**Uptake of doublet therapy for de novo metastatic castration sensitive prostate cancer: a population-based drug utilisation study in Sweden**

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**ABSTRACT**

**Background:** Randomised controlled trials have demonstrated prolonged survival with new upfront treatments in addition to standard androgen deprivation therapy (ADT) in men with de novo metastatic castration-sensitive prostate cancer. We describe patient characteristics, time trends and regional differences in uptake of these new treatment strategies in clinical practice.

**Material and methods:** This descriptive study consisted of men registered in the National Prostate Cancer Register of Sweden from 1 January 2018 to 31 March 2022 with de novo metastatic castration-sensitive prostate cancer defined by the presence of metastases on imaging at the time of diagnosis. Life expectancy was calculated based on age, Charlson Comorbidity Index and a Drug Comorbidity Index.

**Results:** Within 6 months from diagnosis, 57% (1,677/2,959) of men with de novo metastatic castration-sensitive prostate cancer and more than 3 years of life expectancy had received docetaxel, abiraterone, enzalutamide, apalutamide and/or radiotherapy. Over time, there was a 2-fold increase in uptake of any added treatment, mainly driven by a 6-fold increase in use of abiraterone, enzalutamide or apalutamide, with little change in use of other treatments.

**Conclusions:** Slightly more than half of men diagnosed with de novo metastatic castration-sensitive prostate cancer and a life expectancy of at least 3 years received additions to standard ADT as recommended by national guidelines in 2019–2022 in Sweden. There was a 2-fold increase in use of these treatments during the study period; however, efforts to further increase adherence to guidelines are warranted.

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**ARTICLE HISTORY**

Received 10 February 2023

Accepted 28 September 2023

**KEYWORDS** Prostate cancer; castration sensitive prostate cancer; abiraterone; enzalutamide; apalutamide; docetaxel; radiotherapy

**ARTICLE**

**INTRODUCTION**

Median survival for men with de novo metastatic castration sensitive prostate cancer (mCSPC) was estimated to be around 3 years in 2015 in a nationwide population-based study in Sweden [1]. Recently, several new treatments have been shown to increase survival in men with mCSPC when combined with standard androgen deprivation therapy (ADT), that is, doublet therapy. In randomised clinical trials, chemotherapy with docetaxel as well as the use of abiraterone, enzalutamide and apalutamide in addition to ADT improved survival with approximately 1 year in men with de novo mCSPC [2–9]. Furthermore, local radiotherapy in men with low-volume mCSPC improved time to progression and/or survival in recent randomized trials [10,11]. The results of these trials have been the basis for changes in European guidelines for prostate cancer treatment, which now recommend the upfront use of doublet therapy in men with mCSPC unless there is a clear contraindication [12].

However, little is known about the adherence to these recommendations in clinical practice [13].

The Swedish national clinical guidance follows the European guideline concerning treatment of men with de novo mCSPC [14,15]. It is not expected that cost should be a barrier for the individual patient since the Swedish healthcare system automatically covers fees for all legal residents with the patient paying only a small fraction of the fee for examination and daily hospital charges. This also applies to medications where patient only pays the cost for prescription medicines, reimbursed by the government, up to a threshold of currently 2 400 SEK (approximately 205 Euros). Such reimbursement for the indication de novo mCSPC was approved by the Swedish health technology assessment agency (The Dental and Pharmaceutical Benefits Agency, TLV) for abiraterone in June 2018, apalutamide in May 2021 and enzalutamide in January 2022. This study aimed...
to assess uptake of upfront treatment in addition to standard ADT in men with de novo mCSPC as recommended by guidelines and describe patient characteristics, time trends, as well as regional differences in uptake.

Methods

Study design and participants

We selected men with de novo mCSPC registered in National Prostate Cancer Register (NPCR) from 1 January 2018 to 31 March 2022 as study population. De novo mCSPC was defined by the presence of bone metastases and/or visceral metastases on imaging at the time of diagnosis. A dichotomous variable on the number of metastatic foci on bone imaging (1–3 foci or ≥4 foci) is available in NPCR since September 2018. High risk mCSPC was defined as having at least two of these three risk factors: Gleason score 8–10, ≥4 bone metastases or visceral metastases [16]. In order to accommodate a clinical assessment of the utility of an additional treatment based on life expectancy, we characterised a subgroup of men with a life expectancy above 3 years based on the result from our previous study on survival of men with de novo mCSPC. A majority of men (2 959/3 697, 80%) in this study group had a life expectancy of at least 3 years.

