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Prostate Cancer

Association of Radical Local Treatment with Mortality in Men with Very High-risk Prostate Cancer: A Semiecologic, Nationwide, Population-based Study

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Abstract

Background: Current guidelines recommend androgen deprivation therapy only for men with very high-risk prostate cancer (PCa), but there is little evidence to support this stance.
Objective: To investigate the association between radical local treatment and mortality in men with very high-risk PCa.
Design, setting, and participants: Semiecologic study of men aged <80 yr within the Prostate Cancer data Base Sweden, diagnosed in 1998–2012 with very high-risk PCa (local clinical stage T4 and/or prostate-specific antigen [PSA] level 50–200 ng/ml, any N, and M0). Men with locally advanced PCa (local clinical stage T3 and PSA level <50 ng/ml, any N, and M0) were used as positive controls.
Intervention: Proportion of men who received prostatectomy or full-dose radiotherapy in 640 experimental units defined by county, diagnostic period, and age at diagnosis.
Outcome measurements and statistical analysis: PCa and all-cause mortality rate ratios (MRRs).
Results and limitations: Both PCa and all-cause mortality were half as high in units in the highest tertile of exposure to radical local treatment compared with units in the lowest tertile (PCa MRR: 0.51; 95% confidence interval [CI], 0.28–0.95; and all-cause MRR: 0.56; 95% CI, 0.33–0.92). The results observed for locally advanced PCa for highest versus lowest tertile of exposure were in agreement with results from randomized trials (PCa MRR: 0.75; 95% CI, 0.60–0.94; and all-cause MRR: 0.85; 95% CI, 0.72–1.00). Although the semiecologic design minimized selection bias on an individual level, the effect of high therapeutic activity could not be separated from that of high diagnostic activity.
Conclusions: The substantially lower mortality in units with the highest exposure to radical local treatment suggests that radical treatment decreases mortality even in men with very high-risk PCa for whom such treatment has been considered ineffective.
Patient summary: Men with very high-risk prostate cancer diagnosed and treated in units with the highest exposure to surgery or radiotherapy had a substantially lower mortality.

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1. Introduction

There is no randomized controlled trial (RCT), to our knowledge, on the effect of radical local treatment in men with prostate cancer (PCa) in the "gray zone" between locally advanced and metastatic PCa. This risk category is often referred to as very high-risk PCa and is defined by local invasion into adjacent organs or very high levels of serum prostate-specific antigen (PSA) together with negative imaging findings for metastasis [1–4]. The prognosis is poor, and radical local treatment has generally not been considered beneficial, as the local tumor often is too advanced to eradicate and there is a high likelihood of undetected micrometastases. Consequently, clinical guidelines recommend androgen deprivation therapy (ADT) only for men with very high-risk PCa [1,2]. The only studies on radical local treatment for men with very high-risk PCa are small and retrospective [4–10]. These studies reported longer survival in men who underwent radical prostatectomy or full-dose radiotherapy than in men who received ADT only. The comparisons of treatment effects in observational studies are hampered by selection bias because most patients selected for radical local treatment have less adverse cancer characteristics than patients not receiving that treatment. Even if prognostic factors such as stage, grade, and PSA level are included in the analysis, there will be residual confounding in observational studies based on an analysis of treatment exposure on an individual level [11].

The use of radical local treatment for very high-risk PCa has varied during the past 15 years between Swedish counties, which are geographically well-defined administrative units providing health care to the entire population in their catchment area. This provided a natural experiment, allowing us to investigate the association of radical local treatment with mortality from very high-risk PCa in a semiecologic study in which the effects of selection bias for exposure to treatment on an individual level were minimized and comprehensive individual-level data on cancer characteristics, treatment, and outcome could still be used.

There is consistent evidence from RCTs that radiotherapy combined with ADT improves survival of men with locally advanced PCa [12–17]. To assess the validity of our results for very high-risk PCa, we also investigated the association between radical local treatment for locally advanced PCa and mortality with the same method as a positive control. The plausibility of our observations for the treatment effect on very high-risk PCa would be strengthened if we observed an association between radical local treatment of locally advanced PCa and mortality similar to the effect reported from the RCTs.

The aim of this study was to assess the association between radical local treatment and mortality in men with very high-risk PCa by relating exposure to radical local treatment on a population level in experimental units, defined by county, period, and age at diagnosis, to mortality from PCa and all causes using comprehensive individual-level data on cancer characteristics, treatment, and outcome.

2. Methods

Prostate Cancer data Base Sweden (PCBaSe) 3.0 contains information obtained from the National Prostate Cancer Register (NPCR) of Sweden on cancer characteristics at diagnosis and on primary treatment [18–20]. PCBaSe also includes information on comorbidity, assessed by the Charlson Comorbidity Index (CCI) based on discharge diagnosis from the Patient Registry; education level, income, and marital status from the LISA database; and cause and date of death obtained from the Cause of Death Registry [21–25]. The study population within PCBaSe for this study included men aged <80 yr of age diagnosed in 1998–2012 with very high-risk PCa (T4 and/or PSA level 50–200 ng/ml, any N, and M0). To assess the validity of our method, we separately studied the association of local treatment and mortality in men with locally advanced PCa (local clinical stage T3 and PSA level <50 ng/ml, any N, and M0). Registration in NPCR does not distinguish clinical local stage T3a from T3b.

