Changes in treatment and mortality in men with locally advanced prostate cancer between 2000 and 2016: a nationwide, population-based study in Sweden

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Objective
To evaluate whether the effects of radical treatment in men with locally advanced prostate cancer (PCa) on PCa mortality observed in randomised clinical trials are applicable on a population basis.

Patients and methods
We conducted a population-based cohort study using the Prostate Cancer data Base Sweden of 20,350 men diagnosed between 2000 and 2016 with locally advanced PCa, defined as clinical local stage T3/T4, M0, Mx and a prostate-specific antigen level of <100 ng/mL. Cumulative PCa mortality was examined using competing risk analysis of all men with locally advanced PCa, and also including men who did not undergo radical treatment. Multivariate regression analysis, including prognostic factors, was used to calculate hazard ratios (HRs) for all-cause and PCa-specific death.

Results
The proportion of men treated with primary radical radiotherapy (n = 4174) or prostatectomy (n = 1210) increased from 15% in 2000–2003, 25% in 2004–2007, 33% in 2008–2011 to 43% in 2012–2016. The corresponding 5-year PCa mortality decreased from 19%, 18%, 17%, to 15% for all men, with the steepest decrease in men aged 65–74 years, from 16% to 8%. The risk of PCa mortality in men aged <80 years was lower in the last period compared to the first period, with a HR of 0.65 (95% confidence interval 0.56–0.76) in multivariate analysis.

Conclusions
The threefold increase in use of radical treatment was accompanied by a modest decrease in PCa mortality in all men with newly diagnosed locally advanced PCa. For men aged 65–74 years, there was a 50% decrease in the relative risk of PCa death. This indicates that the benefits previously observed in randomised trials can also be achieved in a real-life setting.

Keywords
locally advanced prostate cancer, mortality, prostate cancer, prostatectomy, radiotherapy, survival, #ProstateCancer, #PCSM

Introduction
Currently, ~10% of men with prostate cancer (PCa) in many Western countries, including Sweden, have locally advanced disease at the time of diagnosis. If these men do not receive radical treatment the 8-year PCa mortality is 28–64% depending on Gleason Grade Group (GGG) [1-4]. Radiotherapy (RT) combined with androgen-deprivation therapy (ADT) reduced PCa mortality up to 50% compared to monotherapy with ADT during long-term follow-up in several randomised clinical trials (RCTs) [5-8]. In view of these results, the European Association of Urology and the Swedish national guidelines recommend radical RT with neoadjuvant and adjuvant ADT for men with locally advanced PCa and a life expectancy of >5 years. Consequently, there has been an increased use of this treatment in many countries during the last decade [9,10]. However, if the benefit observed in these RCTs can also be achieved in a real-life setting, is unknown.

The aim of the present study was to assess the influence on the pattern of care and PCa mortality in men with locally...
advanced PCa from previous randomised trials that showed decreased PCa mortality in men who received RT in addition to ADT.

**Patients and methods**

**The registers**

The National Prostate Cancer Register of Sweden (NPCR) holds information on >180 000 PCa cases diagnosed since 1998, with detailed data on cancer characteristics, diagnostics, and primary treatment with a capture of 98% of all newly diagnosed PCa cases as compared with the Swedish Cancer Registry. The Prostate Cancer data Base Sweden (PCBaSe) is a research database created through linkages between NPCR and several other nationwide healthcare registers and demographic databases, including the Patient Registry, Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), Prescribed Drug Registry, and Cause of Death Registry [11].

**Study population**

All men in PCBaSe diagnosed with locally advanced PCa between 2000 and 2016 were included in the study and primary treatment and mortality were assessed in four calendar periods. Locally advanced PCa was defined as clinical local stage T3 or T4 (based on DRE), with a PSA level of < 100 ng/mL and no evidence of metastatic disease (M0 or Mx), and any N stage and any GGG. All N stages were included to prevent bias in comparisons of calendar periods, as pelvic lymphadenectomy only was often performed as a staging procedure in the beginning of the study period. Comorbidity at the date of diagnosis was classified by use of the Charlson Comorbidity Index (CCI), which is a weighted sum of a number of International Classification of Diseases (ICD) codes for discharge diagnoses excluding PCa in the Patient Registry [12]. Radical treatment included primary radical RT, with or without neoadjuvant and adjuvant ADT, and primary radical prostatectomy (RP), performed within 6 months of diagnosis. Information on RT for men diagnosed before 2008 was collected by an audit (retrospective collection of data on RT; RetroRad) in which data were retrieved from RT dose verification systems at oncological departments throughout Sweden. After 2008 a specific form for RT has been in use in the NPCR [13].