The National Board of Health and Welfare provides a service that enables researchers with data from a clinical disease register to submit data on individuals to be linked with national health registers, and aggregated data are then returned to the researcher. Approval by the Swedish Ethical Review Authority was obtained for such linkage as well as for a validation of docetaxel registration in NPCR by a structured review of healthcare records. A dataset with information on prostate cancer characteristics and region from NPCR was linked at the Board of Health and Welfare to the National Patient Register and the Prescribed Drug Register using the unique Swedish personal identity number [17]. Aggregated and tabulated information on the number of men in the different therapeutic groups, stratified by covariate categories, was returned to the research team. Cells with few observations were masked by the Board of Health and Welfare.

Data sources

Since 1998, the NPCR captures 98% of all cases of prostate cancer in Sweden compared to the Cancer Register to which reporting is mandated by law. The primary registration in NPCR contains comprehensive data on diagnostic procedures, cancer characteristics and primary cancer treatment [18]. There is, however, no information in NPCR on progression to metastatic disease or progression to castration resistance other than in a subregister – the Patient-overview Prostate Cancer (PPC) in which longitudinal data are registered [19].

The National Prescribed Drug Register is a compulsory, nationwide register maintained by the Swedish Board of Health and Welfare [20]. It contains detailed and comprehensive individual-level information on all prescribed and dispensed drugs in Sweden since 1 July 2005. This register does not hold information on drugs administered in-hospital. Data are available for analysis 1 month after a prescription has been filled.

The National Patient Register is a compulsory and nationwide register that is maintained by the Swedish Board of Health and Welfare [21]. It collects information on all in-hospital care and out-patient specialist care, but not primary care. The information includes dates for admissions and discharges, department and hospital identifier, hospital discharge diagnoses and surgical procedure codes. This register captures in-patient care since 1987 and specialised out-patient care since 2001 [21]. Hospital discharge diagnoses are coded according to the Swedish clinical modification of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-SE) since 1997. Coding accuracy is diagnosis dependent [22,23].

The regional proportion of men younger than 80 years and with high-risk cancer who were subjected to multidisciplinary care planning was extracted from the NPCR [24]. Regional population counts were provided by Statistics Sweden.

Definitions of treatment exposure

Most men in Sweden diagnosed with mCSPC will receive ADT at their urological department and will subsequently be referred for assessment of eligibility for additional treatment either at a multidisciplinary conference as per guidelines or referred to a consultation at an oncological department.

Exposure to local radiotherapy was captured from registration in NPCR as primary tumour-directed local radiotherapy, excluding lower dose radiotherapy for palliation of local symptoms.

Docetaxel as upfront treatment of men with a diagnosis of prostate cancer was determined from the primary registration in NPCR, available for docetaxel since March 2017. Use of docetaxel was validated as described below.

Exposure to abiraterone (ATC code L02BX03), enzalutamide (L02BB04), apalutamide (L02BB05), bicalutamide (L02BB03) and gonadotropin-releasing hormone (GnRH) agonists (L02AE) was defined as one or more filled prescriptions in The Prescribed Drug Register during a 6-month period after the date of the prostate cancer diagnosis. Five out of 21 healthcare regions in Sweden provide GnRH directly to the patient, without prescription. The Prescribed Drug Register therefore captures GnRH treatment accurately for 16 regions, but other medications are accurately captured in all 21 regions. The GnRH antagonist Degarelix (L02BX02) is used in a very small number of men usually in need of rapid onset of treatment effect due to severe disease symptoms. Degarelix is usually administered in-hospital without a prescription and could therefore not be captured in our study.

Patient characteristics for stratified descriptive analyses

The Charlson Comorbidity Index (CCI) was calculated from hospital discharge diagnoses registered in the in-patient part of the National Patient Register during the 10-year period prior to start of follow-up
plots showing time trends in proportion of given electronic report form at 20 hospitals. The proportion of men did not receive added treatment (Table 1). The proportion of men with a substantially lower burden of comorbidity, compared to men who received additional treatment (57% (1,677/2,959)).

