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ORIGINAL RESEARCH

Target trial emulation using new comorbidity indices provided risk estimates comparable to a randomized trial

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Abstract

Objectives: To quantify the ability of two new comorbidity indices to adjust for confounding, by benchmarking a target trial emulation against the randomized controlled trial (RCT) result.

Study Design and Setting: Observational study including 18,316 men from Prostate Cancer data Base Sweden 5.0, diagnosed with prostate cancer between 2008 and 2019 and treated with primary radical prostatectomy (RP, n = 14,379) or radiotherapy (RT, n = 3,937). The effect on adjusted risk of death from any cause after adjustment for comorbidity by use of two new comorbidity indices, the multidimensional diagnosis-based comorbidity index and the drug comorbidity index, were compared to adjustment for the Charlson comorbidity index (CCI).

Results: Risk of death was higher after RT than RP (hazard ratio [HR] = 1.94; 95% confidence interval [CI]: 1.70−2.21). The difference decreased when adjusting for age, cancer characteristics, and CCI (HR = 1.32, 95% CI: 1.06−1.66). Adjustment for the two new comorbidity indices further attenuated the difference (HR 1.14, 95% CI 0.91−1.44). Emulation of a hypothetical pragmatic trial where also older men with any type of baseline comorbidity were included, largely confirmed these results (HR 1.10; 95% CI 0.95−1.26).

Conclusion: Adjustment for comorbidity using two new indices provided comparable risk of death from any cause in line with results of a RCT. Similar results were seen in a broader study population, more representative of clinical practice.

Keywords: Confounding; Comorbidity; Target trial emulation; Prostate cancer; Mortality; Radical prostatectomy; Radiotherapy

1. Introduction

Accurate measures of comorbidity are essential for most epidemiological studies. The commonly used Charlson comorbidity index (CCI) is based on presence of a limited selection of disease codes [1−3]. We have previously demonstrated that a multidimensional diagnosis-based comorbidity index (MDCI) based on all codes in the International Classification of Diseases version 10 (ICD-10) diagnoses, which quantifies code occurrence, recency, frequency, and total duration of hospitalization with each ICD code, outperforms the CCI [2]. We have also developed a drug comorbidity index (DCI) based on the patient's history of prescribed drugs that also outperforms the CCI [3].

To quantify the added benefit of new comorbidity measures, observational data from clinical practice can be used to emulate an existing randomized controlled trial (RCT) that has compared interventions on the risk of death, and where both treatment decisions in routine clinical care and outcome are clearly influenced by the patient's burden of comorbidity. The effect estimates from the RCT are expected to be unbiased by comorbidity, and adjustment of the observational estimate can be benchmarked against these. If adjustment for the new comorbidity indices in such an observational setting produces estimates of treatment effectiveness closer to those obtained in RCTs, this would quantify the added value of these indices [4].

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What is new?

Key findings

- In an emulation of a target trial of men with localized prostate cancer, risk of death from all causes after radical prostatectomy and radiotherapy was compared. Risk estimates varied depending on which comorbidity indices that were adjusted for.

What this adds to what is known?

- After adjustment for two novel comorbidity indices, risk estimates were similar to those in the trial.

What is the implication and what should change now?

- Comprehensive information on comorbidity available in administrative health care registers should be used to reduce bias in observational studies on treatment effectiveness.

1.1. Aim of the study

The aim of this study was to illustrate how effective new comorbidity indices are to reduce confounding, by benchmarking a target trial emulation against the actual outcome of an RCT. The degree to which adjustment for these new indices can bring the effectiveness estimates in observational data toward the known efficacy estimates from the RCT illustrate their potential to reduce bias in practice.

