Evidence of cancer progression as the cause of death in men with prostate cancer in Sweden

Andri Wilberg Orrason, Johan Styrke, Hans Garmo and Pär Stattin

1Department of Surgical Sciences, Uppsala University Hospital, Uppsala, and 2Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden

Objective
To assess the strength of the evidence indicative of prostate cancer (PCa) progression as the adjudicated cause of death, according to age at death and PCa risk category.

Patients and Methods
Using data from the Prostate Cancer data Base Sweden, we identified a study frame of 5543 men with PCa registered as the cause of death according to the Cause of Death Register. We assessed the evidence of PCa progression through a review of healthcare records for a stratified sample of 495/5543. We extracted data on prostate-specific antigen levels, presence of metastases on imaging, and PCa treatments, and quantified the evidence of disease progression using a points system.

Results
Both no evidence and moderate evidence for PCa progression was more common in men aged >85 years at death than those aged <85 years (29% vs 14%). Among the latter, the proportion with no evidence or moderate evidence for PCa progression was 21% for low-risk, 14% for intermediate-risk, 8% for high-risk, and 0% for metastatic PCa. In contrast, in men aged >85 years, there was little difference in the proportion with no evidence or moderate evidence of PCa progression between PCa risk categories; 31% for low-risk, 29% for intermediate-risk, 29% for high-risk, and 21% for metastatic PCa. Of the 5543 men who died from PCa, 13% (95% confidence interval 5–19%) were estimated to have either no evidence or moderate evidence of PCa progression.

Conclusions
Weak evidence for PCa progression as cause of death was more common in older men with PCa and in those with low-risk PCa. This has implications for interpretation of mortality statistics especially when assessing screening and early treatment of PCa because the beneficial effect of earlier diagnosis could be masked by erroneous adjudication of PCa as cause of death in older men, particular those with localised disease at diagnosis.

Keywords
prostate cancer, cause of death, death certificate, mortality, adjudication of death, #PCSM, #ProstateCancer, #uroonc

Introduction
Prostate cancer (PCa) is the most common cancer in many high-resource countries, including Sweden [1]. During the last two decades there has been both an increased use of radical treatment for PCa and an ~20% decrease in PCa-related mortality [2–4]. However, in Sweden, the decline in PCa mortality has differed by age, with a 50% reduction seen in men aged <80 years compared with a 13% reduction in men aged ≥80 years. One explanation for this age disparity is that older men are often diagnosed with advanced disease and rarely receive radical treatment [5,6]. Furthermore, cancer mortality statistics are based on adjudicated cause of death, which is challenging in older men who often have multiple comorbidities [7–9]. Although several studies have shown that death certificates for men with PCa are highly accurate, many of these have been based on healthy, middle-aged men diagnosed in PCa screening trials who have been followed more closely than men with PCa in the general population [10–15].

We have previously found that among older men with low-risk disease, 10-year cancer-specific survival was 85%, whereas 10-year relative survival, which is independent of cause of
death, was well above 100% [16]. We hypothesise that the reason for this difference is, at least partly, due to adjudication of cause of death in older men with low-risk PCa is subject to a sticky-diagnosis bias – that is, PCa itself is attributed as the cause of death despite there being little evidence for this [17].

The aim of this study was to evaluate the association between evidence indicative of PCa progression and PCa as cause of death among men with PCa cancer. To achieve this, we quantified the evidence for PCa progression from healthcare records of a representative sample of men with PCa in Sweden.

**Patients and Methods**

We identified 18 900 men in Sweden who died from PCa between 2011 and 2018 according to the Cause of Death Register (Fig. 1). Of these, 10% were neither recorded in the Cancer Register nor in the National Prostate Cancer Register (NPCR) of Sweden. Around 4% (~750 men) were registered in the Cancer Register but not in NPCR, mostly due to the date of diagnosis being before 1998, when the NPCR was started. However, the majority (16 008) had been registered in NPCR with data available on cancer characteristics, the diagnostic evaluation, primary treatment, and treating hospital. Among these 16 008 men, we identified 5543 who had been treated at one of 20 hospitals participating in our study – these men constituted our ‘study frame’ (Fig. S1).

