Original Research

Diagnostic characteristics of lethal prostate cancer

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- Clinical characteristics
- Danish Prostate Cancer Registry

Abstract

Background: The diagnostic characteristics of men who eventually die from prostate cancer (PCa) and the extent to which early diagnostic strategies have affected these characteristics are unclear. We aimed to investigate trends in survival and clinical presentation at diagnosis in men who eventually died from PCa.

Patients and methods: Based on the national database, the Danish Prostate Cancer Registry, a nationwide population-based study of all 19,487 men who died from PCa in Denmark between 1995 and 2013 was conducted. Trends in median survival and trends in age, prostate-specific antigen (PSA), clinical stage, and Gleason score (GS) at diagnosis were analysed.

Results: A total of 46.9%, 16.8%, and 36.3% had metastatic (M+), locally advanced/lymph node positive (LaN+), and localised disease, respectively, at diagnosis. Only 0.15% had localised disease, GS/C20, and PSA < 10. Over time, the proportion of men with M+ disease at diagnosis decreased from 54.0% to 38.3% (p < 0.0001), whereas the proportion LaN+ disease increased from 8.6% to 27.3% (p < 0.0001). The proportion of localised disease remained stable at 33.2–41.9%. Median survival increased 2.11 years from 1.88 (95% CI: 1.68–2.08) in 1995 to 3.99 (95% CI: 3.71–4.28) years in 2013, p < 0.0001.

Conclusions: In a large population-based study, the results confirmed concurrent literature that the majority of men who eventually died from PCa had LaN+ or M+ disease at diagnosis. The proportion of men with M+ disease at diagnosis decreased significantly over time, paralleled by an increase in median survival. Taken together, this indicates a lead-time effect on survival, which presently, however, is not substantial enough to result in a reduced PCa-specific mortality.

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1. Introduction

Prostate cancer (PCa) is curable if detection is advanced to a point where the disease is still localised or locally advanced [1]. As a consequence of PCa’s long asymptomatic phase, early detection and treatment strategies have been introduced and advocated to reduce PCa-mortality [2–4]. Prostate-specific antigen (PSA) testing has been the primary driver of early detection strategies and has resulted in dramatic increases in incidences of PCa worldwide [5]. However, only a modest reduction in PCa-mortality has been observed, and currently, systematic PSA screening in healthy men is not advocated in most countries [6,7]. In Denmark, PCa-mortality has remained stable at 0.19/100,000 men (world standard population) [8]. Although PSA screening has never been recommended in Denmark, development in incidence mirrors countries where more systematic PSA screening has been used [5,8]. Central to the debate about early detection is the risk of overdiagnosis and overtreatment. Numerous studies have identified prognostic factors defining patients at risk of PCa-specific mortality [9,10]. Fewer studies have investigated the disease course and characteristics at diagnosis in large population-based studies of patients who ultimately died from PCa. To study such a population, we identified the complete population-based cohort of Danish men who died from PCa between 1995 and 2013 (n = 19,487). We analysed the characteristics at diagnosis and PCa-specific survival and how these changed over time.

2. Patients and methods

2.1. Men with lethal PCa

All men recorded as having died from PCa during 1995–2013 were extracted from the Danish Register of Causes of Death (RCOD), which has been reported to have a 93% concordance rate between PCa registered as the underlying cause of death and manual reviews of patients charts [11,12]. Fig. 1 presents the flow of inclusion. Based on the Danish Civil Registration System (CPR), number assigned to all Danish citizens, diagnostic characteristics and date of diagnosis were identified in the Danish Prostate Cancer Registry (DaPCaR) [13]. DaPCaR is a national database previously described in detail, that holds integrated information on histopathology, clinical findings and survival (vital status) [14]. Tumour classification and date of diagnosis from men not identified in DaPCaR was obtained from the Danish Cancer Registry (DCR) [15]. A total of 6254 men did not have histopathologically verified PCa in DaPCaR, and for these men, manual review of their histopathological history was performed in the Danish Pathology Registry to

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Fig. 1. Flow of inclusion.
verify the histological diagnosis and to extract histopathological characteristics [16]. Date of diagnosis was defined as the date of histopathological diagnosis. Men without histopathological verification of PCa were defined as having clinically diagnosed PCa based on registration in DCR. Men diagnosed post-mortem and men in whom PCa diagnosis could not be identified in DCR, DaPCaR, or Patobank were excluded.