2. Method

2.1. The ProtecT trial

In the ProtecT trial 1,643 men with localized prostate cancer were randomized to radical prostatectomy (RP), radiotherapy (RT), or active monitoring [5]. In an unblinded intention-to-treat analysis all-cause mortality after 10 years was 10.1 per 1,000 person-years (95% confidence interval [CI]: 7.8−13.2) after RP and 10.3 (95% CI: 7.9−13.4) after RT, with an adjusted hazard ratio (HR) of 1.00 (95% CI 0.68, 1.45). Only few cases of prostate cancer death were observed (HR 0.80, 95% CI 0.22, 2.99) (personal communication). When analyzed by received treatment, the risk of death was also similar between RP and RT. See Supplementary Materials for details.

The rationale for using ProtecT as a target trial is that men with localized prostate cancer and a high burden of comorbidity are more likely to be treated with RT than RP in clinical practice, and also have a higher risk of death. Comorbidity is, therefore, expected to introduce strong confounding when all-cause mortality is compared in an observational study. For treatment of localized prostate cancer, comorbidity has previously been shown to mainly affect all-cause risk of death with limited impact on prostate cancer mortality [6].

2.2. Emulation of the ProtecT trial

The fundamental assumption in our study is that there should no clinically meaningful impact of the choice between RT and RP on risk of death from any cause after 10 years of follow-up, if confounding from comorbidity can be effectively adjusted for. We emulated the ProtecT patient selection and analysis strategy (Supplementary Table 1) [5,7]. The assumed causal structure guided selection of covariates (Supplementary Figure 1).

Since the main objective is to study the effectiveness of control of confounding, we also emulate a more pragmatic trial than ProtecT, by removing restrictions on patient inclusion related to high age and baseline comorbidity (Supplementary Table 1). This would indicate the generalizability of our findings to this study population more representative of clinical practice where confounding from comorbidity is expected to be even greater.

We also assume (a) that participation in the ProtecT trial does not have a direct effect on mortality other than through treatment, that (b) treatment variation is irrelevant with respect to mortality, and (c) there is no interference between individuals [8]. See Supplementary Materials for details and justification. The Swedish Research Ethics Authority approved the study.

2.3. Data sources

Prostate Cancer data Base Sweden (PCBaSe) version 5 is a research database linking the National Prostate Cancer Register (NPCR) of Sweden with several other Swedish health care registers including the Patient Register, the Cancer Register, the Prescribed Drug Register and the Cause of Death Register as previously described [9].

The Patient Register includes information on all in-hospital care since 1987 and all out-patient specialist care since 2001. Diagnoses are coded according to ICD-10. The Prescribed Drug Register contains detailed information on all prescriptions dispensed in Sweden. This register includes filled prescriptions.

2.4. Characterization of prostate cancer

Prostate-specific antigen (PSA), tumor, node, and metastasis stage, Gleason score, prostate volume, total number of cores obtained at the diagnostic biopsy session, number of biopsy cores containing cancer, extent of cancer in millimeters, and mode of detection (health check-up or symptomatic [lower urinary tract symptoms or other]), were extracted from the NPCR. Date of treatment was defined as date for RP and date of start of RT.

2.5. Measures of comorbidity

2.5.1. The Charlson comorbidity index (CCI)

The CCI was calculated based on ICD-10 codes registered as a primary or secondary diagnosis in the National Patient Register during the 10-year period preceding the start of follow-up for mortality [10,11]. We excluded ICD-10 codes for prostate cancer (C61), and metastases (C77-80) if they were registered in conjunction with C61, in line with previous adaptations of CCI for cancer studies [12].

2.5.2. The drug comorbidity index (DCI)

The DCI was calculated based on Anatomical Therapeutic Chemical codes (five digits) identified in the Prescribed Drug Register during the 365-day period preceding the date of prostate cancer treatment initiation, using the method and weights originally derived for this index [3].

2.5.3. The multidimensional diagnosis-based comorbidity index (MDCI)

ICD-10 codes in the National Patient Register were extracted from a 10-year look-back period preceding the start of follow-up. Predictor variables were constructed to reflect occurrence, recency, and frequency of each code, as well as total duration of hospital admissions with each code. Those with a relevant predictive ability were included in the summary MDCI score [2].