The following variables in PCBaSe were used: age, year of PCa diagnosis, mode of detection, clinical local tumor stage, N stage, PSA level, Gleason score, CCI, educational level, marital status, primary registered treatment in NPCR, and county of residence. Gleason grade was grouped according to the five-tier Gleason grading groups [26,27]. NPCR includes comprehensive information on radiotherapy since 2008; for men diagnosed before 2008, data were retrieved directly from oncological radiotherapy information systems and local databases in oncology departments on type of radiotherapy, treatment time, total dose, and fractions in RetroRad (Retrospective Registration of Radiotherapy, a nation wide audit) [28]. There are currently 20 counties in Sweden, and a large majority of health care including diagnostic and therapeutic activity for PCa is provided in the county of residence of the patient within a tax-financed equal access system. The study was approved by the Research Ethics Board at Umeå University.

2.1. Statistical methods

Exposure was measured as the proportion of men who received primary radical local treatment, that is, radical prostatectomy or full-dose radiotherapy with or without ADT within 1 yr of diagnosis, for very high-risk and locally advanced PCa in 640 experimental units based on diagnostic county, 2-yr diagnostic periods (plus 2012), and age at diagnosis (<65, 65–69, 70–74, and 75–79 yr). For each experimental unit, the person-years at risk from date of diagnosis until death, emigration, or end of study period (December 31, 2013), whichever event came first, were calculated. In a Poisson model, the logarithm of person-years at risk was used as offset; the numbers of PCa-related deaths and deaths from any cause were used as outcome. Results are presented as mortality rate ratio (MRR) with 95% confidence intervals (CIs) for exposure in tertiles and continuous as a restricted cubic spline. The models included county as a categorical variable, year of diagnosis as a continuous variable, median Gleason grade groups as a

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restricted cubic spline, mean PSA level, and CCI dichotomized into 0 vs ≥1. Separate models were fitted for each age group, and a model for all ages combined was also fitted by including age group as a covariate. Multiple imputation was used to handle missing Gleason grade groups with the multivariate imputation by chained equations (MICE) algorithm [29]. The Gleason grade groups were imputed 20 times using all variables in Table 1 as predictors in the MICE algorithm. A separate model was fitted to the data set in each iteration and the results were then pooled using Rubin's rules [30]. The p value for trend was calculated by including exposure in the model as a continuous variable. Mortality rates per 1000 person-years were calculated by specifying different levels of exposure in the Poisson model and by using the underlying distribution for the other covariates values. All tests were two-sided, and the significance level was set to $p < 0.05$. Statistical analysis was performed with R v.3.1.2 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

There were 106 204 men aged <80 yr diagnosed with PCa in Sweden during the study period. Of these, 7500 men (7%) had very high-risk PCa and 10316 men (10%) had locally advanced PCa; for these men, there was a gradual increase in exposure to radical local treatment in most counties during the study period (Fig. 1) and an increase in the proportion receiving radical treatment in all age groups (Fig. 2). For instance, the proportion of men aged <65 yr with very high-risk PCa who received radical treatment increased from 21% in 1998–1999 to 41% in 2012, whereas the corresponding increase for locally advanced PCa was from 46% to 79%. There was a more than nine-fold difference between the counties with the highest and lowest proportions of radical treatment for very high-risk PCa (28% vs 3%, respectively) and more than two-fold difference of radical treatment for locally advanced PCa (53% vs 20%, respectively) during the full study period in all age groups combined. The use of radical treatment for very high-risk PCa and locally advanced PCa in each county according to calendar year is depicted in Supplementary Figs. 1 and 2.

Clinical characteristics and cancer treatment for men with very high-risk and locally advanced PCa are presented in Table 1. Men in the units in the highest tertile of exposure to radical local treatment compared with men in units with the lowest exposure were younger and had lower PSA levels, fewer comorbidities, and fewer missing data for complete Gleason classification (3% vs 26%, respectively). In an analysis ignoring the restriction to M0 in the very high-risk group, 92% vs 65% of men had undergone bone imaging in the units with highest and lowest exposure, respectively (Supplementary Table 1).

Full-dose radiotherapy combined with ADT was the most common radical treatment; 8% of men with very high-risk PCa and 19% of men with locally advanced PCa received this treatment in the full study population. Details on the delivered radiotherapy are presented in Supplementary Table 2. Age was a strong determinant of receipt of radical local treatment (Supplementary Fig. 3). Among men with very high-risk PCa, radical treatment was used in 32% of men aged <65 yr but only 2% of men aged 75–79 yr, and the corresponding proportions for men with locally advanced PCa were 66% and 6%, respectively.

