.0)		(7.4–29.3)			
PSA, *n* (%)								
0–9 ng/mL	955	(29)	499	(27)	608	(37)	2062	(30)
10–19,9 ng/mL	733	(22)	396	(21)	346	(21)	1475	(21)
20–49,9 ng/mL	1196	(36)	660	(35)	544	(33)	2400	(35)
50–99,9 ng/mL	343	(10)	225	(12)	144	(9)	712	(10)
≥ 100 ng/mL	108	(3)	104	(6)	21	(1)	233	(3)
Hormonal treatment (neoadjuvant//adjuvant), (%)								
Combined androgen blockade/bicalutamide	1362	(41)	1185	(63)	676	(41)	3223	(47)
Combined androgen blockade/GnRH	81	(2)	97	(5)	56	(3)	234	(3)
Combined androgen blockade/combined androgen blockade	100	(3)	236	(13)	259	(16)	595	(9)
GnRH/ bicalutamide	1041	(31)	86	(5)	216	(13)	1343	(20)
GnRH/ GnRH	615	(18)	121	(6)	182	(11)	918	(13)
Bicalutamide/bicalutamide	136	(4)	159	(8)	274	(17)	569	(8)
Duration of adjuvant treatment, *n* (%)								
≤ 6 months	810	(24)	321	(17)	290	(17)	1421	(21)
6–18 months	547	(16)	141	(8)	108	(7)	796	(12)
> 18 months	1814	(54)	1348	(72)	1188	(71)	4350	(63)
Missing	164	(5)	74	(4)	77	(5)	315	(5)
Radiotherapy year, *n* (%)								
2007–2010	608	(18)	111	(6)	261	(16)	980	(14)
2011–2013	666	(20)	344	(18)	437	(26)	1447	(21)
2014–2015	651	(20)	338	(18)	321	(19)	1310	(19)
2016–2017	769	(23)	386	(21)	318	(19)	1473	(21)
2018–2020	641	(19)	705	(37)	326	(20)	1672	(24)
Educational level, *n* (%)								
Low	1172	(35)	574	(31)	473	(28)	2219	(32)
Intermediate	1383	(42)	796	(42)	699	(42)	2878	(42)
High	780	(23)	514	(27)	491	(30)	1785	(26)
Civil status*, *n* (%)								
Married	2111	(63)	1211	(64)	1077	(65)	4399	(64)
Widower	219	(7)	127	(7)	89	(5)	435	(6)
Single	1005	(30)	546	(29)	497	(30)	2048	(30)
Charlson comorbidity index **, *n* (%)								
0	2502	(75)	1394	(74)	1361	(82)	5257	(76)
1	511	(15)	279	(15)	183	(11)	973	(14)
2	207	(6)	120	(6)	75	(5)	402	(6)
3	76	(2)	69	(4)	32	(2)	177	(3)
4+	39	(1)	22	(1)	12	(1)	73	(1)

*Civil status and education from Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA).

**Charlson comorbidity index based on discharge diagnostic codes in the Swedish Patient Registry.

Abbreviations: CF-EBRT: conventionally fractionated external beam radiotherapy; EBRT-HDRBT external beam radiotherapy combined with high-dose brachytherapy boost; Gy: grey; HF-EBRT: hypofractionated external beam radiotherapy; Q: quartile.

Fractionation schedules, that is, number of fractions x dose per fraction = total dose, and the percentage of men receiving each specific treatment schedule:

CF-EBRT: 39x2,0 = 78,0 Gy (85%), 40x2,0 = 80,0 Gy (8%), 35x2,2 = 77,0 Gy (3%), others (4%).

HF-EBRT: 29x2,5 = 72,5 Gy (44%), 22x3,0 = 66,0 Gy (34%), 20x3,0 = 60,0 Gy (8%), 7x6,1 = 42,7 Gy (5%), others (9%).

EBRT-HDRBT: 25x2,0 + 2x10,0 Gy (75%), 14x3,0 + 1x14,5 Gy (14%), 13x3,0 + 1x15,0 Gy (3%), others (8%).

Table 2. Misclassification of androgen suppression therapy based on intended use and filled prescriptions for bicalutamide, GnRH and combined androgen blockade, data from the National Prostate Cancer Register and the Prescribed Drug Registry.