Follow-up started at date of diagnosis and ended 31 December 2017, date of emigration, or date of death, whichever event came first. Cumulative incidence of PCa death was plotted treating other causes of death as a competing risk. In the last calendar period with men diagnosed between 2012 and 2016, the full 5-year follow-up was only available for men diagnosed in 2012 and 2013. Men diagnosed in 2014, 2015, and 2016 contributed to follow-up with 3, 2, and 1 year, respectively.

Three separate Cox regression models were used to assess the association of calendar period with PCa and all-cause hazard of death: (i) unadjusted; (ii) adjusted for age, PSA level, T and M stage (T3, T4, M0, Mx), comorbidity (CCI 0, 1, ≥2), civil status and educational level; and (iii) additionally adjusted for radical treatment, i.e. RT or RP. All models were stratified by age groups. The analysis was performed using the R software, version 3.4.2 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the Research Ethics Board in Uppsala.

**Results**

A total of 20 350 men were registered with locally advanced PCa in the NPCR during the study period (Table 1). A strong grade migration was observed with an increase in GGG 4 and 5 from 27% in 2000–2003 up to 48% in 2012–2016. In contrast, the PSA level and distribution of T stage remained essentially unchanged, with a small decrease in the median PSA level from 24 to 20 ng/mL, and a small decrease in the proportion of T4 cancers from 8% to 6%.

The proportion of primary radical treatment for locally advanced PCa increased stepwise from 15%, 25%, 33% to 43%, in the four calendar periods (Table 2). This increase was observed for men of all ages; however, the increase was particularly strong in men aged 65–74 years, for whom the proportion who received radical treatment increased from 23% to 74%, whereas almost no men aged ≥80 years received radical treatment (n = 48, 1%). More men were treated with radical RT (n = 4174) than RP (n = 1210) (22% vs 6%). Between 2000–2003 and 2012–2016, the use of RT increased from 660 (12%) to 1435 (33%) and RP increased from 165 (3%) to 448 (10%). Data on ADT were only available after 2006 in the Prescribed Drug Registry. In 2006–2016, 90% of men who received RT also received neoadjuvant and adjuvant ADT [14]. Data on adjuvant or salvage RT were available from 2007 until 2015; with 227/698 (33%) men who underwent primary RP in these years subsequently receiving RT. In contrast, RP was very rarely performed after RT, only 36/4174 (1%) men underwent salvage RP between 2000 and 2016.

The use of external beam RT with a total dose of ≥74 Gy increased from 20% to 44% from the first to the last period and the use of moderately hypofractionated RT (dose fraction ≥2.4 Gy) increased from 1% to 22% (Fig. 1 and Table S1). Robot-assisted laparoscopic RP (RALP) became increasingly common during the study period, with an increase from none in 2000–2003 to 304/439 (69%) of all RPs in 2012–2016 (Fig. S1).

The cumulative incidence of PCa death at 5 years in all men with locally advanced PCa decreased from 19%, 18%, 17%, to...
15% in the four time periods (Table 3, Fig. 2). The decline in mortality was observed for all ages except for men aged >85 years, for whom mortality remained virtually unchanged, 30% in 2000–2003 and 32% in 2012–2016. The steepest decrease in mortality was seen in men aged 65–74 years from 16% down to 8%, whereas the decrease in PCa mortality in men aged 75–79 years was smaller, down from 19% to 15%.

The cumulative mortality at 5 years due to other causes than PCa decreased marginally from 21% in 2000–2003 to 19% in 2012–2016. The decrease was most prominent in men aged 75–79 years, from 25% to 16%. For men aged <70 years mortality from other causes was virtually unchanged, down from 8% to 7%.