3.1. Mortality according to exposure to local treatment

Men with very high-risk PCa in the units in the highest tertile of exposure to radical local treatment had half the mortality of men in the lowest tertile (PCa MRR: 0.51; 95% CI, 0.28–0.95; and all-cause MRR: 0.56; 95% CI, 0.33–0.92) (Table 2 and Fig. 3). The association between radical treatment and PCa mortality for highest versus lowest tertile of exposure was observed in all age groups up to 75 yr (age <65 yr, MRR: 0.64; 95% CI, 0.30–1.38; age 65–69 yr, MRR: 0.32; 95% CI, 0.10–1.02; and age 70–74 yr, MRR: 0.88; 95% CI, 0.12–6.41). The absolute PCa-specific mortality for men with very high-risk PCa was 30 per 1000 person-years in the highest tertile of treatment and 58 per 1000 person-years in the lowest tertile; the absolute all-cause mortality for men with very high-risk PCa was 44 per 1000 person-years in the highest tertile and 79 per 1000 person-years in the lowest tertile.

Mortality in men with locally advanced PCa was also related to exposure to radical local treatment for the highest versus lowest tertile of exposure (PCa MRR: 0.75; 95% CI, 0.60–0.94; and all-cause MRR: 0.85; 95% CI, 0.72–1.00). The association between radical treatment and PCa mortality was observed in all age groups up to 75 yr (age <65 yr, MRR: 0.75; 95% CI, 0.55–1.03; age 65–69 yr, MRR: 0.73; 95% CI, 0.51–1.04; and age 70–74 yr, MRR: 0.36; 95% CI, 0.11–1.13). All comparisons between tertiles of exposure to radical treatment showed a statistically significant association with PCa and all-cause MRR ($p < 0.05$). Too few men aged >75 yr received radical treatment to allow a separate analysis in this age group (Supplementary Fig. 3).

4. Discussion

In men with very high-risk PCa, mortality from PCa and that from all causes were half as high in units with the highest exposure to radical local treatment as in the units with the lowest exposure in this semiecologic, nationwide, population-based study. This strong association suggests that radical local treatment decreases mortality even in men with very high-risk PCa for whom radical treatment has previously been considered ineffective.

The semiecologic study design has several strengths [31,32]. Exposure to treatment could be assessed on a population level, which minimized selection bias on an individual level, while at the same time comprehensive, high-quality individual-level data for cancer characteristics, comorbidity, cancer treatment, and cause of death could be used [18–20,28].

Residual confounding cannot be ruled out. Some counties consistently had a higher use of radical local

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Table 1 – Distribution (percentage and interquartile range) of baseline characteristics for men with very high-risk and locally advanced prostate cancer according to experimental units in Prostate Cancer data Base Sweden 3.0