2.6. Other covariates

Life expectancy was computed using age, the MDCI and the DCI using a modified model in line with [8]. Civil status (married or unmarried) and educational level (low [< 10 years], middle [10−12 years], or high [13+ years] were determined at date of treatment.

2.7. Follow-up and outcome

Follow-up started on date of treatment and ended on June 30, 2021 or at the date of death as registered in the Cause of Death Register.

2.8. Statistics

We estimated the 10-year risk of death from any cause, and corresponding absolute risk difference and HRs for time to death. These were obtained by estimating unadjusted survival using Kaplan-Meier curves and a Cox proportional hazards regression model. Propensity models were used to estimate the association between covariates and treatment. We used overlap weights to handle incomplete overlap of propensity score distributions and estimated adjusted survival curves and adjusted HRs [13,14]. Treatment is unconditioned, time-fixed, and therefore our procedure using baseline characteristics is appropriate [15,16]. The following baseline variables were included in the propensity models: age at treatment, year of treatment, PSA, prostate volume, Gleason sum, proportion of needle cores with cancer, T stage, bone imaging (yes/no), mode of detection of the cancer, civil status and educational level.

For each propensity model, we assessed discrimination and calibration by extracting the calibration curve, c-statistic and Brier score using the R package *CalibrationCurves*. Diagnostics of the weights was performed by comparing the standardized mean difference (SMD) between the treatment groups of each covariate. We computed percentile-based 95% CIs by use of bootstrapping (2,000 resamplings). See Supplementary Materials for details. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

3. Results

3.1. Emulation of the ProtecT trial

There were 18,316 men diagnosed with localized prostate cancer who fulfilled the inclusion criteria for the emulation of the ProtecT trial, out of which 14,379 (78.5%) underwent RP and 3,937 (22.5%) underwent RT (Fig. 1). Men treated with RP were somewhat younger than men treated with RT, with a median age of 63 years for RP and 65 years for RT. They also had more favorable prostate cancer characteristics (eg, median PSA 6 vs 7 ng/mL), and longer life expectancy (median 21 vs. 19 years) (Table 1). Compared to the ProtecT study population, age was similar but tumor characteristics were overall more favorable in ProtecT Supplementary Table 2).

Median follow-up was 7 years and there were 1,034 deaths within 10 years, most (82%) due to other causes than prostate cancer (Supplementary Table 3). Unadjusted risk of death was 7.9% (95% CI 7.3%−8.5%) after RP and 14.1% (95% CI 12.6%−15.6%) after RT (HR 1.94; 95% CI 1.70−2.21) (Table 2 and Figs. 2 and 3). The unadjusted prostate-cancer specific risk of death was 1.4% (95% CI 1.2%−1.7%) after RP and 3.4% (95% CI 2.6%−4.3%) after RT (HR 2.61; 95% CI 1.92−3.52) (Supplementary Figs. 2-3).

3.2. Adjusted estimates

Adjustment for age and cancer characteristics attenuated the difference but RT remained associated with an increased mortality risk (HR 1.41; 95% CI 1.13−1.77). This difference was only slightly attenuated when additionally adjusting for comorbidity with the CCI (HR 1.32; 95% CI 1.06−1.66), but