The present study was approved by the Danish National Data Protection Agency (file number: 2012-41-0390), the Danish Health and Medicines Authority (file number: 3-3013-858/1) and the ethical committee of The Capital Region of Denmark (protocol number: H-4-2014-FSP).

2.2. Clinical characteristics at diagnosis

Until 2004, PCa was registered in DCR according to the World Health Organization (WHO) classifications as localised, regionally advanced or distant metastatic. After 2004, the tumour, lymph node, and metastases (TNM) classification of malignant tumours (ICD 10) was used. We reclassified men with WHO ‘localised disease’ to TNM ‘cT1-2, N0/X, M0/X’, WHO ‘regionally advanced’ to TNM ‘cT3-4 and/or N+, M0’ and WHO ‘distant metastatic disease’ to TNM ‘Tx, Nx, M+'. For analysis, men were ultimately classified as having ‘localised’, ‘locally advanced/lymph node positive (N+)’ or ‘metastatic (M+)’ disease at diagnosis, Table S1 (supplements). Men with localised disease were further grouped according to PSA and Gleason score (GS). To investigate temporal trends and the impact of early detection strategies, men were stratified into four groups based on the period of death; 1995–1999, 2000–2004, 2005–2008 and 2009–2013, respectively.

2.3. Time from diagnosis to PCa death

Survival was calculated as median time from diagnosis to death. Since all men in the cohort per definition died from PCa, survival refers to PCa-specific survival. Men were stratified according to the year of death.

2.4. Statistical analyses

Calculations and comparison of clinical characteristics were done with the Mann–Whitney U test and the chi-square test, whereas calculations and comparison of median time from diagnosis to death were done with the Kaplan–Maier method and log-rank testing, respectively. Data management and analyses were performed using IBM SPSS Statistics 22, Armonk, NY, USA.

3. Results

Fig. 2 shows trends in incidence and mortality of PCa in Denmark from 1995 to 2013. Incidence rates have increased dramatically, whereas mortality rates have remained stable.

A total of 20,492 were registered to have died from PCa in the period 1995–2013. Of these, 1005 men were excluded as PCa diagnosis could not be verified (n = 955) or because diagnosis was based on autopsy without available clinical information (n = 50). Among the 19,487 men included, 2777 (14.3%) had PCa diagnosed based on clinical findings only, i.e. digital rectal examination, significantly elevated PSA and positive bone scans (Fig. 1).

Table 1 demonstrates baseline demographics and Fig. 3 presents trends in diagnostic characteristics for men who died from PCa during 1995–2013. Among men with complete tumour classification available

Fig. 2. Incidence and mortality in Denmark, based on NORDCAN data [8].
46.9% had M+ disease, 16.8% had locally advanced/N+ disease and 36.3% had localised disease at the time of diagnosis (Fig. 3). Overall, 84.2% had GS ≥ 7 at diagnosis (Table 1). Significant changes in age, PSA and diagnostic characteristics were observed over the period studied. Median age at diagnosis was reduced by 6 months from 75.1 to 74.6, p = 0.003, and the median PSA decreased from 218.0–60.1 ng/ml (p < 0.0001). The proportion of men with M+ disease at diagnosis significantly decreased from 54.0% (died 2000–2004) to 38.3% (died 2009–2013) (p < 0.0001), and the proportion of men with regionally advanced/N+ disease increased from 8.6%–27.3% (p < 0.0001). The proportion of men who had localised disease at diagnosis remained stable ranging from 33.2%–41.9%. Among men with localised disease, 43.6% had GS ≥ 8, and this proportion increased over time from 42.7–46.5% (p < 0.0001). The median age at diagnosis in men with localised disease was 75.1 years (IQR: 69.5–80.5) and did not change significantly over time. Median age at diagnosis decreased from 75.0 years (IQR: 68.6–80.5) to 73.8 years (66.8–80.5), p = 0.004, for men diagnosed with locally advanced/N+ PCa and from 74.8 years (IQR: 67.8–80.2) to 73.6 years (IQR: 66.6–80.2), p < 0.0001, for men diagnosed with M+ disease. A total of 0.8% of men who died from PCa presented with lower risk (GS ≤ 6 and PSA < 20) localised PCa at diagnosis and this proportion increased during the study period from 0.1–1.6% (p < 0.0001). In total, only 0.15% had D’Amico low-risk disease at diagnosis (localised, GS ≤ 6, PSA < 10) [17].