Characteristics of men who received any treatment in addition to ADT

During the 45-month study period, there were 3,697 men in NPCR diagnosed with de novo mCSPC. An additional treatment with docetaxel, abiraterone, enzalutamide, apalutamide and/or radiotherapy was provided to 46% of these men (1,683/3,697) within 6 months of diagnosis. In the subgroup of men with a life expectancy ≥3 years, the overall proportion receiving additional treatment was 57% (1,677/2,959).

Characteristics of men who received drug treatment in addition to ADT

Men treated with docetaxel were younger, had a lower burden of comorbidity and life expectancy, but they had a lower burden of metastases (Table 1). The radiotherapy for men diagnosed with de novo mCSPC was started within 6 months in 51%, within 9 months in 83% and within 1 year in 93%.

Characteristics of men who received radiotherapy in addition to ADT

Radiotherapy to the prostate was provided to 13% of men (483/3,697) within 6 months of diagnosis, and 39% of these men (187/483) also received an additional drug treatment within 6 months from the date of diagnosis. The absolute majority of treatment doses were hypofractioned >2.5 Gy to a biologically effective dose of at least 36 Gy.

The characteristics of these men were largely similar to those for men who received any added treatment regarding age, comorbidity and life expectancy, but they had a lower burden of metastases (Table 1). The radiotherapy for men diagnosed with de novo mCSPC was started within 6 months in 51%, within 9 months in 83% and within 1 year in 93%.

Validation of docetaxel registration in NPCR

A structured review of healthcare records was performed for 500 randomly selected men from NPCR being <80 years old and diagnosed with mCSPC during 2018–2020. The age limit was applied since few men aged above 80 with mCSPC receive docetaxel (data on file). Information on treatment with docetaxel (yes/no), date for first administration, number of treatment cycles and if abiraterone was provided in case of prematurely discontinued treatment with docetaxel was extracted by research nurses using a structured electronic report form at 20 hospitals.

Statistical analysis

Since only descriptive analyses were performed in the presentation of drug utilisation, missing values were not imputed. The scatter-plots showing time trends in proportion of given treatment were smoothed using locally weighted polynomial regression. Associations between continuous variables were visualised with linear regression.

Life expectancy was calculated based on the follow-up of 12,836 men in NPCR diagnosed with de novo metastatic prostate cancer during the period 2007-01-01 to 2019-12-30. The median duration of follow-up was 6.4 years, and life expectancy was estimated as the area under the simulated survival function, where the simulation accounted not only for age, CCI and DCI at the start of follow-up but also for annual changes in age, CCI and DCI [30].

In the validation of the docetaxel registration, diagnostic test statistics with exact confidence intervals (CI) were calculated using the R EpiR package (version 2.0.39).

Results

Overall proportion receiving additional treatment

During the 45-month study period, there were 3,697 men in NPCR diagnosed with de novo mCSPC. An additional treatment with docetaxel, abiraterone, enzalutamide, apalutamide and/or radiotherapy was provided to 46% of these men (1,683/3,697) within 6 months from date of diagnosis. In the subgroup of men with a life expectancy ≥3 years, the overall proportion receiving additional treatment was 57% (1,677/2,959).

Time trends in frequency of added treatment

The overall proportion of men who received any additional treatment increased almost 2-fold during the study period (Figure 1). This increase was mainly driven by the increased use of abiraterone, enzalutamide or apalutamide that increased more than 6-fold from around 5% to more than 30%. During the initial phase of the COVID-19 pandemic in 2020, there was a decrease in the use of docetaxel.

Regional differences in the proportion of men who received added treatment

To reduce potential impact from differences in case mix between regions, we restricted these analyses to men with a life expectancy ≥3 years. Amongst these men, use of any additional
treatment varied substantially between regions, from 46% to 93% between the regions with the lowest and highest use (Figure 2). The regional proportion of men who received any added treatment did not increase with the proportion of patients discussed in multidisciplinary conference and did not appear related to patient volume in the region or regional population (Figure S1).

There were even bigger differences in the use of specific treatments, with the use of any of abiraterone, enzalutamide or apalutamide ranging from 5% to 50%, docetaxel from 9% to 56% and use of radiotherapy from 1% to 23% (Figure 3). The corresponding proportions for the full study population, without restriction for life expectancy, are displayed in Figure S2 and S3.