Through use of individuals’ unique Swedish person identity number, data for men in the NPCR have been linked with other national healthcare registers, including the National Patient Register, the Prescribed Drug Register, and the Cause of Death Register, and are available for research purposes in the – Prostate Cancer data Base Sweden (PCBaSe) 4.0 [18]. The study protocol was approved by the Research Ethics Board in Uppsala.

**Stratified Sampling**

Within our study frame we undertook stratified random sampling of 510 men according to age and risk category (Table S1). Age groups were based on age at PCa-related death: <70, 70–74, 75–79, 80–84, 85–89, and ≥90 years, with ‘older men’ defined as those aged ≥85 years, and ‘younger men’ defined as those aged <85 years. Risk category at diagnosis was defined according to a modified National Comprehensive Cancer Network (NCCN) categorisation: ‘low-risk’, clinical stage T1–T2, Gleason score 6 and PSA level of <10 ng/mL; ‘intermediate-risk’, T1–T2, Gleason score 7 and/or PSA level of 10–19.9 ng/mL; ‘high-risk localised or locally advanced’, T3, Gleason score 8–10 and/or PSA level of 20–49.9 ng/mL; ‘regionally metastatic’, T4, N1 and/or PSA level of 50–99.9 ng/mL; ‘distant metastases’, M1 or PSA level of ≥100 ng/mL. Due to the limited number of study men, Gleason Score 3 + 4 and 4 + 3 were analysed as a single entity (i.e., Gleason score 7) in order to restrict the number of Gleason scores to four categories with distinctly different prognosis. A standard technique to improve precision in stratified sampling is to apply oversampling [19]. Men who died aged 85–89 years, and men with low- or intermediate-risk PCa, were oversampled to improve estimate precision based on our hypothesis that a higher proportion of these men would have little evidence for PCa progression as the likely cause of death. We did not sample men aged ≥90 years (who composed 13% of our study frame) as they are rarely monitored for PCa progression, and instead assumed that they had the same score as men aged 85–89 years. For similar reasons, no sampling was performed amongst men with missing data on risk category (3% of our study frame), and we assumed these men had the same score as men with
intermediate-risk PCa [20]. To mask the hospital staff extracting the data on the registered cause of death, data for an additional 100 men in the NPCR were added to the sample, who according to the Cause of Death Register had not died from their PCa.

We assessed the degree of evidence indicative of PCa progression. We used data in the PCBaSe 4.0 and healthcare records to determine the following: the five most recent measurements of serum PSA, evidence of metastasis on imaging (bone scintigraphy, X-ray, CT, positron emission tomography, and MRI), treatment with a GnRH agonist or orchidectomy, and whether the PCa was castration resistant. The latter was defined as a PSA level of ≥50 ng/mL in men on GnRH, or treatment with chemotherapy, androgen receptor-targeted drugs or Radium-223, in addition to clinical assessment. We created a point system to assess the evidence for PCa progression that was based on factors related to progressive disease and prostate cancer death, based on our clinical judgement and published literature in the field [21–25]. We then attributed points to each factor to reflect the strength of association to progressive disease and PCa death. Factors related to high or rapidly increasing serum levels of PSA were attributed one point, verified bone metastases at imaging two points, more than three bone metastases or visceral metastases three points, treatment with GnRH agonists or orchidectomy one point, and diagnosis of castration-resistant PCa (CRPC) was attributed three points. The strength of the evidence indicative of PCa progression was classified as: no evidence (0 point), moderate evidence (one point), and strong evidence (2–9 points). Staff at each hospital who regularly register data in the NPCR for incident cases of PCa extracted data from the patient’s hospital record, including records from urology, surgery, internal medicine, oncology, geriatrics, and palliative care departments, as well as records from community healthcare providers and nursing homes. Data were extracted into a specifically created on-line form. Hospital staff were each given a written manual for reporting, attended a tutorial session on how to extract the data, and a helpdesk was established that could be reached by mail or telephone.