Table 1 Baseline characteristics for men with locally advanced prostate cancer in the Prostate Cancer data Base Sweden (PCBaSe) 4.0 according to calendar period of diagnosis.

| Characteristic                        | 2000–2003 | 2004–2007 | 2008–2011 | 2012–2016 | 2000–2016 |
|--------------------------------------|-----------|-----------|-----------|-----------|-----------|
| No. of patients                      | 5659      | 5428      | 4600      | 4663      | 20 350    |
| Age, years                           |           |           |           |           |           |
| Median (IQR)                         | 75 (68–80)| 74 (67–81)| 75 (67–81)| 75 (68–81)| 75 (68–81)|
| 0–64, n (%)                          | 817 (14)  | 943 (17)  | 681 (15)  | 624 (13)  | 3065 (15) |
| 65–69, n (%)                         | 794 (14)  | 804 (15)  | 770 (17)  | 758 (16)  | 3126 (15) |
| 70–74, n (%)                         | 1132 (20) | 977 (18)  | 826 (18)  | 875 (19)  | 3810 (19) |
| 75–79, n (%)                         | 1286 (23) | 1120 (21)| 891 (19)  | 893 (19)  | 4190 (21) |
| 80–84, n (%)                         | 1031 (18) | 966 (18)  | 813 (18)  | 867 (19)  | 3677 (18) |
| ≥85, n (%)                           | 599 (11)  | 616 (11)  | 619 (13)  | 646 (14)  | 2482 (12) |
| Clinical T stage, n (%)              |           |           |           |           |           |
| T3                                   | 5224 (92) | 5019 (92)| 4278 (93) | 4363 (94) | 18 884 (93)|
| T4                                   | 435 (8)   | 409 (8)   | 322 (7)   | 300 (6)   | 1466 (7)  |
| M Stage*, n (%)                      |           |           |           |           |           |
| M0                                   | 2419 (43) | 2178 (40)| 1572 (34) | 2878 (62) | 9047 (44) |
| Mx                                   | 3240 (57) | 3250 (60)| 3028 (66) | 1785 (38) | 12 303 (56)|
| Serum PSA level, ng/mL               |           |           |           |           |           |
| Median (IQR)                         | 24 (12–46)| 22 (11–42)| 22 (11–44)| 20 (10–40)| 22 (11–43)|
| <10, n (%)                           | 1000 (18) | 1177 (22)| 1030 (22)| 1172 (25)| 4379 (21)|
| 10–19.9, n (%)                       | 1300 (23) | 1283 (24)| 1059 (23)| 1056 (23)| 4698 (23)|
| 20–49.9, n (%)                       | 1998 (35) | 1821 (33)| 1509 (33)| 1516 (32)| 6344 (34)|
| 50–99.9, n (%)                       | 1236 (22) | 1052 (19)| 921 (20) | 874 (19)  | 4083 (20)|
| Missing, n (%)                       | 125 (2)   | 95 (2)   | 81 (2)   | 45 (1)    | 342 (2)  |
| Gleason Grade Group, n (%)           |           |           |           |           |           |
| 1                                    | 1161 (21) | 932 (17) | 483 (11) | 308 (6)   | 2884 (14)|
| 2                                    | 925 (16) | 1034 (19)| 897 (20) | 865 (19)  | 3721 (18)|
| 3†                                   | 1032 (18) | 1202 (22)| 990 (22) | 1015 (22)| 3627 (18)|
| 4                                    | 786 (14) | 966 (18) | 947 (21) | 873 (19)  | 3572 (18)|
| 5‡                                   | 724 (13) | 840 (16)| 1051 (23)| 1369 (29)| 3984 (20)|
| WHO grading‡                         | 975 (17) | 360 (7) | 126 (3) | 90 (2)    | 1551 (8) |
| Missing                              | 56 (1)   | 94 (1)   | 106 (2)  | 143 (3)   | 399 (2)  |
| Primary treatment, n (%)             |           |           |           |           |           |
| (RT or RP)                           | 825 (15) | 1221 (22)| 1455 (32)| 1883 (40)| 5384 (27)|
| RT                                   | 600 (12) | 881 (16)| 1198 (26)| 1435 (31)| 4174 (21)|
| RP                                   | 165 (3)  | 340 (6) | 257 (6) | 448 (10) | 1210 (6)|
| Conservative treatment§              | 4495 (79)| 3791 (70)| 2968 (64)| 2414 (52)| 13671 (67)|
| Missing                              | 339 (6)  | 416 (8) | 177 (4) | 363 (8)   | 1295 (6) |
| Charlson Comorbidity Index, n (%)    |           |           |           |           |           |
| 0                                    | 3897 (69) | 3733 (69)| 3114 (68)| 3116 (68)| 13 860 (68)|
| 1                                    | 1001 (18) | 920 (17)| 772 (17) | 763 (16) | 3456 (17)|
| 2§                                   | 761 (13) | 775 (14)| 714 (15) | 784 (17) | 3034 (15)|
| Educational level†, n (%)            |           |           |           |           |           |
| Low                                  | 2927 (52) | 2602 (48)| 2031 (44)| 1878 (40)| 9438 (46)|
| Intermediate                         | 1804 (32)| 1873 (34)| 1644 (36)| 1734 (37)| 7055 (35)|
| High                                 | 779 (14) | 870 (16) | 879 (19) | 1003 (22)| 3531 (17)|
| Missing                              | 149 (3)  | 83 (2) | 46 (1) | 48 (1)    | 326 (2)  |
| Civil status, n (%)                  |           |           |           |           |           |
| Married/partnership                  | 3768 (67)| 3484 (64)| 2875 (63)| 2818 (60)| 12 945 (64)|
| Unmarried                            | 1891 (33)| 1944 (36)| 1725 (37)| 1845 (40)| 7405 (36)|