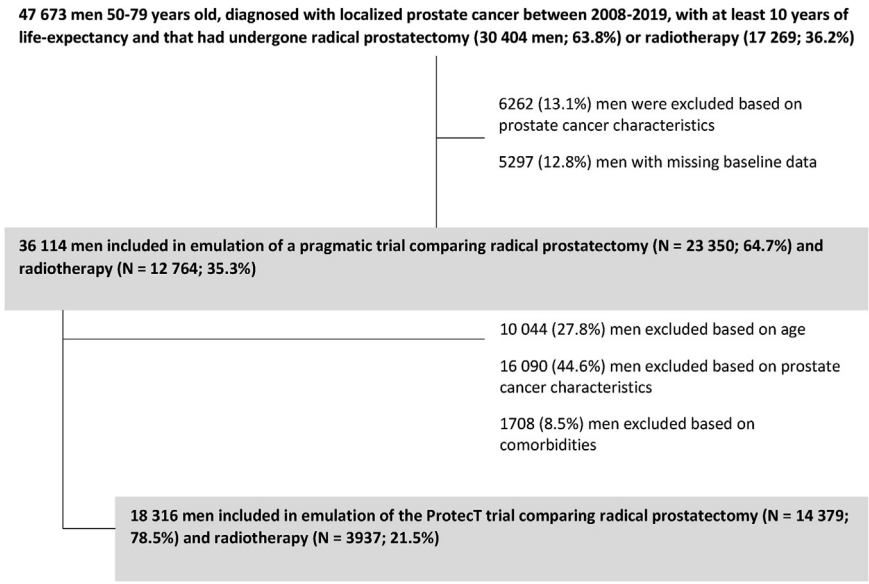

Figure 1. Study flow chart.

further attenuated when adjusting for MDCI and the DCI (HR 1.14; 95% CI 0.91−1.44) (Fig. 3). Adding CCI to MDCI and DCI did not materially change the estimate (data not shown), and a similar pattern was seen for the difference in absolute risk of death (Table 2).

The difference in net risk of prostate cancer mortality for RT compared to RP was attenuated when adjusting for age and cancer characteristics (HR 1.26; 95% CI 0.75−2.05), with somewhat smaller HRs when additionally adjusting for comorbidity (Supplementary Figs. 2-3).

3.3. Emulation of a more pragmatic trial

In the emulation of a hypothetical more pragmatic trial than ProtecT, 65% (23,350) underwent RP and 35% (12,764) RT within 1 year of diagnosis (Fig. 1). There were larger differences between the groups in terms of age, cancer characteristics and life expectancy compared to the emulation of the ProtecT trial (Supplementary Table 4).

Median follow-up time was 6 years with 2,858 deaths within 10 years, and 76% died from other causes than prostate cancer (Supplementary Table 3). Risk of death from any cause after 10 years was higher than in the emulation of the ProtecT trial, both for men that underwent RP (10.2%; 95% CI 9.6%−10.7%) and RT (21.2%; 95% CI 20.1−22.2), with an unadjusted HR of 2.21 (95% CI 2.05−2.38) (Table 2, Figs. 2-3). Net risk of death from prostate cancer after 10 years was lower, 2.1% (95% CI 1.9%−2.4%) and 6.7% (95% CI 6.0−7.4), respectively, with an unadjusted HR of 3.14 (95% CI 2.70−3.64) (Supplementary Figs. 2 and 3). After adjustment for MDCI and the DCI no substantial difference in risk of death from any cause remained (HR 1.10; 95% CI 0.95−1.26) (Fig. 3, Table 2).

3.4. Assessment of propensity models, scores, and weights

The propensity models performed similarly in terms of discrimination and calibration although the model with best discrimination and calibration included MDCI and DCI (c-index 0.75, Brier score 0.14) (Supplementary Fig. 4). There was some lack of overlap in the tails of the distributions of the propensity scores for RP and RT (Supplementary Fig. 5). Balance in baseline characteristics was achieved; the SMDs were large (up to 36%) for CCI, MDCI and DCI whenever these were excluded, yet $<6\%$ for CCI when MDCI and DCI were included but not CCI (Supplementary Table 5).

In the emulation of a hypothetical pragmatic trial the propensity models performed similarly as in the emulation of the ProtecT trial and produced propensity scores with somewhat more complete overlap with similar balance in baseline characteristics (Supplementary Fig. 4 and 5).