Co-Variates

The following patient variables were extracted from the PCBaSe: age at death (from the Cause of Death Register), data for calculation of the Charlson Comorbidity Index (CCI), orchidectomy and Radium-233 therapy (from the National Patient Register), and use of opioids, GnRH agonist, abiraterone, and enzalutamide (from the Prescribed Drug Register).

Statistical Analysis

Baseline characteristics of the final sample were described using frequency counts and percentages for categorical variables and mean with standard deviation (sd) or median with interquartile range (IQR) for continuous variables. The quantitative strength of evidence indicative of PCa progression was described using frequency counts and percentages for men in the sample, with CIs estimated using standard statistical methods for stratified sampling for men in the study frame [19]. Evidence for PCa progression as cause of death was analysed by age at death and risk category separately, as well as by the two variables combined. To assess the representativity of men in our study frame, we compared cancer characteristics of all men diagnosed with PCa at the participating hospitals with all men with prostate cancer in the NPCR.

Results

Baseline Characteristics

Medical records were unavailable for 15/510 men in the stratified sample, leaving 495/510 (97%) men for analysis. Compared with younger men, older men received radical treatment less often (12% vs 54%) and had more comorbidities at the date of PCa diagnosis (45% vs 26% for CCI ≥3) (Table 1). The factors used for quantifying the strength of evidence indicative of PCa progression are shown in Table 2, and the distribution of these factors according to age is shown in Table 3. Compared with younger men, older men had a lower PSA value at the last measurement before death (mean 61 vs 165 ng/mL), and were less likely to have a PSA doubling time <6 months (28% vs 44%), documented bone pain (47% vs 63%), use of strong opioids (46% vs 54%), treatment with GnRH or orchidectomy (77% vs 84%) and treatment for CRPC (8% vs 50%) (Table 1). Older men were also less likely to have PCa metastases on imaging (61% vs 84%), both with regards to visceral metastases (15% vs 26%) and multiple bone metastases (48% vs 74%).

Evidence Indicative of PCa Progression

A summary of the consolidated quantified evidence indicative of PCa progression is shown in Table 4, according to age at death and risk category. No evidence or moderate evidence was more common in older men than younger men (29% vs 14%), while strong evidence was less common among older men (71% vs 86%). The proportion of men with either no evidence or moderate evidence of PCa progression decreased with increasing risk category; e.g., no evidence or moderate evidence was attributed to 25% of men with low-risk PCa, 20% with intermediate-risk disease, 17% with high-risk disease, and 9% with regional/distant metastases. Analyses by both age at death and risk category showed that among younger men, the proportion with no evidence or moderate evidence of PCa progression clearly decreased with increasing risk category; 21% for low-risk disease, 14% for...
intermediate-risk disease, 8% for high-risk disease, and 0% for regional/distant metastatic PCa (Fig. 2, Table S2). In contrast, among older men, there was little difference in the proportion with either no evidence or moderate evidence between risk categories; 31% for low-risk, 29% for intermediate-risk, 29% for high-risk, and 21% for metastatic PCa. The strength of evidence indicative of PCa progression among the 5543 men in our study frame are also shown in Table 4 by age at death and risk category. A total of 5% (95% CI 0–11%) had no evidence and 13% (95% CI 5–19%) had either no evidence or moderate evidence. A total of 35% (1924/5543) were older men, and among these, 25% (95% CI 10–41%) had no evidence or moderate evidence indicative of PCa progression.

A total of 6% (274/5543) had low-risk PCa at diagnosis, of whom 24% (95% CI 12–36%) had no evidence or moderate evidence of PCa progression.

There was no material difference in the distribution of age at PCa diagnosis, PSA levels, or risk categories between men diagnosed between 1998 and 2018 at the participating hospitals and all men in the NPCR during this period (Table S3). The median age at PCa diagnosis was 70 years in both groups, the median PSA level at diagnosis was 10 ng/mL for men in the participating hospitals and 11 ng/mL for all men in the NPCR, and a similar proportion of men had low- or intermediate-risk PCa at diagnosis (51% vs 54%).