	Bicalutamide		GnRH	
	Proportion of intended AST-time covered by filled prescriptions	Percentage of non-users	Proportion of intended AST-time covered by filled prescriptions	Percentage of non-users
Intended neoadjuvant treatment according to NPCR*				
Bicalutamide	1.02	1%	0.10	87%
GnRH	0.27	29%	0.90	8%
Combined androgen blockade	0.89	2%	0.81	9%
Intended adjuvant treatment according to NPCR**				
Bicalutamide	0.97	3%	0.09	76%
GnRH	0.10	82%	0.66	18%
Combined androgen blockade	0.25	36%	0.46	24%

*Neoadjuvant period ranged from 90 days before start of radiotherapy to 90 days after start of radiotherapy.
**Adjuvant period ranged from 90 days after start of radiotherapy to $\geq$ 270, $\geq$ 455 or $\geq$ 540 days after start of radiotherapy.
Degree of misclassification was assessed by determining the period of neoadjuvant and adjuvant time covered by filled prescriptions for bicalutamide, GnRH and combined androgen blockade. A proportion of intended AST-time >1 indicates that more than the necessary prescriptions to cover the intended neo-/adjuvant period were filled. Proportion of non-users refers to men supposed to get a type of hormonal treatment who failed to fill out prescriptions for that treatment. Among men for whom adjuvant CAB was intended (according to NPCR) there was a proportion of non-users of bicalutamide of 36% indicating misclassification of CAB-use.