4. Discussion

4.1. Summary of findings

In this target trial emulation, adjustment for the new comorbidity indices MDCI and DCI provided mortality risk estimates comparable to the randomized ProtecT trial [5]. In contrast, in unadjusted analyses and when adjusting only for age, health-care and cancer characteristic and the CCI there was an increased risk of death after RT compared to RP in line with previous observational studies [17]. Thus, there was a relevant reduction of bias in an observational study of treatment effectiveness, when comorbidity is a strong confounder. The emulation of a hypothetical more

Table 1. Baseline characteristics of the study population in Prostate Cancer data Base Sweden (PCBaSe) 5 in the emulation of the ProtecT trial of primary radical prostatectomy vs radical radiotherapy.

	All (*N* = 18,316)	Prostatectomy (*N* = 14,379)	Radiotherapy (*N* = 3,937)
Age at diagnosis, years			
Median (IQR)	63 (59–66)	63 (59–66)	65 (61–67)
50–59	4,952 (27)	4,281 (30)	671 (17)
60–69	13,364 (73)	10,098 (70)	3,266 (83)
Year of diagnosis			
2008–2012	8,061 (44)	6,433 (45)	1,628 (41)
2013–2016	6,400 (35)	5,086 (35)	1,314 (33)
2017–2019	3,855 (21)	2,860 (20)	995 (25)
PSA (ng/mL)			
Median (IQR)	6 (4–8)	6 (4–8)	7 (5–9)
3–9	16,562 (90)	13,321 (93)	3,241 (82)
10–19	1,754 (10)	1,058 (7)	696 (18)
Prostate volume (mL)			
Median (Q1, Q3)	34 (27–44)	34 (26–44)	34 (27–44)
<35	9,357 (51)	7,375 (51)	1,982 (50)
35+	8,959 (49)	7,004 (49)	1,955 (50)
Gleason score			
6	6,285 (34)	5,346 (37)	939 (24)
7 (3 + 4)	7,752 (42)	6,158 (43)	1,594 (40)
7 (4 + 3)	2,761 (15)	2,017 (14)	744 (19)
8	906 (5)	563 (4)	343 (9)
9–10	612 (3)	295 (2)	317 (8)
Proportion of needle cores with cancer			
<50%	11,599 (63)	9,491 (66)	2,108 (54)
≥50%	6,717 (37)	4,888 (34)	1,829 (46)
T stage			
1c	11,962 (65)	9,809 (68)	2,153 (55)
2	6,354 (35)	4,570 (32)	1,784 (45)
Mode of detection			
Health check-up	12,431 (68)	9,778 (68)	2,653 (67)
Lower urinary tract symptoms	4,066 (22)	3,181 (22)	885 (22)
Other symptoms	1,819 (10)	1,420 (10)	399 (10)
Underwent bone scan			
Yes	5,027 (27)	3,211 (22)	1,816 (46)
No	13,289 (73)	11,168 (78)	2,121 (54)
CCI			
0	14,903 (81)	12,075 (84)	2,828 (72)
1	2336 (13)	1,622 (11)	714 (18)
2	774 (4)	506 (4)	268 (7)
3+	303 (2)	176 (1)	127 (3)
Life expectancy (years)			
10–15	1,178 (6)	534 (4)	644 (16)
15–20	6,640 (36)	4,828 (34)	1,812 (46)
20+	10,498 (57)	9,017 (63)	1,481 (38)
Civil status			
Married or living with partner	12,325 (67)	9,892 (69)	2,433 (62)
Not married or living with partner	5,991 (33)	4,487 (31)	1,504 (38)

(*Continued*)

Table 1. Continued

	All (*N* = 18,316)	Prostatectomy (*N* = 14,379)	Radiotherapy (*N* = 3,937)
Educational level			
Low	4,327 (24)	3,251 (23)	1,076 (27)
Middle	8,089 (44)	6,301 (44)	1,788 (45)
High	5,900 (32)	4,827 (34)	1,073 (27)

IQR, interquartile range, CCI, Charlson comorbidity index; PSA, prostate-specific antigen.

pragmatic trial, where also older men with any type of baseline comorbidity were included, also largely confirmed the results. Our findings support that the new comorbidity indices can provide a relevant increased effectiveness in control of confounding.