1M0, no signs of distant metastases on bone imaging. Mx, unknown distant metastatic status. *Information on secondary Gleason grade was missing in 612 patients between 2000 and 2007. †Only WHO grading available. ‡Active surveillance, watchful waiting or ADT. §Low: no more than 9 years (elementary school). Intermediate: 9–12 years (secondary school). High: >12 years (college/university). © 2020 The Authors BJU International published by John Wiley & Sons Ltd on behalf of BJU International
the risk remained lower for the last period; HR 0.65 (95% CI 0.56–0.76). However, after including radical treatment in the model, the 95% CI for the risk estimate included unity; HR 0.89 (95% CI 0.76–1.05), indicating that increased use of radical treatment affected mortality. When models were stratified by age, the association between treatment and risk

# Table 2

Use of primary radical treatment in men with locally advanced prostate cancer per calendar period and age.

| Age at diagnosis, years | 2000–2003, % (n/N) | 2004–2007, % (n/N) | 2008–2011, % (n/N) | 2012–2016, % (n/N) | 2000–2016, % (n/N) |
|------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| All ages               |                     |                     |                     |                     |                     |
| RT or RP               | 15 (825/5320)       | 25 (1221/5012)      | 33 (1455/4423)      | 43 (1883/4300)      | 28 (5384/19055)     |
| RT                     | 12                  | 18                  | 27                  | 33                  | 22                  |
| RP                     | 3                   | 7                   | 6                   | 10                  | 6                   |
| <65                    |                     |                     |                     |                     |                     |
| RT or RP               | 17 (825/4735)       | 28 (1221/4417)      | 38 (1454/3826)      | 51 (1880/3695)      | 32 (5380/16673)     |
| RT                     | 14                  | 20                  | 31                  | 39                  | 25                  |
| RP                     | 3                   | 8                   | 7                   | 12                  | 7                   |
| 65–69                  |                     |                     |                     |                     |                     |
| RT or RP               | 55 (393/709)        | 69 (564/810)        | 76 (494/655)        | 82 (474/577)        | 70 (1925/2751)      |
| RT                     | 41                  | 47                  | 56                  | 51                  | 48                  |
| RP                     | 14                  | 22                  | 20                  | 31                  | 22                  |
| 70–74                  |                     |                     |                     |                     |                     |
| RT or RP               | 37 (253/696)        | 53 (379/720)        | 66 (486/735)        | 78 (544/700)        | 58 (1662/2851)      |
| RT                     | 30                  | 38                  | 55                  | 57                  | 45                  |
| RP                     | 7                   | 15                  | 11                  | 21                  | 13                  |
| 75–79                  |                     |                     |                     |                     |                     |
| RT or RP               | 15 (159/1059)       | 26 (232/894)        | 46 (360/784)        | 69 (549/795)        | 37 (1300/3532)      |
| RT                     | 14                  | 21                  | 41                  | 56                  | 31                  |
| RP                     | 1                   | 5                   | 5                   | 13                  | 6                   |
| 80–84                  |                     |                     |                     |                     |                     |
| RT or RP               | 1.2 (1/261)         | 4.4 (42/1064)       | 12.3 (108/861)      | 34 (280/819)        | 11 (449/4005)       |