	Very high-risk PCa			Total
	Radical treatment in experimental unit, %			
	0–33	34–66	67–100	
Age at diagnosis, yr				
<65	13 (0–0)	63 (0–100)	44 (0–100)	19 (0–0)
65–69	17 (0–0)	30 (0–100)	45 (0–100)	19 (0–0)
70–74	30 (0–100)	7 (0–0)	8 (0–0)	27 (0–100)
75–79	40 (0–100)	0 (0–0)	3 (0–0)	36 (0–75)
Mode of detection[a]				
Symptoms	36 (0–62)	41 (20–67)	48 (24–67)	37 (0–62)
Screening	17 (0–26)	27 (11–33)	27 (0–50)	18 (0–29)
Other reason	43 (20–75)	29 (0–44)	21 (0–25)	41 (15–67)
Missing	4 (0–0)	3 (0–0)	3 (0–0)	4 (0–0)
T stage				
T1a/T1b	2 (0–0)	1 (0–0)	1 (0–0)	2 (0–0)
T1c	12 (0–20)	20 (0–29)	18 (0–33)	13 (0–20)
T2	27 (15–36)	25 (10–38)	26 (0–40)	27 (14–36)
T3	44 (33–56)	41 (25–50)	47 (25–61)	43 (33–56)
T4	14 (0–20)	11 (0–20)	7 (0–3)	13 (0–20)
TX/missing	1 (0–0)	1 (0–0)	2 (0–0)	1 (0–0)
N stage				
N0	8 (0–17)	24 (0–40)	26 (0–53)	10 (0–20)
N1	4 (0–5)	8 (0–17)	4 (0–0)	4 (0–7)
NX/missing	89 (75–100)	68 (50–86)	69 (44–100)	86 (69–100)
PSA level, ng/ml				
<20	4 (0–5)	3 (0–0)	2 (0–0)	4 (0–4)
20–<50	4 (0–6)	2 (0–0)	2 (0–0)	4 (0–5)
50–<75	41 (30–50)	49 (33–60)	58 (48–81)	42 (33–54)
75–<100	23 (14–33)	20 (0–33)	23 (0–35)	22 (12–33)
100–<200	28 (18–38)	26 (12–33)	15 (0–25)	28 (17–36)
Gleason grade group[b]				
1	14 (0–21)	13 (0–20)	13 (0–21)	14 (0–20)
2	13 (0–21)	19 (0–33)	14 (0–25)	13 (0–24)
3	13 (0–26)	19 (0–25)	29 (0–45)	14 (0–27)
4	17 (7–29)	22 (7–33)	24 (0–33)	18 (6–29)
5	16 (0–25)	19 (0–26)	18 (0–35)	17 (0–26)
Missing	26 (0–33)	8 (0–0)	3 (0–0)	24 (0–25)
Charlson Comorbidity Index				
0	69 (60–83)	83 (78–100)	91 (81–100)	71 (62–88)
1	16 (0–24)	9 (0–18)	4 (0–0)	15 (0–22)
≥2	15 (0–20)	8 (0–9)	5 (0–0)	14 (0–19)
Education level				
Low, <10 yr	50 (37–64)	32 (20–50)	32 (0–45)	48 (33–61)
Intermediate, 10–12 yr	34 (22–45)	42 (27–56)	44 (28–76)	35 (23–50)
High, >12 yr	15 (0–22)	25 (10–33)	21 (0–26)	16 (0–25)
Missing	1 (0–0)	1 (0–0)	2 (0–0)	1 (0–0)
Marital status				
Unmarried	10 (0–17)	18 (0–27)	13 (0–21)	11 (0–20)
Married	66 (56–75)	62 (50–75)	66 (50–81)	66 (52–75)
Divorced	15 (0–22)	18 (0–25)	16 (0–21)	15 (0–23)
Widower	9 (0–14)	3 (0–0)	5 (0–0)	9 (0–12)
Missing	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Primary treatment				
Radical prostatectomy	1 (0–0)	12 (0–18)	13 (0–25)	3 (0–0)
Radiotherapy with ADT	4 (0–6)	31 (22–50)	68 (50–100)	8 (0–20)
Radiotherapy only/other radical local treatment	2 (0–0)	6 (0–10)	2 (0–0)	2 (0–0)
All ADTs	79 (70–90)	44 (33–53)	16 (0–25)	75 (60–87)
GnRH with or without AA flare protection	54 (40–67)	27 (16–38)	13 (0–25)	51 (30–64)
GnRH with AA continuous	2 (0–0)	3 (0–0)	0 (0–0)	3 (0–0)
AA monotherapy	14 (0–25)	12 (0–20)	3 (0–0)	14 (0–22)
Surgical castration	9 (0–12)	2 (0–0)	0 (0–0)	8 (0–10)
Conservative/other noncurative/missing	14 (0–20)	7 (0–11)	1 (0–0)	13 (0–17)
	Locally advanced PCa			Total
	Radical treatment in experimental unit, %			
	0–33	34–66	67–100	
Age at diagnosis, yr				
<65	3 (0–0)	29 (0–100)	61 (0–100)	22 (0–0)

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Table 1 (*Continued*)

	Locally advanced PCa Radical treatment in experimental unit, %			Total
	0–33	34–66	67–100	
65–69	8 (0–0)	40 (0–100)	31 (0–100)	23 (0–0)
70–74	32 (0–100)	29 (0–100)	6 (0–0)	26 (0–0)
75–79	58 (0–100)	1 (0–0)	1 (0–0)	29 (0–100)
Mode of detection[a]				
Symptoms	34 (0–60)	31 (10–54)	36 (20–57)	34 (3–57)
Screening	18 (7–25)	31 (14–39)	37 (20–50)	26 (11–37)
Other reason	44 (14–76)	31 (12–47)	24 (0–33)	36 (12–50)
Missing	3 (0–3)	7 (0–3)	4 (0–0)	5 (0–2)
T stage				
T3	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
N stage				
N0	10 (0–17)	31 (17–43)	33 (10–53)	21 (0–38)
N1	3 (0–5)	9 (0–17)	8 (0–12)	6 (0–10)
NX/missing	87 (78–100)	60 (46–76)	59 (40–87)	73 (50–97)
PSA level, ng/ml				
<20	55 (44–67)	63 (50–71)	67 (57–79)	60 (50–71)
20–<50	45 (33–56)	37 (29–50)	33 (21–43)	40 (29–50)
Gleason grade group[b]				
1	20 (6–29)	21 (0–28)	19 (0–30)	20 (0–29)
2	16 (0–25)	21 (4–30)	24 (12–33)	19 (0–29)
3	12 (0–22)	18 (0–29)	22 (10–33)	16 (0–27)
4	14 (2–20)	16 (6–26)	15 (0–22)	15 (0–23)
5	12 (0–20)	13 (0–25)	15 (0–25)	13 (0–23)
Missing	27 (0–37)	12 (0–9)	5 (0–0)	18 (0–17)
Charlson Comorbidity Index				
0	69 (61–81)	79 (70–88)	83 (75–100)	75 (67–88)
1	17 (8–23)	12 (0–19)	10 (0–17)	14 (0–21)
≥2	14 (6–18)	9 (0–13)	7 (0–11)	11 (0–15)
Education level				
Low, <10 yr	52 (43–66)	41 (33–57)	34 (23–45)	45 (33–60)
Intermediate, 10–12 yr	32 (21–41)	38 (27–48)	42 (31–55)	36 (25–45)
High, >12 yr	15 (6–20)	20 (5–27)	24 (9–31)	18 (6–25)
Missing	1 (0–0)	1 (0–0)	1 (0–0)	1 (0–0)
Marital status				
Unmarried	8 (0–12)	11 (0–18)	14 (0–24)	10 (0–17)
Married	71 (62–80)	68 (58–78)	66 (56–80)	69 (58–79)
Divorced	11 (0–17)	17 (6–25)	17 (0–24)	14 (0–21)
Widower	10 (0–14)	5 (0–8)	3 (0–0)	7 (0–10)
Missing	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Primary treatment				
Radical prostatectomy	2 (0–0)	12 (0–20)	19 (0–25)	8 (0–12)
Radiotherapy with ADT	5 (0–8)	27 (16–38)	45 (30–71)	19 (0–37)
Radiotherapy only/other radical local treatment	4 (0–5)	14 (0–20)	16 (0–25)	9 (0–14)
All ADTs	62 (50–76)	33 (27–44)	15 (0–20)	44 (22–62)
GnRH with or without AA flare protection	42 (27–53)	20 (11–30)	10 (0–12)	29 (9–40)
GnRH with AA continuous	1 (0–0)	2 (0–0)	2 (0–0)	2 (0–0)
AA monotherapy	12 (0–21)	9 (0–17)	4 (0–5)	10 (0–15)
Surgical castration	6 (0–11)	1 (0–0)	0 (0–0)	4 (0–4)
Conservative/other noncurative/missing	27 (14–36)	15 (0–18)	5 (0–7)	19 (0–25)