4.2. Interpretation

Three key assumptions need to hold for identification of the causal effect of exposure (treatment) on the outcome (death by any cause): (1) conditional exchangeability, (2) positivity, and (3) consistency. Conditional exchangeability is met when all confounders are measured, and this assumption was the primary focus in our study. The available register-based information on prostate cancer characteristics was very comprehensive and few men died of prostate cancer during follow-up. Taken together, this suggests that bias due to insufficient control for tumor characteristics in our trial emulation is likely not a major concern.

Comorbidity commonly confounds comparisons in observational studies of treatment effectiveness, and in particular in studies of men with prostate cancer who often are old and have a high risk of death from other causes. Recommendations in guidelines for prostate cancer treatments are based on life expectancy [18] for which age and comorbidity are important predictors [19]. We found that adjustment without including any comorbidity index or when using only CCI did not result in estimates comparable to the ProtecT target trial estimates. This suggests residual confounding from comorbidities not captured by the CCI. Including the MDCI and DCI in the propensity models brought mortality estimates much closer to that of the ProtecT trial. The remaining difference could reflect residual confounding and/or random error in our observational analysis, and remaining uncertainty in the estimates of the target trial.

The assumption of positivity for a causal interpretation is violated when only one treatment is used in certain strata of the confounders. We found such violations of positivity in the tails of the propensity score distributions, and therefore focused our analysis on the average treatment effect in the subgroup of men with similar characteristics using overlap weights.

The assumption of consistency for a causal interpretation means that treatment is sufficiently well-defined and that there are no relevant versions of treatment not accounted for. We argue that this is the case in our analyses (see Supplementary Materials for an expanded discussion).

Table 2. Ten-year risk of death from any cause in the emulation of the ProtecT trial and of a hypothetical pragmatic trial

	Prostatectomy		Radiotherapy		Risk difference	
	Risk (%)	(95% CI)	Risk (%)	(95% CI)	Δ[a]	(95% CI)
Emulation of the ProtecT trial						
1. Unadjusted	7.9	(7.3–8.5)	14.1	(12.6–15.6)	6.2	(4.6–7.8)
2. Age and cancer characteristics	9.9	(8.6–11.3)	13.2	(10.9–15.6)	3.3	(0.6–6.1)
3. [2] + CCI	10.3	(8.9–11.7)	13.0	(10.7–15.3)	2.7	(0.0–5.5)
4. [2] + MDCI + DCI	11.1	(9.6–12.7)	12.3	(10.1–14.8)	1.2	(−1.4 to 4.1)
Emulation of pragmatic target trial						
1. Unadjusted	10.2	(9.6–10.7)	21.2	(20.1–22.2)	11.0	(9.8–12.2)
2. Age and cancer characteristics	13.7	(12.3–15.1)	17.6	(16.0–19.4)	4.0	(1.8–6.1)
3. [2] + CCI	13.9	(12.6–15.4)	17.4	(15.8–19.2)	3.5	(1.4–5.7)
4. [2] + MDCI + DCI	14.8	(13.4–16.3)	16.7	(15.1–18.5)	1.9	(−0.3 to 4.2)

Covariates were sequentially included in the propensity models to illustrate the added value of the Multidimensional Diagnosis-based Comorbidity Index (MDCI) and the Drug Comorbidity Index (DCI) compared to the Charlson Comorbidity Index. Age and cancer characteristics also included year of treatment, civil status and educational level.

CCI, Charlson comorbidity index.