Discussion
In this study of men in Sweden with PCa recorded as the cause of death, older age at death and low-risk PCa at diagnosis were associated with having less evidence indicative of PCa progression. A quarter of men aged >85 years at death, and a quarter of men with low-risk PCa at diagnosis, had either no evidence or only moderately strong evidence of PCa progression. When we estimated the quantified evidence of PCa progression for all men in our study frame, 13% had either no evidence or moderate evidence of PCa progression as cause of death.

Strengths of our study are the inclusion of all men who died from PCa in Sweden in our study frame (2011–2018) and the availability of healthcare records for 97% of men in our stratified sample. Our study frame, therefore, can be
considered representative of all men who died from PCa in Sweden during that time period, giving our findings good external validity, including to countries with similar public health systems. Additionally, the level of missing data was low – data were available on PSA in the year before death for ~90% of men in our sample, and data on PSA at any time were only completely missing for one case. Limitations of our study included the small size of the stratified sample that limited the statistical power to conduct meaningful subgroup analyses by comorbidity. Also, our point system was based on our informed, albeit subjective clinical assessment of the strength of the relationship between selected factors and the likelihood that PCa was the cause of death. Despite the use of a standard technique to improve precision in stratified sampling there were several steps in the selection of the frame that may have led misclassification of the proportion of men with PCa progression: e.g., exclusion of men aged >90 years as well as those with missing risk category. We conservatively

Table 3 Strength of evidence in support of PCa progression in 495 study men who died from PCAs during 2011-2018 according to the Cause of Death Register.

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<th>Age, years</th>
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Table 4 Strength of evidence in support of PCa progression in the 495 men in the stratified sample and the 5543 men in the study frame who died from PCa during 2011-2018 according to age at death and risk category at date of diagnosis.

The normal distribution assumption was not met; therefore, confidence levels might deviate from 95%.

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assumed that men aged >90 years, who had little follow-up, would have the same score as men aged 85–89 years. Based on previous studies, we assumed that men with missing disease risk category, had similar evidence of PCa progression as men with intermediate-risk PCa [20]. Lastly, no validation of our score was possible because no ‘gold standard’ exists for comparison.

In our assessment we accredited multiple foci of bone metastases and visceral metastasis an extra point on top of two points for bone metastases on imaging, as these factors have been associated with particularly poor survival in population-based studies and post hoc analyses of randomised controlled trials [21–23]. High and rapidly rising PSA levels are also strong indicators of progression and associated with risk of PCa death and were also included [24]. Chemotherapy, androgen receptor-targeted drugs, and radionuclides were used to indicate CRPC because it was the only indication for these treatments during the study period. Initially, we included bone pain and opioid use in our assessment because bone pain is often present in men with metastatic PCa, but we subsequently excluded these factors as they are not specific for PCa progression, especially in older men with multiple comorbidities [26,27].

Men in our study frame had been diagnosed with PCa in one of 20 hospitals, which accounted for ~30% of all PCa-related deaths in Sweden. Men diagnosed at these hospitals had similar cancer characteristics to all men in the NPCR, which captures 98% of all PCa cases in the mandatory National Cancer Register. Around 13% of men who died from PCa in 2011–2018 in Sweden were not registered in the Cancer Register or in the NPCR, and their cause of death was based on death-certification only. In a previous study, such men had more advanced PCa and more comorbidities than men identified in the NPCR or the Cancer Register [28]. Improvements in diagnostics over the last two decades, has led to an increase of men diagnosed with low- and intermediate-risk PCa in Sweden, and at the same time life-expectancy has increased [3,29]. Both these changes are likely to have increased erroneous adjudication of PCa as cause of death. In 2020, 41% (921/2243) of all men who died from prostate cancer in Sweden were aged ≥85 years. However, assuming that men with PCa death, based on death certificate only, had undiagnosed PCa progression, our estimated proportion of men with no evidence or moderate evidence of PCa progression, and hence PCa as cause of death, would drop from 13% to 10%.