Experimental units according to age at diagnosis, diagnostic year, and county of residency. AA = per oral antiandrogen; ADT = androgen deprivation therapy; GnRH = gonadotropin-releasing hormone agonist; IQR = interquartile range; PSA = prostate-specific antigen.

[a] Data available for cases diagnosed after January 1, 2000.

[b] According to the five-tier Gleason grade groups according to the International Society of Urological Pathology [26,27], Gleason grade group 1 = Gleason score 2–6; Gleason grade group 2 = Gleason score 7 (3 + 4); Gleason grade group 3 = Gleason score 7 (4 + 3); Gleason grade group 4 = Gleason score 8; and Gleason grade group 5 = Gleason score 9–10.

treatment, and there may have been factors unrelated to treatment causing the lower mortality in these counties. Although the analysis was adjusted for county and year of diagnosis, there may have been interactions between these two factors that were left unaccounted for. High exposure to radical local treatment was linked to high exposure to staging investigations, including bone and lymph node imaging and complete Gleason classification. The design of the study allowed for an investigation of the association of a high diagnostic activity and a high therapeutic activity, assessed on a population level, with oncological outcome, assessed on an individual level, but the effects of diagnostic and therapeutic activity could not be separated.

Most men aged <75 yr with very high-risk PCa die of their cancer [33,34]. Despite this, radical local treatment of the primary tumor in addition to ADT has only been