The median survival for men with lethal PCa improved by 2.11 years in the period studied from 1.88 years (95% CI: 1.68–2.08) in 1995 to 3.99 years (95% CI: 3.71–4.28) in 2013, p < 0.0001, see Fig. S1a (supplements) and Table 2. Fig. S1b (supplements), present

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics at diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>75.1 (68.5–80.9)</td>
</tr>
<tr>
<td>PSA, ng/ml</td>
<td>n (%)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>1062 (18.4)</td>
</tr>
<tr>
<td>20–100</td>
<td>2093 (36.2)</td>
</tr>
<tr>
<td>100–300</td>
<td>1125 (19.5)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>1497 (25.9)</td>
</tr>
<tr>
<td>GS</td>
<td>n (%)b</td>
</tr>
<tr>
<td>≤6</td>
<td>2123 (15.8)</td>
</tr>
<tr>
<td>7</td>
<td>4131 (30.8)</td>
</tr>
<tr>
<td>≥8</td>
<td>7162 (53.4)</td>
</tr>
<tr>
<td>NA</td>
<td>6071 (31.2)c</td>
</tr>
<tr>
<td>Disease stage</td>
<td>n (%)</td>
</tr>
<tr>
<td>T-category</td>
<td>5923 (30.4)</td>
</tr>
<tr>
<td>cT1</td>
<td>1191 (20.1)</td>
</tr>
<tr>
<td>cT2</td>
<td>1155 (19.5)</td>
</tr>
<tr>
<td>cT3</td>
<td>2416 (40.8)</td>
</tr>
<tr>
<td>cT4</td>
<td>698 (11.8)</td>
</tr>
<tr>
<td>cTx</td>
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<tr>
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<tr>
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<tr>
<td>WHO</td>
<td>8950 (45.9)</td>
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<tr>
<td>Localized</td>
<td>3847 (43.0)</td>
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<tr>
<td>Reg. advanced</td>
<td>926 (10.3)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>4177 (46.7)</td>
</tr>
<tr>
<td>NA</td>
<td>4614 (23.7)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR: interquartile range; PSA: prostate specific antigen; GS: Gleason score; NA: not available.

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a PSA available on 5777 (29.65%) patients.
b Percentage of available GS.
c Percentage of all patients.
Fig. 3. Clinical characteristics at diagnosis of lethal prostate cancer. (A) Overall, (B) died between 1995 and 1999, (C) died between 2000 and 2004, (D) died between 2005 and 2008, and (E) died between 2009 and 2013.
temporal trends in time from diagnosis to PCa-specific death, stratified by diagnostic stage. Survival was prolonged by 3.23 years for men with localised disease, 2.34 years for men with locally advanced/N+ disease and 1.04 years for men with M+ disease, respectively. Table 2.

4. Discussion

The introduction of PSA and intensified detection strategies has changed the clinical characteristics of PCa at diagnosis dramatically. Today, more that 50% of men diagnosed with PCa present with localised disease [18]. Furthermore, it has been demonstrated that the risk of dying from localised PCa in a contemporary PSA-driven early detection scenario is low, regardless of treatment modality [19].