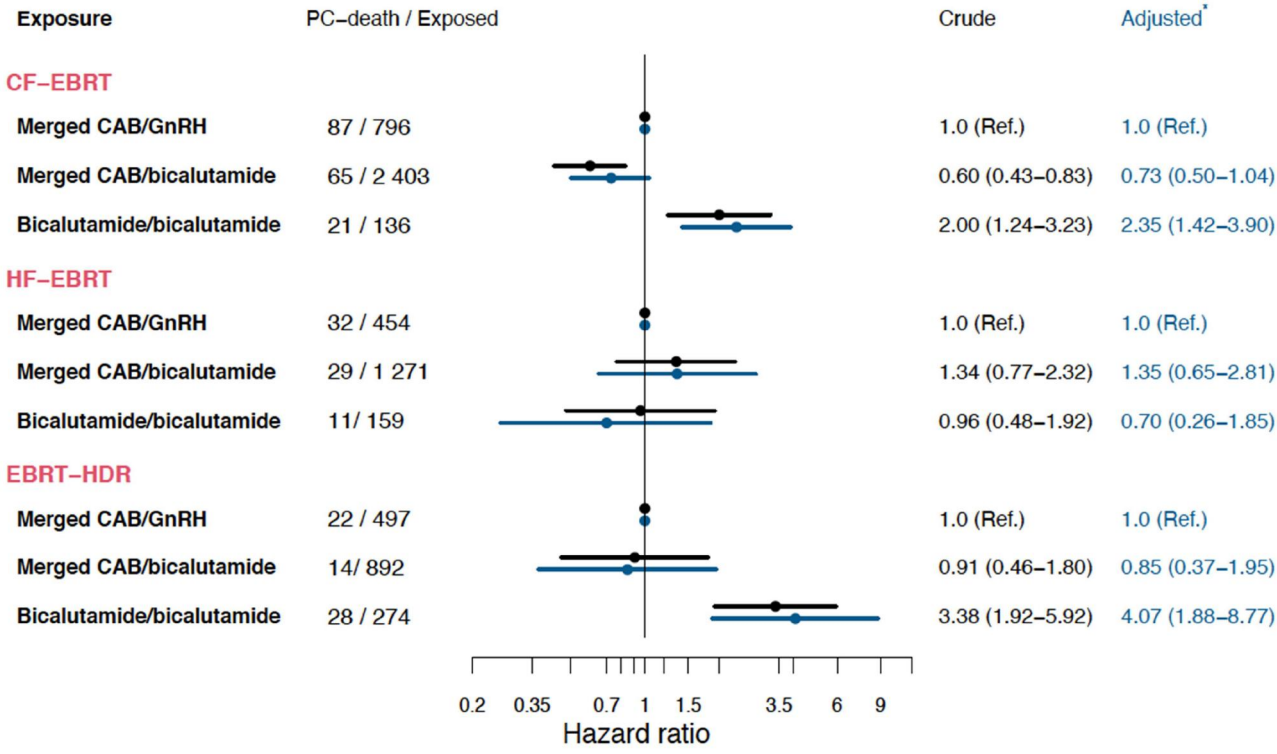

Figure 1. Risk of prostate cancer death for men in Prostate Cancer data Base Sweden 5 with localized high-risk prostate cancer treated with radical radiotherapy according to type of radiotherapy and neoadjuvant and adjuvant therapy (merged androgen suppression therapy groups).
* Model including age at date of radiotherapy, local clinical T stage, N stage, Gleason score, PSA at diagnosis, percentage of positive cores, year of radiotherapy, duration of adjuvant treatment, CCI, educational level and civil status.
Abbreviations: CF-EBRT: conventionally fractionated external beam radiotherapy;EBRT-HDRBT external beam radiotherapy combined with high-dose brachytherapy boost; HF-EBRT: hypofractionated external beam radiotherapy;
Hazard ratio **greater** than one favors reference group. The groups [(CAB/GnRH) (CAB/CAB) (GnRH/GnRH)] were merged into *merged CAB/GnRH* which is the reference group. The groups [(CAB/bicalutamide) (GnRH/bicalutamide)] were merged into *merged CAB/bicalutamide*. The group bicalutamide/bicalutamide remained unaltered.

In an interaction test the association between neo-/adjuvant therapy on risk of Pca death differed according to RRT type (crude p-value: 0.0025, adjusted *p*-value: 0.0007). Consequently, we analyzed risk of Pca death according to neo-/adjuvant therapy for each RRT type separately. Despite a cohort of almost 7 000 men, this risk analysis presented with wide confidence intervals (Supplementary Figure 1). Due to observed misclassification of adjuvant GnRH in the CAB group (Table 2), we merged CAB and GnRH-groups in the main analysis (Figure 1).

In the main risk analysis mCAB/GnRH was used as reference therapy. The association between neo-/adjuvant therapy on risk of Pca death still differed according to RRT type with the merged groups (crude *p*-value: 0.008, adjusted *p*-value: 0.006) and therefore results were presented for each type of RRT separately.

For men treated with CF-EBRT, there was no increased risk of Pca death for mCAB/bicalutamide (HR: 0.73, 95% CI: 0.50-1.04) versus the reference mCAB/GnRH. Risk of Pca death was increased for men receiving bicalutamide/bicalutamide (HR: 2.35, 95% CI: 1.42–3.90) versus the reference mCAB/GnRH.

For men treated with HF-EBRT, there was no increased risk of Pca death for mCAB/bicalutamide (HR: 1.35, 95% CI: 0.65–2.81) or bicalutamide/bicalutamide (HR: 0.70, 95% CI: 0.26–1.85) versus the reference mCAB/GnRH.

For men treated with EBRT-HDRBT, there was no increased risk of Pca death for mCAB/bicalutamide (HR: 0.85, 95% CI: 0.37–1.95) versus the reference mCAB/GnRH. Risk of Pca death was increased for men receiving bicalutamide/bicalutamide (HR: 4.07, 95% CI: 1.88–8.77) versus the reference mCAB/GnRH.

Discussion

In this population-based register study of almost 7 000 men, there was no difference in risk of Pca death between men with high-risk Pca treated with RRT together with mCAB/GnRH vs mCAB/bicalutamid. Monotherapy with neo-/adjuvant bicalutamide associated with up to fourfold increased risk of Pca death versus mCAB/GnRH among men treated CF-EBRT or EBRT-HDRBT.

A few limitations to our study should be mentioned. First, this was an observational study prone to selection bias. No additional information was available regarding the selection of patients to different forms of AST but a multivariate analysis with adjustments for Pca characteristics and socioeconomic factors was performed in order to mitigate possible selection bias. Secondly, the short follow-up time in our study but since we only included men with high-risk Pca we still had a substantial number of events. It is also worth noting the verified misclassification of adjuvant CAB. About 40% of men with intended adjuvant CAB in NPCR did not fill out prescriptions for bicalutamide. For that reason, and due to similar biological activity, the groups CAB and GnRH were merged in the risk analysis.