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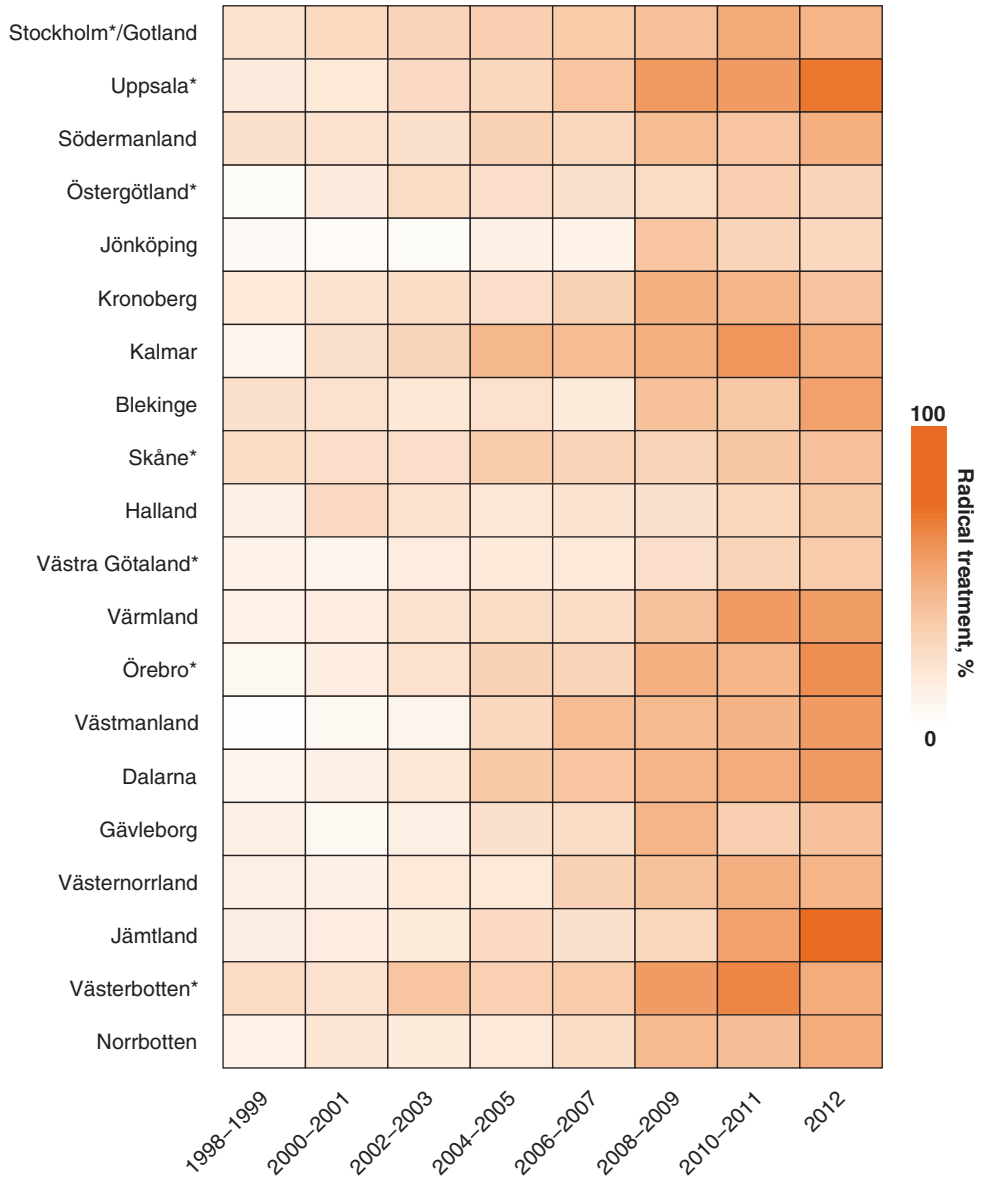

Fig. 1 – Distribution of exposure to radical local treatment in experimental units of county and 2-yr periods of diagnosis in men with locally advanced and very high-risk prostate cancer.
*** Counties with a university hospital.**

evaluated in some reports from small, single-institution case series [4–10]. These studies reported longer survival for men with very high-risk PCa who received full-dose radiotherapy or prostatectomy in addition to ADT, but selection bias cannot be ruled out as the only cause of these findings. In contrast, multimodal treatment of very advanced breast cancer is a well-researched area. There is strong evidence from RCTs that combinations of local and systemic treatment prolong survival, and combined treatment has long been the standard of care for women with very advanced breast cancer [35].

RCTs of ADT and radical prostatectomy or radiotherapy in men with very high-risk PCa (with or without confirmed limited metastatic spread) are ongoing [36–40], but their results will not be available for many years. Results from large, well-designed studies based on registers with high-quality data can fill the current lack of evidence. This study included virtually all PCa cases in an entire nation, with comprehensive data from high-quality health care registries and demographic databases on cancer characteristics, cancer treatment, comorbidity, socioeconomic factors, and health care providers [18–20]. We also investigated the association between radical local treatment and mortality from locally advanced PCa (local clinical stage T3). The magnitude of the association between high exposure to radical local treatment and the decrease in mortality in men with locally advanced PCa was in accordance with the effect of local treatment reported from RCTs [12–17], implying that the methods we used yielded accurate risk estimates.

In this study, lymph node metastasis detected at surgery (pN1) was not used as an inclusion criterion because men

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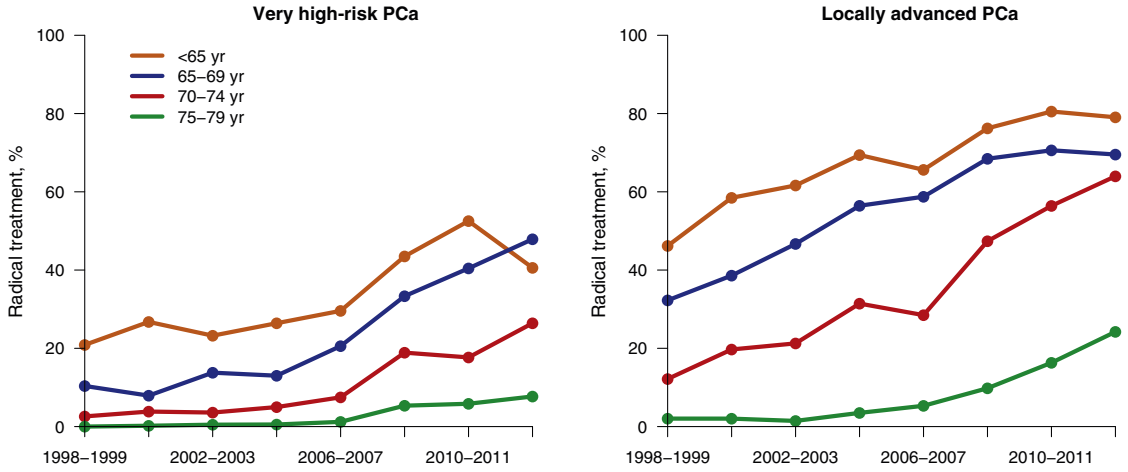

Fig. 2 – Percentage of men with very high-risk (local clinical stage T4 and/or prostate-specific antigen [PSA] level 50–200 ng/ml, any N, and all M0) or locally advanced (local clinical stage T3 and PSA level <50 ng/ml, any N, and all M0) prostate cancer who received primary radical local treatment in 2-yr periods stratified according to age groups.
PCa = prostate cancer.