In Denmark, as in many Western countries, the incidence of PCa has increased while mortality has remained relatively stable (Fig. 1) [8]. It can be argued that while resources are used to detect and treat slow-growing low-risk tumours that are more susceptible to be detected through early detection, fast-growing high-risk tumours escape early detection strategies only to surface clinically at a point in time where cure is not possible [20].

In an attempt to explain this development, we believe that our large population-based study over a 19-year period provides new insights into both characteristics at diagnosis and survival in men who died from PCa. The database used for our analysis originates from integration of histopathological and clinical data from highly validated national registers which allowed us to identify 19,487 men who died from PCa and track their course of disease back to diagnosis [12–16].

The overall clinical characteristics at diagnosis in the cohort of men with lethal PCa are displayed in Table 1 and Fig. 3A. The majority of men had M+ (46.9%) or locally advanced and/or N+ disease (16.8%) at diagnosis. A total of 36.3% had localised disease with predominantly GS ≥ 8 (53.4%) or GS = 7 (30.8%). Men with localised disease were old at diagnosis (median 75.1 years). Less than 0.15% of the cohort was diagnosed with D’Amico low-risk disease, emphasizing that low-risk localised PCa holds very limited lethal potential [17].

Two recent studies have focused on the characteristics of patients with lethal PCa. A small French study (N = 113) included men dying with metastatic castration-resistant PCa and observed that 55.8% and 44.2% had metastatic and non-metastatic PCa, respectively, at the time of initial diagnosis [21]. Among the latter, 64% had GS ≥ 7 at diagnosis. The study is small, and the population is highly selected, as all patients were identified among men enrolled in clinical trials. This is reflected in the relatively young age at diagnosis (median 63–64 years) and calls for caution when comparing with data from population-based studies. None-the-less, the study confirms that most men dying from PCa have metastatic disease already at diagnosis. A register-based study from the UK identified 50,066 men diagnosed with PCa [22]. Of the 10,053 dying from PCa, 57.5%, 2.5% and 39.9% of patients had M+, locally advanced/N+, and localised disease at the time of diagnosis, respectively. While the percentage of M+ at diagnosis concurs with our study, the marked difference in locally advanced/N+ and localised disease most likely is explained by significant under-staging in the UK cohort, as suggested by the authors. Our data show that, on a population-based level, the majority of men who die from PCa have advanced or M+ disease at the time of diagnosis.

The observed median survival for men with lethal PCa in this study was short compared to reports from clinical trials including men with high-risk M + PCa [23]. However, it must be emphasised that this may reflect a selection problem as men in clinical trials typically have performance status greater than two. (2) Second, survival here was calculated only for men who died of PCa and thus do not include those long-term responders to ADT who die of other causes and add significantly to the survival estimates. Also, median OS survival for men diagnosed with PCa in Denmark is shorter than compared to other countries [24].

In a further attempt to characterise the ‘killer’ PCa and investigate the impact of diagnostic and therapeutic interventions, we stratified our population of 19,487 men dying from PCa into four groups according to period of death. Changes in diagnostic characteristics (Table 1 and Fig. 3B–E) were analysed and survival, which in this context, where all died from PCa, is PCa-specific survival, was calculated.

We realise the methodological risks, confounders, and biases involved in this kind of analysis in which the study population is defined by death from PCa, and characteristics at diagnosis are retrieved retrospectively. In an attempt to interpret our data on patient
characteristics at diagnosis and survival in four cohorts in sequential time periods, it may be useful to consider how changes in external parameters may affect the cohorts over time. Such external parameters may be introduction of effective and even curative therapy, change in prognostic factors within the cohorts, and introduction of lead time because of increase in diagnostic activity. Focussing on how characteristics at diagnosis, PCa-specific survival and PCa-mortality may be affected by such external parameters, the following scenarios may be hypothesised:

A) If an effective treatment is introduced, PCa-specific survival will improve and a decrease in PCa-mortality may be seen. In the latter situation, patient characteristics at diagnosis change because men saved from PCa-mortality are excluded from the cohort as they no longer fulfil the criterion for being included.