| RT                     | 1                   | 4                   | 12                  | 32                  | 11                  |
| RP                     | 0.2                 | 0.4                 | 0.3                 | 2                   | 0.7                 |
| ≥85                    |                     |                     |                     |                     |                     |
| RT or RP               | 0.1 (1/1010)        | 0.4 (4/929)         | 0.8 (6/791)         | 4 (33/804)          | 1 (44/3534)         |
| RT                     | 0                   | 0.1                 | 0.4                 | 4                   | 1                   |
| RP                     | 0.1                 | 0.3                 | 0.4                 | 0                   | 0.2                 |
| Men with unknown primary treatment (n = 1295, 6%) not included in calculations. |

Fig. 1 Type, fraction, and dose of radiotherapy for men with locally advanced prostate cancer between 2000 and 2016 in Sweden. EBRT, external beam radiotherapy; HDR, high dose-rate.
of PCa death was more pronounced in men aged <75 years than for those >75 years (Fig. 3).

There were large geographical differences in the proportion of men who received radical treatment and in PCa mortality. In the two last periods, i.e. in 2008–2016, the proportion of men with locally advanced PCa who received radical therapy was 44% in the county with the lowest proportion of radical treatment and 73% in county with the highest proportion (Fig. S2 and Tables S2,S3). During the same period, the 5-year cumulative PCa mortality varied from 7% to 19% between counties. However, the numbers of treated men and men who died of PCa in each county were modest, so random fluctuation affected comparisons between counties.

Discussion

In this nationwide, population-based study in Sweden, the proportion of men with locally advanced PCa who received radical therapy increased almost threefold between 2000 and 2016. At the same time, the 5-year PCa cumulative mortality decreased modestly in all men diagnosed with locally advanced PCa, also including those who did not receive radical therapy. In men aged 65–74 years, for whom the use of radical therapy increased the most, there was a 50% relative reduction in 5-year mortality.

Strengths and limitations

There was an increased use of bone imaging with time, so some men in the earlier periods may have had undetected bone metastases. This likely contributed to the increased survival; however, to limit the effect of diagnostic activity we adjusted for M0 and Mx status in the multivariate model. Higher Gleason grades became more common in the later calendar periods due to changes in the International Society of Urological Pathology (ISUP) classification and an increase in the number of biopsy cores obtained with an ensuing grade migration [15]. Therefore, we did not include Gleason grading in our multivariate analysis, as this would have exaggerated the decrease in risk of PCa death.

Strengths of our present study include that the NPCR of Sweden has a 98% capture rate compared to the Swedish Cancer Registry to which reporting is mandated by law. Thus, our present study included virtually all men diagnosed with locally advanced PCa in a well-defined population during a 17-year period with a recent end of follow-up. In addition, completeness and validity of data in the NPCR have been assessed and found to be high and we also had access to data of high quality from other national healthcare registers and demographic databases [16-18].
Fig. 2 Cumulative incidence of prostate cancer death at 5 years, considering other causes of death as competing risk, for men with locally advanced prostate cancer per calendar period and age.

Changes in locally advanced PCa treatment/mortality
On a group level, PSA level is a very good measure of cancer extent, and in our present study, the median PSA level remained essentially unchanged and the proportion of locally very advanced cancers (T4) also remained essentially the same. This supports the view that there has been little change in case mix within the locally advanced PCA category in our cohort that could have affected the temporal comparisons.