Table 1. Characteristics of 3,697 men with de novo metastatic castration sensitive prostate cancer (mCSPC) in The National Prostate Cancer Register (NPCR) of Sweden diagnosed between 1 April 2018 and 1 March 2022, stratified by treatment added to standard androgen deprivation therapy.

<table>
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<th>Patient characteristics</th>
<th>Any treatment</th>
<th>Any drug treatment</th>
<th>Radiotherapy</th>
<th>No added treatment</th>
<th>Total</th>
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<td>N = 1,788</td>
<td>N = 1,492</td>
<td>N = 483</td>
<td>N = 1,909</td>
<td>N = 3,697</td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>151</td>
<td>136</td>
<td>38</td>
<td>52</td>
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<td>156</td>
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<td></td>
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<td>62</td>
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<td>627</td>
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<td>273</td>
<td>274</td>
<td>490</td>
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<td>780</td>
<td>82</td>
<td>694</td>
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<td>439</td>
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<td></td>
</tr>
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<td>61</td>
<td>292</td>
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<tr>
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<td>777</td>
<td>728</td>
<td>96</td>
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<td>387</td>
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<td>1,305</td>
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<td>1,434</td>
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<tr>
<td>Ablatio testis</td>
<td>29</td>
<td>27</td>
<td>4</td>
<td>64</td>
<td>3.4</td>
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</table>

*Docetaxel, abiraterone, enzalutamide, apalutamide or radiotherapy; †Docetaxel, abiraterone, enzalutamide or apalutamide; ‡A comorbidity measure based on drug prescriptions filled the year before the index date [27]. Quartile 1 contains men with the lowest baseline mortality risk from comorbidity, and quartile 4 contains those with the highest comorbidity burden; §Life expectancy for metastatic prostate cancer was calculated based on age, CCI and DCI as described previously [30]; ‡High risk mCSPC was defined as having at least two of these three risk factors: Gleason score 8–10, ≥4 bone metastases or visceral metastases [16]; Not mutually exclusive categories; ¶Five out of 21 healthcare regions in Sweden provide GnRH directly to the patient, without prescription. This treatment is therefore not captured in the Prescribed Drug Register. In this row, men from these 5 regions have therefore been removed from the denominator to reduce bias in the estimated proportions; ©Bicalutamide as monotherapy, as flare protection with GnRH analogue during 1 month, or combined with GnRH analogue for maximal androgen blockade.

mCSPC: metastasised castration-sensitive prostate cancer; ADT: androgen deprivation therapy.
Figure 1. Calendar time-trends in the proportion of men with de novo mCSPC who received treatment in addition to standard ADT within 6 months after diagnosis amongst 3,697 men with metastatic castration sensitive prostate cancer at diagnosis. Treatment with abiraterone, enzalutamide and/or apalutamide has been aggregated to one common category (Abi/Enza/Apa).

Figure 2. Proportion per region in 2,959 men with de novo mCSPC and ≥3 years life expectancy in Sweden, who received added drug or local radiotherapy along with standard ADT (left panel) or added drug treatment along with standard ADT (right panel).
Validation of docetaxel registration in NPCR

Healthcare records of 500 men with mCSPC from 24 hospitals were reviewed, and 216 men who had been treated with docetaxel were identified, whereas in NPCR, 166 of these men were registered as treated with docetaxel. This corresponds to 84% (95% CI: 80% to 87%) being correctly classified. The sensitivity for docetaxel registration in NPCR was 0.70 (95% CI: 0.63 to 0.76), and the specificity was 0.95 (95% CI: 0.91 to 0.97). The positive predictive value was 0.91 (95% CI: 0.86 to 0.95), and the negative predictive value was 0.81 (95% CI: 0.76 to 0.85) (Table S1 and Table S2).

Discussion

In this population-based drug utilization study of men in Sweden with de novo mCSPC, 57% of men with a life expectancy of at least 3 years received upfront treatment as recommended by national guidelines with docetaxel; any of abiraterone, enzalutamide or apalutamide; and/or radiotherapy in addition to standard ADT. There was a 2-fold increase in use of these treatments during the study period, likely indicating a continued gradual process of implementation.