[a] Difference in percentage points, that is, Δ = risk [%] radiotherapy − risk [%] prostatectomy.

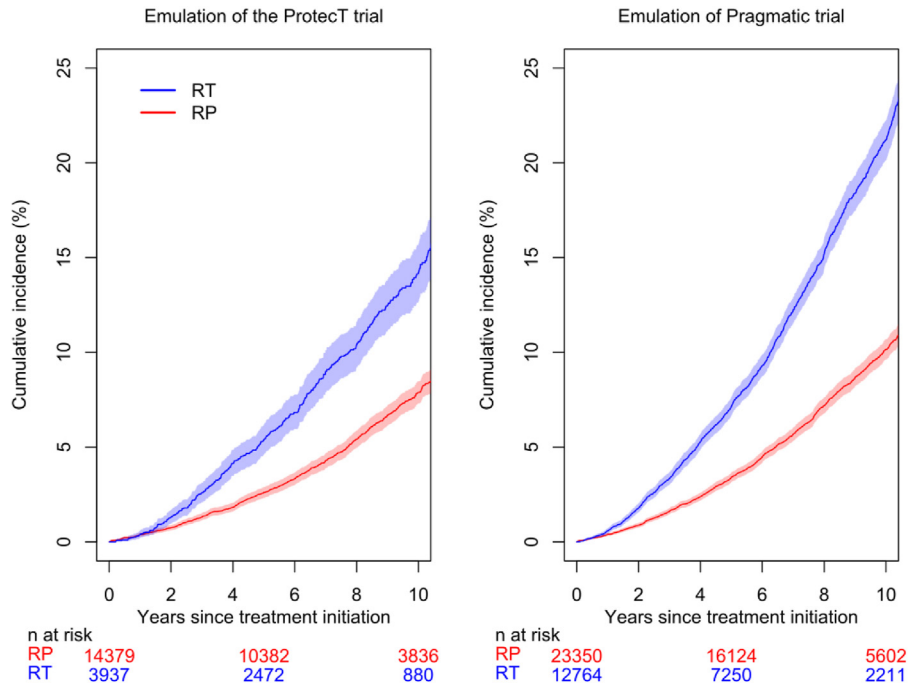

Figure 2. Unadjusted cumulative risk of death from any cause in emulated target trials in men receiving radical prostatectomy (RP) vs radiotherapy (RT). Shaded areas represent 95% confidence intervals.

4.3. Reliability of the benchmarking against a target trial as an indicator of confounding control

Adjustment for the expected imbalance of measured baseline characteristics moved the risk estimates in our confounded observational register-based study closer toward results obtained in an RCT. However, conflicting results from observational studies and RCT's can also be due to other reasons than residual confounding bias [4], for example, differences in study populations, definitions of outcomes, and definition of causal estimands [20]. Because these differences may affect the estimates in opposite directions, the conclusion that agreement between results from the RCT and the observational analysis means that adjustment has removed confounding completely may still be erroneous. This limitation applies to our study.

The emulation of an RCT can be difficult since the definition of the target trial is fixed and may be impossible to apply to observational data. The eligibility criteria in ProtecT could in our study be closely adhered to since key baseline information, including laboratory data, was available in PCBaSe. The treatments were provided in routine clinical care during a short time period under conditions very similar to the trial setting.

4.4. Previous studies

We are not aware of any previous studies that have considered different comorbidity indices' ability to reproduce the result of a randomized trial, although there are many studies that have attempted to reproduce results from randomized trials using propensity score methods [21].