Table 2 – Mortality rate ratio with 95% confidence intervals by risk group, age group, and percentage with radical treatment

	Age at diagnosis, yr									Total (<75)		
	<65			65–69			70–74					
	Person-years	MRR	(95% CI)	Person-years	MRR	(95% CI)	Person-years	MRR	(95% CI)	Person-years	MRR	(95% CI)
Very high-risk PCa												
Death from PCa												
Radical treatment, %												
0–33	6156.6	1.00	(Reference)	7460.8	1.00	(Reference)	11 900.6	1.00	(Reference)	25 518	1.00	(Reference)
34–66	2944.7	0.80	(0.65–0.99)	1100.2	0.81	(0.58–1.12)	248.4	0.73	(0.37–1.44)	4293.3	0.80	(0.67–0.96)
67–100	260.3	0.64	(0.30–1.38)	219.8	0.32	(0.10–1.02)	23.7	0.88	(0.12–6.41)	503.8	0.51	(0.28–0.95)
Death from all causes												
Radical treatment, %												
0–33	6156.6	1.00	(Reference)	7460.8	1.00	(Reference)	11 900.6	1.00	(Reference)	25 518	1.00	(Reference)
34–66	2944.7	0.84	(0.70–1.01)	1100.2	0.92	(0.71–1.20)	248.4	0.80	(0.47–1.36)	4293.3	0.86	(0.74–1.00)
67–100	260.3	0.59	(0.29–1.20)	219.8	0.53	(0.25–1.13)	23.7	0.54	(0.07–3.91)	503.8	0.56	(0.33–0.92)
Locally advanced PCa												
Death from PCa												
Radical treatment, %												
0–33	1652.0	1.00	(Reference)	3400.6	1.00	(Reference)	12 326.2	1.00	(Reference)	17 378.8	1.00	(Reference)
34–66	8644.3	0.77	(0.57–1.04)	10 292.6	0.93	(0.74–1.18)	5548.3	0.81	(0.66–1.00)	24 485.3	0.84	(0.72–0.98)
67–100	7847.3	0.75	(0.55–1.03)	3227.6	0.73	(0.51–1.04)	433.2	0.36	(0.11–1.13)	11 508.2	0.75	(0.60–0.94)
Death from all causes												
Radical treatment, %												
0–33	1652.0	1.00	(Reference)	3400.6	1.00	(Reference)	12 326.2	1.00	(Reference)	17 378.8	1.00	(Reference)
34–66	8644.3	0.77	(0.60–0.99)	10 292.6	0.97	(0.82–1.15)	5548.3	0.91	(0.79–1.05)	24 485.3	0.91	(0.81–1.01)
67–100	7847.3	0.79	(0.61–1.02)	3227.6	0.86	(0.67–1.11)	433.2	0.63	(0.35–1.14)	11 508.2	0.85	(0.72–1.00)
Locally advanced and very high-risk PCa												
Death from PCa												
Radical treatment, %												
0–33	4129.4	1.00	(Reference)	11 145.6	1.00	(Reference)	26 397	1.00	(Reference)	41 672	1.00	(Reference)
34–66	18 861.5	0.97	(0.81–1.15)	13 172.5	0.98	(0.85–1.13)	3851.5	1.00	(0.81–1.23)	35 885.5	0.98	(0.88–1.09)
67–100	4514.4	0.82	(0.63–1.06)	1383.4	0.83	(0.56–1.23)	232.1	0.44	(0.14–1.38)	6129.9	0.80	(0.65–1.00)
Death from all causes												
Radical treatment, %												
0–33	4129.4	1.00	(Reference)	11 145.6	1.00	(Reference)	26 397	1.00	(Reference)	41 672	1.00	(Reference)
34–66	18 861.5	0.95	(0.82–1.10)	13 172.5	0.97	(0.87–1.09)	3851.5	1.02	(0.87–1.18)	35 885.5	0.98	(0.90–1.06)
67–100	4514.4	0.82	(0.66–1.02)	1383.4	0.92	(0.69–1.23)	232.1	0.55	(0.26–1.16)	6129.9	0.84	(0.71–1.00)

CI = confidence interval; MRR = mortality rate ratio; PCa, prostate cancer.