The specific reason for the low adherence and the large differences between regions in our study cannot be deduced from our data. Differences between healthcare providers have been observed previously both regarding implementation of treatments and outcome of cancer care [31,32], and hospital-level variability in guideline adherence has translated into effects on overall survival [33,34]. Some factors that have previously been associated with non-adherence to treatment guidelines are access to cancer specialists [31], facility patient volume [35], social determinants [36] and cost of care [37]. We argue that assessments in the regions of cost/benefit ratio had a strong impact on adherence since the cost for doublet therapy is carried by each region.

Surprisingly, more frequent use of multidisciplinary conferences was not associated with higher adherence in our study. We argue that the key component to reduce differences in healthcare is to publicly report quality process indicators to benchmark the performance of each healthcare provider [38]. This is a useful basis for a discussion between stakeholders such as department leadership, administration, patient organisations and politicians.

Comorbid conditions may explain why these additional treatments are not provided to all men [35], not even for all men with a life expectancy of 3 years or more, and it is not possible to pinpoint the exact proportion of these men for whom there was a valid indication for additional treatment. Whilst we have calculated life expectancy based on a statistical model combining age and two measures of comorbidity [30], this estimation may be more difficult on the individual man in clinical practice. An underestimation of life expectancy by the clinician could contribute to the results seen in this study [39].

There was a two-fold range in uptake of any additional treatment between the 21 administrative regions in Sweden in men with at least 3 years life expectancy, and for specific treatments for mCSPC, the range in uptake was even larger, with a 10-fold difference between regions with highest vs lowest uptake of any of abiraterone, enzalutamide or apalutamide, and use of local radiotherapy. We have previously observed similar differences between regions in uptake of chemotherapy, abiraterone and enzalutamide in Sweden [40–42]. Taken together, these results indicate that other factors than those measured in this study strongly affect treatment decisions. It is notable that this regional variability is seen even though treatment decisions...
are made after multi-disciplinary team meetings in overall 90% of men <80 years old with de novo metastatic prostate cancer, with regional proportions varying between 76% and 100% [43].

Local radiotherapy to the prostate was only provided to 13% of men within 6 months of diagnosis. The low proportion and slow increase over time are notable. According to a systematic review and The European Association of Urology guidelines, local radiotherapy of the prostate should be considered in men with low-volume metastatic disease [12,40]. There is, however, uncertainty regarding the optimal definition of low metastatic burden (oligometastatic) prostate cancer, and our data had limited ability to characterise metastatic burden. Perceived guideline clarity has been implicated as an important driver of physician behaviour [41].

Our restriction to capture radiotherapy only during the first 6 months after primary diagnosis was intended to limit our analysis to de novo/synchronous metastatic disease but may have resulted in a too conservative estimate. The low proportion of men who received primary local radiotherapy may therefore to some extent be due to limitations in our data and warrants further evaluation of the potential for improvement.

Another consideration in the interpretation of these results is the impact of the COVID-19 pandemic on prostate cancer care. During the latter part of the study period coinciding with the pandemic, there were likely incentives to limit use of healthcare resources potentially resulting in reduced use of docetaxel and radiotherapy. Data for the early phase of the pandemic in the first quarter in 2020 indicate an increased use of abiraterone, enzalutamide or apalutamide, and a corresponding decrease in use of docetaxel.

The main strength of this drug utilization study is the use of registers with nationwide, population-based coverage with rapid and near complete capture of data. NPCR provided data on the diagnosis of de novo mCSPC, cancer characteristics and use of docetaxel and radiotherapy. The Prescribed Drug Register, which was used both to define exposure to abiraterone, enzalutamide and apalutamide and to measure comorbidity by use of a drug comorbidity index, has a virtually complete capture of all filled prescriptions [27,28].

The estimation of life expectancy in the current study was based on men diagnosed with de novo metastatic prostate cancer, and not men free of prostate cancer. It is therefore expected to result in a conservative selection of men with at least 3 years of life expectancy, and consequently also providing a conservative estimate of the proportion of men without additional treatment in this subgroup.

There are some limitations in our study that should be acknowledged. Only aggregated and tabulated information on the number of men in the different therapeutic groups, stratified by covariate categories, was available to the research team. Cells with few observations were masked for legal reasons. To comply with this mandated restriction, the number of covariates had to be limited. Information on, for example, nodal metastases and specific indications for bicalutamide was therefore not included, and the ability to perform sensitivity analyses is limited. Since the times of approval of reimbursement for the indication de novo mCSPC have substantial impact on the pattern of utilization of these drugs, including off-label use of enzalutamide for mCSPC, subgroup analyses for these individual treatments are not meaningful.