B) Any change in the distribution of prognostic factors within the cohort, be it removal of poor prognosis patients (i.e. epidemic comorbidity causing other mortality among weak patients) or good prognosis patients (benefitted by treatment) will reduce mortality (patients die from something else and are therefore excluded from the cohort eventually dying from PCa). Survival and patient characteristics at diagnosis will change, respectively, according to whether good or poor prognostic patients are removed from the cohort.

C) If time of diagnosis is advanced, i.e. as a lead-time, both diagnostic characteristics and PCa-specific survival will improve. If this lead-time becomes sufficiently long, it may result in reduced PCa-mortality because of improved outcome of therapy.

The present study covers a time span of 19 years during which PCa-mortality was stable (Fig. 1). When analysing the four cohorts of men with lethal PCa, a marked decrease in incidence of M+ disease (15.7%) is paralleled by a significant decrease in PSA at diagnosis (Fig. 3B–E, Table 1). This strongly suggests an earlier diagnosis and a situation as described in scenario (C). However, when interpreting the increase in survival of 2.1 years as a lead time, it is intriguing that the median age at diagnosis only is reduced by 0.5 years. This indicates that the explanation for this increase in survival very likely is multifactorial including improved treatments (scenario A), better management of comorbidities and refined palliation [25–28]. These improvements may be life-prolonging but have not yet substantially reduced PCa-specific mortality [8]. Introduction of lead time caused by awareness and use of PSA thus seems to play a significant role in patients who die from PCa. Still, a lead time up to 2.1 years appears modest compared to a lead time of up to 8 years in screening as reported from the European Randomised Study of Screening for Prostate Cancer [29].

The present study has limitations. Caution is needed when interpreting the decrease in incidence of M+ at diagnosis (Fig. 3B–E). The development of more sensitive imaging modalities and increased use of imaging as more men are considered for curative treatment might lead to an underestimation of the reduction in the proportion of M+ in the cohort. Also, data were collected retrospectively. PSA data were only available for a less than one-third of the patients, and the change in GS grading system introduced by the ISUP 2005 consensus GS was not compensated for in our analysis due to the magnitude of the data. Stage of disease is based on register data and detailed information about staging procedures and imaging modalities are lacking. Also, in the early phases of our study period, the WHO staging system was employed and had to be ‘translated’ and combined with the TNM system into M+, locally advanced/N+ and localised disease. Strengths of our study include the population-based design, the large patient numbers and the use of validated registries. Our aim was to focus on significant PCa, and thus the cohort was defined by the ultimate criterion for significant disease—death from PCa. However, cohorts defined by death from PCa are problematic, especially when it comes to comparison between cohorts over time where improvements in diagnostics and therapy may influence the staging and risk of PCa-mortality, respectively—the latter with a logical consequence for whether a patient qualifies for inclusion in the cohort or not. However, the magnitude of the cohorts and the fact that PCa-mortality during the study period was stable lend credibility to our observations and cautious interpretations.

5. Conclusion

In a population-based study over a 19-year period, the diagnostic characteristics of men eventually dying from PCa were described. Most men dying from PCa has either M+ or locally advanced/N+ disease at diagnosis. Men dying from PCa and originally diagnosed with localised disease are old and harbour aggressive tumours. We demonstrated important temporal changes in diagnostic characteristics and survival. Over time, diagnostic characteristics improved, and most markedly, the proportion of patients diagnosed with de novo M+ disease decreased by 15.7%. Survival increased by 2.1 years. PCa-mortality has not yet been affected, and despite the methodological concerns accounted for, our results seem to indicate an introduction of a relatively modest lead time in men ultimately dying from PCa. Although this may suggest that we actually do detect some of the ‘killer’ PCa’s earlier, the stable mortality, unfortunately, emphasizes that the currently achieved lead time is insufficient to affect PCa-mortality.

Conflict of interest statement

All the authors declare no conflicts of interest to disclose.
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The study could not be completed without expert contributions from data manager, Günther Momsen. His knowledge of national registries and the computational skills in integrating data from these is invaluable to the creation and maintenance of the Danish Prostate Cancer Registry (DaPCaR).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.07.007.

References