Confounding by indication for treatment is a very strong limitation when comparing outcome after different treatments in observational studies. In the present study, we tried to overcome this limitation by assessing mortality in all men with locally advanced PCA, also including men who did not receive radical treatment. In a previous study using the PCBaSe, we tried to avoid confounding by use of another analytical approach, namely by use of a semi-ecological design, i.e., exposure to treatment measured as the proportion of men who received radical therapy and not data on an individual basis [19]. In our previous study, men treated in units with a high proportion of radical treatment had lower PCA mortality than men treated in units with little treatment.

RT, which was the most common radical therapy in our present study, has been improved substantially. Several RCTs have shown that increases in RT doses lead to lower PCA mortality and in our present study there were substantial increases in RT doses between the first and last time period [20,21]. Furthermore, the precision in delivery to the target organ has been improved by the introduction of conformal RT [22]. However, additionally adjusting for RT dose in the Cox regression model had only marginal effects on the risk estimates (data not shown). Advances in diagnostic imaging may also have contributed to more accurate staging with a lower probability of undetected metastases in the later periods. During the study period, RALP largely replaced retropubic RP; however, there is little evidence that this has improved survival [23].

**Interpretation**

To our knowledge, the present study is the first to relate time trends in treatment for locally advanced PCAs with mortality in a population-based cohort with data on stage; PSA level; Gleason grading; and comprehensive data on type, fraction and dose of RT; and type of RP.

In our present study, the decrease in risk of PCA death by calendar period remained after adjusting for known prognostic risk factors, but was no longer significant when radical treatment was included in the model, suggesting that most of the decrease in PCA mortality was due to more frequent use of radical treatment in the more recent time periods. We were unable to assess to what extent an increase in use of chemotherapy and androgen receptor targeting drugs in men with disease progression to castrate-resistant PCAs contributed to the temporal decrease in PCA mortality during the study period. We argue that effect of these treatments was small given that the uptake of these treatments has been quite modest and recent [24,25].

In order to assess if results from RCTs are generalisable to an entire population, data from a real-life setting are needed. Our present data are in line with results from previous RCTs that have shown that ADT plus RT decreases the risk of PCA mortality up to 50% [5-8]. The difference in cumulative PCA mortality between men treated with RT and ADT and ADT monotherapy continued to increase well beyond 5 years of follow-up in the Scandinavian Prostate Cancer Group-7 (SPCG-7) study and the Intergroup study, so the benefit of radical therapy will likely increase with longer follow-up also in our study population [6,7]. Our present results show that randomised trials can influence the pattern of care in a nation; however, it is noteworthy that there had been an increased use of radical therapy already before the publication of SPCG-7 in 2009. Radical treatment, in particular RT, of locally advanced PCA in the Swedish population increased substantially after the publication of SPCG-7 and there was a subsequent decrease in PCA mortality in all men diagnosed with locally advanced disease [5].

We argue that our present data are generalisable to other Western populations given the same distribution of risk category and similar risk of death from other causes. Although the decrease in risk of PCA death was modest, it should be noted that this decrease was measured among all men with locally advanced PCA, including those who did not receive radical treatment who made up a substantial proportion of all men with locally advanced PCAs. Finally, men with locally advanced PCA is a rather large group, so in absolute terms this modest relative gain will translate to a substantial number of life-years gained.

There are no RCTs comparing outcome after RT and RP. Most observational studies comparing these treatments have favoured RP, but there has been confounding by indication for treatment in these studies, with more men with favourable cancer characteristics receiving RP [26]. In a study in the PCBaSe with comprehensive data on cancer characteristics and treatment, men with high-risk cancer who received RT or RP had similar risk of PCA death [14]. To date, there is evidence from several RCTs that compared to ADT, RT and ADT decreases mortality in men with locally advanced PCA, whereas there is less evidence for RP [6-7,27-29]. Currently, a RCT on RT and ADT vs RP is recruiting participants in Scandinavia [30].