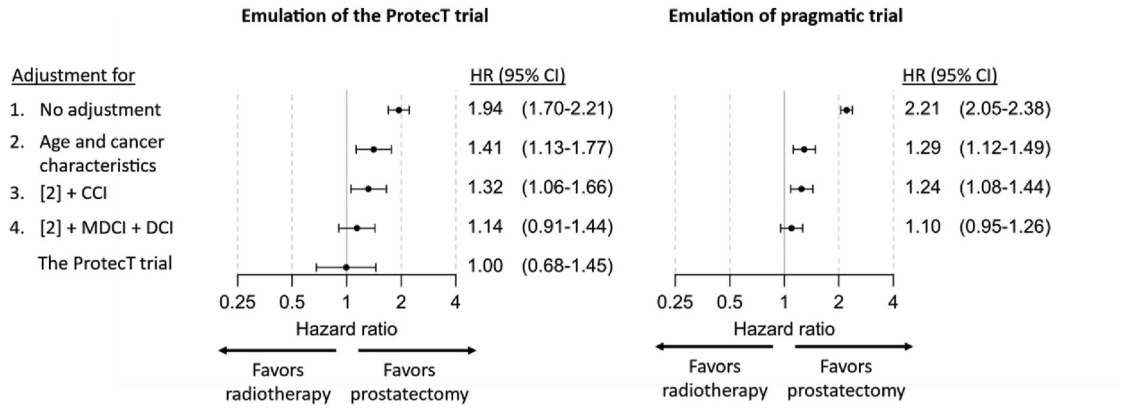

Figure 3. Unadjusted and adjusted hazard ratios for risk of death by any cause in men that have undergone radical prostatectomy (RP) or radiotherapy (RT) in the emulation of the ProtecT trial and of a hypothetical pragmatic trial.

4.5. Strengths and limitations

This population-based study has several strengths, including a large sample size and data from nationwide health care registers with documented quality [22−24]. This richness of information enabled us to create more accurate comorbidity indices for predicting risk of death.

While we consider the treatment strategies, definition of outcome and causal estimand to be well aligned between our study and ProtecT, there are remaining limitations. The benchmarking against an RCT assumes no unmeasured confounding at baseline conditional on measured confounders. This may be violated in spite of the rich information available at baseline in our trial emulation. The ProtecT trial and the emulated trial might also differ in the distribution of potential treatment effect modifiers. Randomization in ProtecT was done with stochastic minimization to improve the balance across the groups. This is likely one reason for the differences in baseline characteristics between ProtecT and our emulation. The ProtecT study was not blinded and there was switch to other treatment arms after randomization in substantial proportions of patients. It is, therefore, relevant for our benchmarking purposes that also an as-treated analysis of ProtecT found no difference in all-cause mortality [25]. All these issues may, however, potentially threaten the validity of the benchmarking and should be recognized as potential limitations.

The focus of our study is on confounding from baseline differences in comorbidity. Although it cannot be ensured that control of confounding from comorbidity was optimal, adjustment for the new comorbidity measures moved the estimates closer to those obtained in an RCT.

5. Conclusion

Benchmarking of a target trial emulation against an existing RCT demonstrated that new comorbidity indices generated estimated relative and absolute differences in risk of death comparable to the results of an RCT. The similar effectiveness of control of confounding in the emulation of a broader pragmatic trial supports the generalization to observational studies in a clinical practice setting.

Disclaimer

Rolf Gedeborg is employed by the Medical Products Agency (MPA) in Sweden. The MPA is a Swedish Government Agency. The views expressed in this article may not represent the views of the MPA.

CRediT authorship contribution statement

Marcus Westerberg: Writing − review & editing, Writing − original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Hans Garmo:** Writing − review & editing, Visualization, Software, Methodology, Conceptualization. **David Robinson:** Writing − review & editing, Conceptualization. **Pär Stattin:** Writing − review & editing, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Rolf Gedeborg:** Writing − review & editing, Writing − original draft, Methodology, Conceptualization.

Data availability

Data is confidential, but can be made available on a remote server upon request to the PCBaSe reference group, contact par.stattin@uu.se. For analytic code, see https://doi.org/10.5281/zenodo.12798383.

R code (Original data) (Zenodo).

Declaration of competing interest

There are no competing interests for any author.

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Supplementary data

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