Most previous studies on the adjudication of PCa as cause of death have been based on randomised trials of healthy middle-aged men, who are carefully monitored during follow-up according to study protocol [30,31]. For example, in the European Randomized Study of Screening for Prostate Cancer trial, the adjudication of PCa death was evaluated by an expert committee using available evidence of disease progression [31]. In some of these men, PCa death was deemed to be ‘probable’ but not ‘definitive’ yet was still considered to be the underlying cause of death in the absence of evidence of another cause of death. All types of evidence for PCa progression were given the same weight and neither location nor number of metastases were considered. We argue that quantification of specific factors that are related to PCa progression and PCa death provides a more reproducible and objective assessment than expert assessment, especially in a real-world setting where men are generally older and there are less data to assess compared with participants in screening programmes. Without disease progression, PCa cannot be the cause of death whereas in cases of disease progression, competing causes of death may well be the cause of death. Our study only investigated evidence for the requisite of PCa progression and not the actual cause of death. We argue that our objective quantification of evidence indicative of PCa progression can be used as a valuable part of cause of death adjudication in men with PCa, and, when
needed, be supplemented by data on competing causes of death.

Autopsy is the ‘gold standard’ in assessing cause of death. As in most Western countries, there has been a decline in autopsy rates in Sweden, decreasing from 49% in 1970 to 11% in 2016 (and <1% in very old men) [32,33]. This has likely decreased the quality of data in the Swedish Cause of Death Register, because previous research has shown that strong contributing causes of death are missed in more than half of cases if autopsy is not performed [34], and death certificates will be increasingly reliant on medical records. Physicians need to be aware of the importance of identifying the correct cause of death and could be helped through the uptake of training programmes aimed at improving cause of death adjudication and which have shown success in this area [35].

Our results are likely generalisable to countries with a similar public healthcare system to Sweden. Our results are in line with studies from Norway and Estonia, in which a third of PCa-related deaths were considered over-reported after expert committee review, exceeding 60% in men aged ≥90 years [13,14]. In an earlier population-based study from Sweden of men who died from PCa between 1987 and 1999, those aged >75 years at death and those with localised disease had a 5% excess of PCa-related death, when data were used from medical records compared to when data were used from the Cause of Death Register [15]. In contrast, two studies from the United States showed a high correlation between expert committee review and death certificates in men with PCa [36,37]. However, one of these studies only included men who died in hospital who would likely have had more evidence for disease progression than those who died at home/in a nursing home [36].

Conclusion

Among men with prostate cancer in Sweden, either no evidence or moderate evidence for PCa progression as cause of death was more common in older men and in those with low-risk PCa. This has implications for the interpretation of mortality statistics, in particular when assessing screening and early treatment of PCa because the beneficial effect of earlier diagnosis could in part be masked by an erroneous adjudication of PCa as the cause of death in older men, especially those with localised disease at diagnosis.

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Disclosure of Interests

The authors have no disclosure of interest in any stage of this research work.

References


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Evidence of prostate cancer death


Correspondence: Andri Wilberg Orrason, Department of Surgical Sciences, Uppsala University Hospital, 751 85 Uppsala, Sweden.
e-mail: andri.wilberg@surgsci.uu.se

Abbreviations: CCI, Charlson Comorbidity Index; CRPC, castration-resistant PCa; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; NPCR, National Prostate Cancer Register; PCa, prostate cancer; PCBaSe, Prostate Cancer data Base Sweden.

Supporting Information

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

**Table S1.** Sample sizes according to age at death and risk category at date of diagnosis for 495 men in the study frame of 5543 men who died from prostate cancer according to the Cause of Death Register.

**Table S2.** Amount of evidence in three categories in support of prostate cancer death according to age at death and risk category at date of diagnosis for the 495 study men who died from prostate cancer according to the Cause of Death Registry during 2011–2018.

**Table S3.** Baseline characteristics of men diagnosed with prostate cancer between 1999 and 2018 in the selected 20 hospitals compared with all men in the NPCR.

**Fig. S1.** Location of the 20 hospitals in Sweden that comprised the study frame from which the stratified sample was selected.