**Conclusion**

Our present results show that radical treatment for locally advanced PCAs is increasingly used in Sweden and our results indicate that the decreased risk of PCA death observed in
Fig. 3 Hazard ratio (HR) of death from prostate cancer and all causes in men diagnosed with locally advanced prostate cancer per calendar period and age in Cox multivariate regression analyses. HRs shown with 95% CIs. *Adjusted for age, PSA level, clinical T stage, M stage, Charlson Comorbidity Index, civil status and educational level. **Additionally adjusting for radical treatment.

### Age < 65

| Year of Diagnosis | Death from all causes | Univariate model | HR | 95% CI | P  |
|-------------------|-----------------------|------------------|----|--------|----|
| 2000−2003         | Ref                   |                  |    |        |    |
| 2004−2007         | 0.75 0.63−0.89 <0.01  |                  |    |        |    |
| 2008−2011         | 0.96 0.78−1.27 0.66  |                  |    |        |    |
| 2012−2016         | 0.60 0.42−0.86 <0.01  |                  |    |        |    |
|                   | 0.65 0.49−0.87 <0.01  |                  |    |        |    |

### Age 65−69

| Year of Diagnosis | Death from all causes | Univariate model | HR | 95% CI | P  |
|-------------------|-----------------------|------------------|----|--------|----|
| 2000−2003         | Ref                   |                  |    |        |    |
| 2004−2007         | 0.75 0.64−0.89 <0.01  |                  |    |        |    |
| 2008−2011         | 0.92 0.74−1.13 0.43  |                  |    |        |    |
| 2012−2016         | 0.60 0.41−0.86 <0.01  |                  |    |        |    |
|                   | 0.64 0.48−0.86 <0.01  |                  |    |        |    |

### Age 70−74

| Year of Diagnosis | Death from all causes | Univariate model | HR | 95% CI | P  |
|-------------------|-----------------------|------------------|----|--------|----|
| 2000−2003         | Ref                   |                  |    |        |    |
| 2004−2007         | 0.88 0.74−1.06 0.18  |                  |    |        |    |
| 2008−2011         | 1.24 0.99−1.55 0.06  |                  |    |        |    |
| 2012−2016         | 0.87 0.60−1.28 0.49  |                  |    |        |    |
|                   | 0.88 0.64−1.19 0.40  |                  |    |        |    |

### Age 75−79

| Year of Diagnosis | Death from all causes | Univariate model | HR | 95% CI | P  |
|-------------------|-----------------------|------------------|----|--------|----|
| 2000−2003         | Ref                   |                  |    |        |    |
| 2004−2007         | 0.89 0.78−1.01 0.07  |                  |    |        |    |
| 2008−2011         | 0.80 0.68−0.94 <0.01 |                  |    |        |    |
| 2012−2016         | 0.72 0.57−0.91 <0.01 |                  |    |        |    |
|                   | 0.66 0.57−0.78 <0.01 |                  |    |        |    |

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RCTs on radical RT can also be achieved on a population basis. Data from nationwide population-based registers are an important complement to RCTs in order to assess if their results are also applicable in a real-life setting.

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Conflict of interest
All authors have filled in the ICMJE form for disclosure of potential conflict of interest and have nothing to disclose.

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Abbreviations: ADT, androgen-deprivation therapy; CCI, Charlson Comorbidity Index; GGG, Gleason Grade Group; HR, hazard ratio; NPCR, National Prostate Cancer Register of Sweden; PCa, prostate cancer; PCBaSe, Prostate Cancer data Base Sweden; RALP, robot-assisted laparoscopic RP; RCT, randomised clinical trial; RP, radical prostatectomy; RT, radiotherapy; SPCG-7, Scandinavian Prostate Cancer Group-7.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Type of radical prostatectomy per calendar period.
Fig. S2. Proportion of primary radical treatment and 5-year cumulative prostate cancer mortality in all men aged <80 years in Sweden diagnosed with locally advanced prostate cancer per county between 2008 and 2016.
Table S1. Dose and type of radiotherapy per calendar period.
Table S2. Primary radical treatment per calendar period and county.
Table S3. Cumulative incidence of prostate cancer mortality at 5 years for men with locally advanced prostate cancer per calendar period and county.