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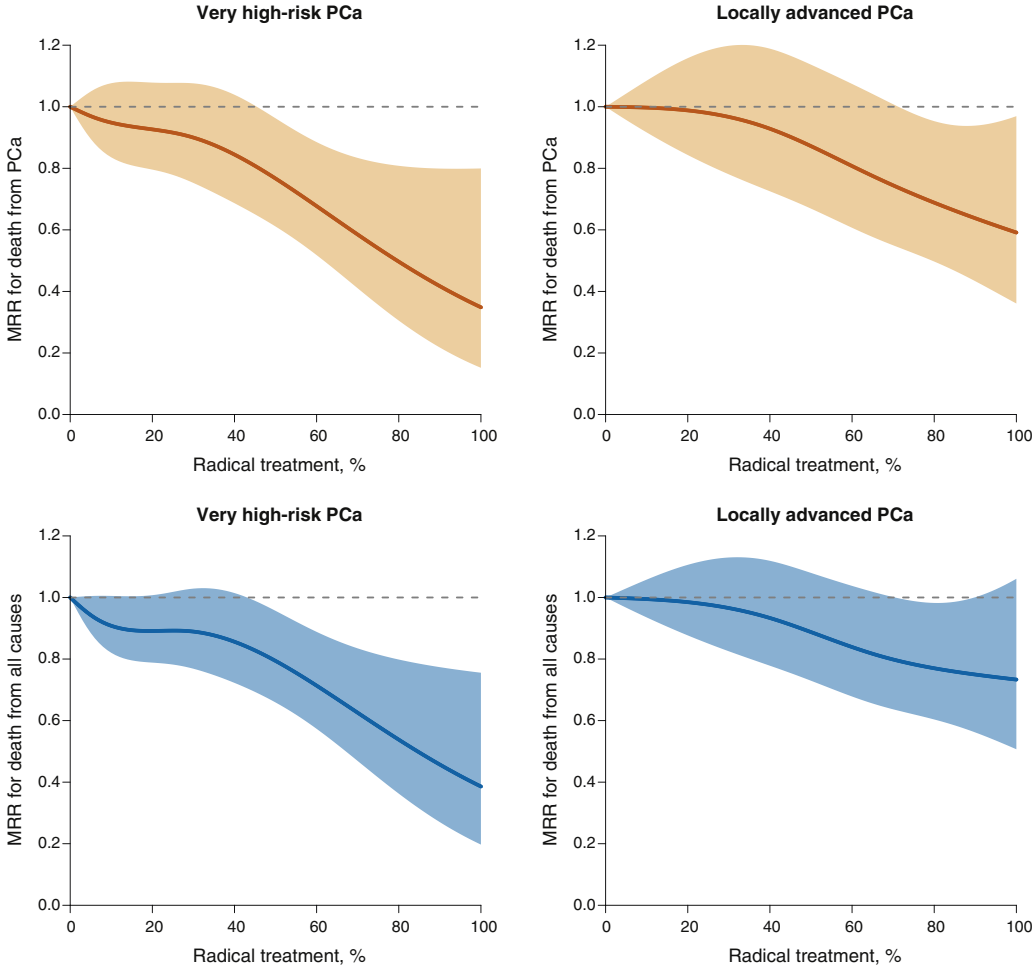

Fig. 3 – Mortality rate ratio for death from prostate cancer (PCa) (orange) and all causes (blue) with 95% confidence interval in men with very high-risk (local clinical stage T4 and/or prostate-specific antigen [PSA] level 50–200 ng/ml, any N, and all M0) or locally advanced (local clinical stage T3 and PSA level <50 ng/ml, any N, and all M0) PCa according to proportion of men undergoing primary radical local treatment in experimental units based on age, year of diagnosis, and county.
MRR = mortality rate ratio.

with pN1 detected at prostatectomy for clinically localized PCa have a better prognosis than men with stage T4 cancer or a PSA level of 50–200 ng/ml [8,33]. Had pN1 disease been included in the very high-risk PCa group, more men in this subgroup with favorable prognosis would have been included in units with high exposure to radical local treatment, and this would have introduced selection bias.

5. Conclusions

In this semiecologic, nationwide, population-based study, mortality among men with very high-risk PCa (defined as local stage T4, PSA level 50–200 ng/ml, and M0) in experimental units with the highest exposure to radical local treatment was half that from PCa and all causes in units with the lowest exposure. This suggests that radical local treatment decreases mortality in men with very high-risk PCa for whom radical treatment has previously been considered ineffective. RCTs are needed to conclusively evaluate the effect of radical local treatment in men with very high-risk PCa.

Author contributions: Pär Stattin 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: Stattin, Sandin, Garmo, Jonsson, Bratt.
Acquisition of data: Stattin, Robinson, Lissbrant, Bratt.
Analysis and interpretation of data: Stattin, Sandin, Thomsen, Garmo, Robinson, Lissbrant, Jonsson, Bratt.
Drafting of the manuscript: Stattin, Thomsen.
Critical revision of the manuscript for important intellectual content: Stattin, Sandin, Thomsen, Garmo, Robinson, Lissbrant, Jonsson, Bratt.
Statistical analysis: Stattin, Sandin, Thomsen.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.07.023.

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