



European Association of Urology



## Prostate Cancer

# Mortality Among Men with Locally Advanced Prostate Cancer Managed with Noncurative Intent: A Nationwide Study in PCBaSe Sweden

Olof Akre<sup>a,\*</sup>, Hans Garmo<sup>b</sup>, Jan Adolfsson<sup>c</sup>, Mats Lambe<sup>c,d</sup>, Ola Bratt<sup>e</sup>, Pär Stattin<sup>f</sup>

<sup>a</sup> Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

<sup>b</sup> Regional Oncological Center, Uppsala, Sweden

<sup>c</sup> Oncological Center, CLINTEC Department, Karolinska Institutet, Stockholm, Sweden

<sup>d</sup> Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

<sup>e</sup> Department of Urology, Helsingborg Hospital, Lund University, Sweden

<sup>f</sup> Department of Surgical and Perioperative sciences, Urology and Andrology, Umeå University, Umeå, Sweden

### Article info

#### Article history:

Accepted May 23, 2011

Published online ahead of  
print on June 1, 2011

#### Keywords:

Prostate cancer

Prognosis

Locally advanced

### Abstract

**Background:** There are limited prognostic data for locally advanced prostate cancer (PCa) to guide in the choice of treatment.

**Objective:** To assess mortality in different prognostic categories among men with locally advanced PCa managed with noncurative intent.

**Design, setting, and participants:** We conducted a register-based nationwide cohort study within the Prostate Cancer DataBase Sweden. The entire cohort of locally advanced PCa included 14 908 men. After the exclusion of 2724 (18%) men treated with curative intent, 12 184 men with locally advanced PCa either with local clinical stage T3 or T4 or with T2 with serum levels of prostate-specific antigen (PSA) between 50 and 99 ng/ml and without signs of metastases remained for analysis.

**Measurements:** We followed up the patient cohort in the Cause of Death Register for  $\leq 11$  yr and assessed cumulative incidence of PCa-specific death stratified by age and clinical characteristics.

**Results and limitations:** The PCa-specific mortality at 8 yr of follow-up was 28% (95% confidence interval [CI], 25–32%) for Gleason score (GS) 2–6, 41% (95% CI, 38–44%) for GS 7, 52% (95% CI, 47–57%) for GS 8, and 64% (95% CI, 59–69%) for GS 9–10. Even for men aged  $>85$  yr at diagnosis with GS 8–10, PCa was a major cause of death: 42% (95% CI, 37–47%). Men with locally advanced disease and a PSA  $< 4$  ng/ml at diagnosis were at particularly increased risk of dying from PCa. One important limitation is the lack of bone scans in 42% of the patient cohort, but results remained after exclusion of patients with unknown metastasis status.

**Conclusions:** The PCa-specific mortality within 8 yr of diagnosis is high in locally advanced PCa, suggesting undertreatment, particularly among men in older age groups. Our results underscore the need for more studies of treatment with curative intent for locally advanced tumors.

© 2011 European Association of Urology. Published by Elsevier B.V. All rights reserved.

\* Corresponding author. Karolinska Institutet, Department of Medicine Solna, Clinical Epidemiology Unit, Eugeniahemmet T2, SE-171 76 Stockholm, Sweden. Tel: +46 0 709 640404; Fax: +46 0 8 517 9304. E-mail address: [olof.akre@ki.se](mailto:olof.akre@ki.se) (O. Akre).

## 1. Introduction

A large proportion of men with locally advanced prostate cancer (PCa) are currently treated conservatively due to lack of

data on outcome for various treatment strategies and lack of evidence of the efficacy of treatment with curative intent [1]. Existing data on outcomes for conservatively and curatively treated men are based on rather small single-center studies

**Table 1 – Descriptive characteristics of the entire cohort of men with locally advanced prostate cancer**

	Entire cohort, No.	%	Clinical T3–4 tumor, No.	%
Patients	12 184	100	10 676	100
Mean follow-up time, yr (SD)	4 (2.5)		4 (2.5)	
Age, yr				
<65	887	7.3	787	7.4
65–69	1242	10.2	1094	10.2
70–74	2359	19.4	2081	19.5
75–79	3308	27.2	2910	27.3
79–84	2724	22.4	2363	22.1
≥85	1664	13.7	1441	13.5
Year of diagnosis				
1997–1999	3677	30.2	3199	30.0
2000–2002	3836	31.5	3393	31.8
2003–2006	4671	38.3	4084	38.3
Tumor stage				
2	1508	12.4	–	–
3	9632	79.1	9632	90.2
4	1044	8.6	1044	9.8
Metastasis status <sup>a</sup>				
M0	7082	58.1	6418	60.1
Mx	5102	41.9	4258	39.9
PSA, ng/ml				
<4	261	2.1	261	2.4
4–9.9	1257	10.3	1257	11.8
10–19.9	2282	18.7	2282	21.4
20–99	8118	66.6	6610	61.9
Missing data	266	2.2	266	2.5
Gleason score				
2–6	2727	22.4	2328	21.8
2–6	2037	16.7	1751	16.4
WHO grade 1	690	5.7	577	5.4
7	5125	42.1	4455	41.7
(3 + 4)	1267	10.4	1127	10.6
(4 + 3)	1109	9.1	966	9.0
Unspecified sum	1126	9.2	952	8.9
WHO grade 2	1621	13.3	1408	13.2
8–10	4002	32.8	3598	33.7
8	1623	13.3	1422	13.3
9–10	1480	12.1	1356	12.7
WHO grade 3	899	7.4	820	7.7
Missing data	330	2.7	295	2.8
Charlson comorbidity index				
0	7365	60.4	6470	60.6
1	2431	20.0	2128	19.9
2	1397	11.5	1223	11.5
≥3	991	8.1	855	8.0
Primary treatment				
Watchful waiting	2332	19.1	2044	19.1
AA	1132	9.3	988	9.3
GnRH	6878	56.5	6024	56.4
Orchiectomy	1547	12.7	1356	12.7
Other conservative treatment	295	2.4	264	2.5
Cause of death <sup>b</sup>				
Prostate cancer (C61)	3075	25.2	2746	25.7
Other cancer (Chapter C, not C61)	585	4.8	509	4.8
Circulatory diseases (Chapter I)	1847	15.2	1605	15.0
Other cause (Not chapter C or I)	964	7.9	825	7.7
Alive at the end of follow-up	5713	46.9	4991	46.7