The validity of docetaxel exposure data was assessed by a patient record review, and for approximately 20% of men who had received docetaxel according to the patient records, there was no registration in NPCR. However, since docetaxel only contributed with 20% to ‘any added drug’, this underreporting did not materially affect the main outcome. Furthermore, neither NPCR nor the Patient Register hold data on performance status such as the Eastern Cooperative Oncology Group/WHO Health organization Performance status (ECOG), meaning that we lacked data on patient characteristics not captured by our comorbidity indices, which may affect treatment decisions and hence potentially contributed to unmeasured differences in case mix between regions. There is also some delay in reporting to NPCR, and capture reaches 80% at 6 months and 95% around 9 months after the date of diagnosis, which is clearly illustrated by the low proportion of radiotherapy during the last study period. Since the study data were extracted in June 2022, data for the first quarter in 2022 should be interpreted with caution.

To assess generalisability of the results to other countries and healthcare systems, it is essential to understand the set-up of healthcare in Sweden. In the Swedish healthcare system, 21 independent regions provide universal low-cost care to all residents, and the NPCR captures 98% of all cases of prostate cancer in Sweden. Thus, our study is population based, and there is little concern for bias due to selection mechanisms related to access to care. This improves the generalisability of our results.

In conclusion, slightly more than half of men in Sweden diagnosed with de novo mCSPC between January 2018 and March 2022 and who had a life expectancy of at least 3 years received upfront docetaxel, abiraterone, enzalutamide, apalutamide and/or radiotherapy in addition to standard hormonal treatment as recommended by current guidelines. There was a 2-fold increase in use of these treatments during the study period. Our results indicate that further efforts are needed to increase adherence to guidelines.

Acknowledgements

This project was made possible by the continuous work of the National Prostate Cancer Register of Sweden (NPCR) steering group: David Robinson, Ingela Franck Lissbrant, Johan Styrke, Johan Stranne, Jon Kindblom, Camilla Thellenberg, Andreas Josefsson, Ingrida Verbiene, Hampus Nugin, Stefan Carlsson, Anna Kristiansen, Mats Andén, Thomas Jiborn, Olof Ståhl, Olof Akre, Per Fransson, Eva Johansson, Magnus Törnblom, Fredrik Jäderling, Marie Hjälmen Eriksson, Lotta Renström, Jonas Hugosson, Ola Bratt, Maria Nyberg, Fredrik Sandin, Camilla Byström, Mia Brus, Mats Lambe, Anna Hedström, Nina Hageman, Christofer Lagerros, Hans Joelsson and Gert Malmberg.
Data used in the present study were extracted from the Prostate Cancer Database Sweden (PCBaSe), which is based on the National Prostate Cancer Register (NPCR) of Sweden. The data cannot be shared publicly because the individual-level data contain potentially identifying and sensitive patient information and cannot be published due to legislation and ethical approval (https://etikprovningsmyndigheten.se). Use of data from national health-data registers is further restricted by the Swedish Board of Health and Welfare (https://www.socialstyrelsen.se/en/) and Statistics Sweden (https://www.scb.se/en/), which are Government Agencies providing access to the linked healthcare registers. The data will be shared on reasonable request in an application made to the steering group of PCBaSe. For detailed information, please see www.npcr.se/in-english, where registration forms, manuals and annual reports from NPCR are available alongside a full list of publications from PCBaSe. The statistical program code used for the present study analyses can be provided on request (contact: rolf.gedeborg@surgsci.uu.se).

Authors’ contributions
Conceptualization: Pär Stattin; Methodology: Fredrik Sandin, Hans Garmo, Rolf Gedeborg; Formal analysis and investigation: Fredrik Sandin, Rolf Gedeborg; Writing – original draft preparation: Rolf Gedeborg; Writing – review and editing: Pär Stattin, Rolf Gedeborg, Camilla Thellenberg-Karlsson, Johan Styrke, Ingela Franck Lissbrant, Hans Garmo; Funding acquisition: Pär Stattin; Resources: Pär Stattin; Supervision: Pär Stattin.

Ethics approval
Approved by the Swedish Ethical Review Authority: Dnr 2020-03889.

Consent to participate
The requirement for informed consent was waived by the Ethical Review Authority.

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