Strengths of our study include the nationwide based study group encompassing all men treated at all hospitals in Sweden whereas previous studies included less than four hundred men [24,25]. The strength of a nationwide register-based observational study is that it includes all men who meet inclusion criteria so that it mirrors men met in clinical practice. In contrast, men in RCTs are younger and have less comorbidities than men treated in clinical practice [26]. Other strengths include the high quality of data in NPCR and other national health care registries [13,17], as well as the high number of study men with high-risk disease and the inclusion of several forms of RRT which allowed for a stratified analysis.

To the best of our knowledge, this is the first large study comparing risk of Pca death in men with high-risk Pca receiving combinations of neo-/adjuvant GnRH versus bicalutamide in addition to RRT. Available data come from small single-center retrospective studies on biochemical relapse-free survival (bRFS) that was used as proxy for Pca death [24,25]. In an analysis of 318 men with intermediate and high-risk Pca similar 5-year bRFS was found for GnRH/GnRH and bicalutamide/bicalutamide, 86% versus 88% [25]. The 5-year overall survival was 97% both for men treated with GnRH and bicalutamide ($p = 0.410$) and notably bRFS was assessed for all types of RRT combined (80% HF-EBRT, 20% CF-EBRT). In our study, the effect of neo-/adjuvant treatment on risk of Pca death differed between RRT type. Men in the HF-EBRT group particularly stood out regarding risk of Pca death when compared with men in the CF-EBRT and EBRT-HDRBT groups. We speculate the heterogeneity of radiation therapy regimens administered to men in the HF-EBRT might have played a role in this.

For men in the HF-EBRT group, we observed no difference in risk of Pca death for those treated with adjuvant bicalutamide vs GnRH. This data is in line with the reported results by Buwenge et al. which included 254 men treated with HF-EBRT [25]. For men who received CF-EBRT and EBRT-HDRBT, we observed an increased risk of Pca death for those who received bicalutamide/bicalutamide versus mCAB/GnRH. Even though bicalutamide/bicalutamide is not recommended for men with high-risk Pca in combination with RRT almost 600 men in our study had received this treatment. We found no significant difference in risk for Pca death between men treated with CAB/bicalutamide vs CAB/GnRH in three RRT groups.

Data from a randomized trial with 802 participants comparing risk of Pca death between men with locally advanced Pca who received no, 3, or 6 months of neoadjuvant and concurrent CAB in addition to CF-EBRT showed a decreased risk of Pca death by 50% for men treated for 6 months compared to men who did not receive neoadjuvant therapy [3]. CAB confers a stronger testosterone suppression than bicalutamide monotherapy so neoadjuvant CAB may sensitize prostate cancer cells better for radiotherapy than bicalutamide. This could be why we found CAB to be the best neoadjuvant therapy. By far the strongest risk for Pca death was experienced by men who received bicalutamide as neoadjuvant therapy in our study and since a neoadjuvant therapy including GnRH (either GnRH alone or CAB) confers testosterone suppression we speculate that choice of neoadjuvant treatment is the most important decision regarding the combination of AST with RRT.

As stated above, our results showed that risk of Pca death according to AST differed between type of RRT. This is surprising given that data from a multicenter phase 3 trial showed no difference in time to biochemical and clinical failure for men with localized Pca who received CF-EBRT vs HF-EBRT, combined with GnRH or bicalutamide alone [27]. A biological mechanism as an explanation for these differences

is implausible and we speculate that the differences between RRT types were due to remaining confounding despite the multivariate analysis.

Conclusion

Risk of Pca death was similar for men treated with radical radiotherapy (RRT) who received either bicalutamide or GnRH as adjuvant therapy following neoadjuvant CAB. Monotherapy with neo-/adjuvant bicalutamide in combination with RRT associated with increased risk of Pca death for men treated with CF-EBRT and EBRT-HDRBT.

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Disclosure statement

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ORCID

Per Nilsson http://orcid.org/0000-0002-7983-9778

Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available. The data are not publicly available due to restrictions, for example, their containing information that could compromise the privacy of research participants.

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