SD = standard deviation; Mx = unknown distant metastasis status; PSA = prostate-specific antigen; WHO = World Health Organization; AA = antiandrogen treatment; GnRH = gonadotropin-releasing hormone.

<sup>a</sup> M0 is defined as either radiologically confirmed M0 or PSA <20 ng/ml.

<sup>b</sup> According to International Classification of Diseases 10.

[2,3], and there are virtually no data on outcomes for men with locally advanced disease from population-based studies. Recent data from a randomized clinical trial suggested a survival benefit from radiotherapy in men with locally advanced disease [3]. Moreover, radical prostatectomy has been offered to selected patients with locally advanced disease with fairly good results, although surgical treatment has not been evaluated in randomized trials [4–9].

There are also limited data on the absolute risks of fatal disease to guide patients and physicians in the choice of treatment for locally advanced PCa. Therefore, we assessed the PCa-specific and overall mortality and the influence of tumor grade and serum prostate-specific antigen (PSA) levels on prognosis in a nationwide cohort of 12 184 patients in Sweden with locally advanced PCa managed with noncurative intent.

**Table 2 – Descriptive characteristics of the excluded group of men with locally advanced prostate cancer who received curative treatment**

	Entire cohort, No.	%	Clinical T3-4 tumor, No.	%
Patients	2724	100.0	2565	100.0
Mean follow-up time, yr (SD)	4.9 (2.6)		4.9 (2.6)	
Age, yr				
<65	1245	45.7	1165	45.4
65–69	877	32.2	829	32.3
70–74	519	19.1	493	19.2
75–79	72	2.6	69	2.7
79–84	7	0.3	6	0.2
≥85	4	0.1	3	0.1
Year of diagnosis				
1997–1999	577	21.2	524	20.4
2000–2002	786	28.9	748	29.2
2003–2006	1361	50.0	1293	50.4
Tumor stage				
2	159	5.8	0	0.0
3	2541	93.3	2541	99.1
4	24	0.9	24	0.9
Metastasis status				
M0	2625	96.4	2478	96.6
Mx	99	3.6	87	3.4
PSA, ng/ml				
<4	93	3.4	93	3.6
4–9.9	759	27.9	759	29.6
10–19.9	820	30.1	820	32.0
20–99	1021	37.5	862	33.6
Missing data	31	1.1	31	1.2
Gleason score				
2–6	806	29.6	756	29.5
2–6	745	27.3	703	27.4
WHO grade 1	61	2.2	53	2.1
7	1297	47.6	1218	47.5
3 + 4	525	19.3	507	19.8
4 + 3	384	14.1	357	13.9
Unspecified sum	219	8.0	202	7.9
WHO grade 2	2169	6.2	152	5.9
8–10	609	22.4	579	22.6
8	8324	11.9	306	11.9
9–10	221	8.1	213	8.3
WHO grade 3	364	2.3	60	2.3
Missing	12	0.4	12	0.5
Charlson comorbidity index				
0	2241	82.3	2107	82.1
1	275	10.1	261	10.2
2	146	5.4	138	5.4
≥3	62	2.3	59	2.3
Primary treatment				
Curative therapy	2724	100.0	2565	100.0
Cause of death*				
Prostate cancer (C61)	191	7.0	180	7.0
Other cancer (Chapter C, not C61)	82	3.0	75	2.9
Circulatory diseases (Chapter I)	63	2.3	59	2.3
Other cause (Not chapter C or I)	38	1.4	36	1.4
Alive at the end of follow up	2350	86.3	2215	86.4

SD = standard deviation; Mx = unknown distant metastasis status; PSA = prostate-specific antigen; WHO = World Health Organization.

\* According to International Classification of Diseases 10.

2. Methods

2.1. The registers

The Prostate Cancer DataBase Sweden (PCBaSe) [10] is a database created through record linkages between the National Prostate Cancer Register (NPCR) of Sweden [11] and a number of other population-based health and social databases. The database has been described in detail [10].

Demographic data in PCBaSe Sweden were obtained from the Register of the Total Population. The quality and completeness of the data are high and notifications are regularly reviewed by Statistics Sweden. Data on causes of death in PCBaSe Sweden were retrieved from the nationwide Cause of Death Register, which contains data on date of death and underlying and contributing causes of death. The overall agreement between the Cause of Death Register and reviewed medical record data has been estimated to be 86% (95% confidence interval [CI], 85–87%) [12]. For each man in PCBaSe, the Charlson comorbidity index

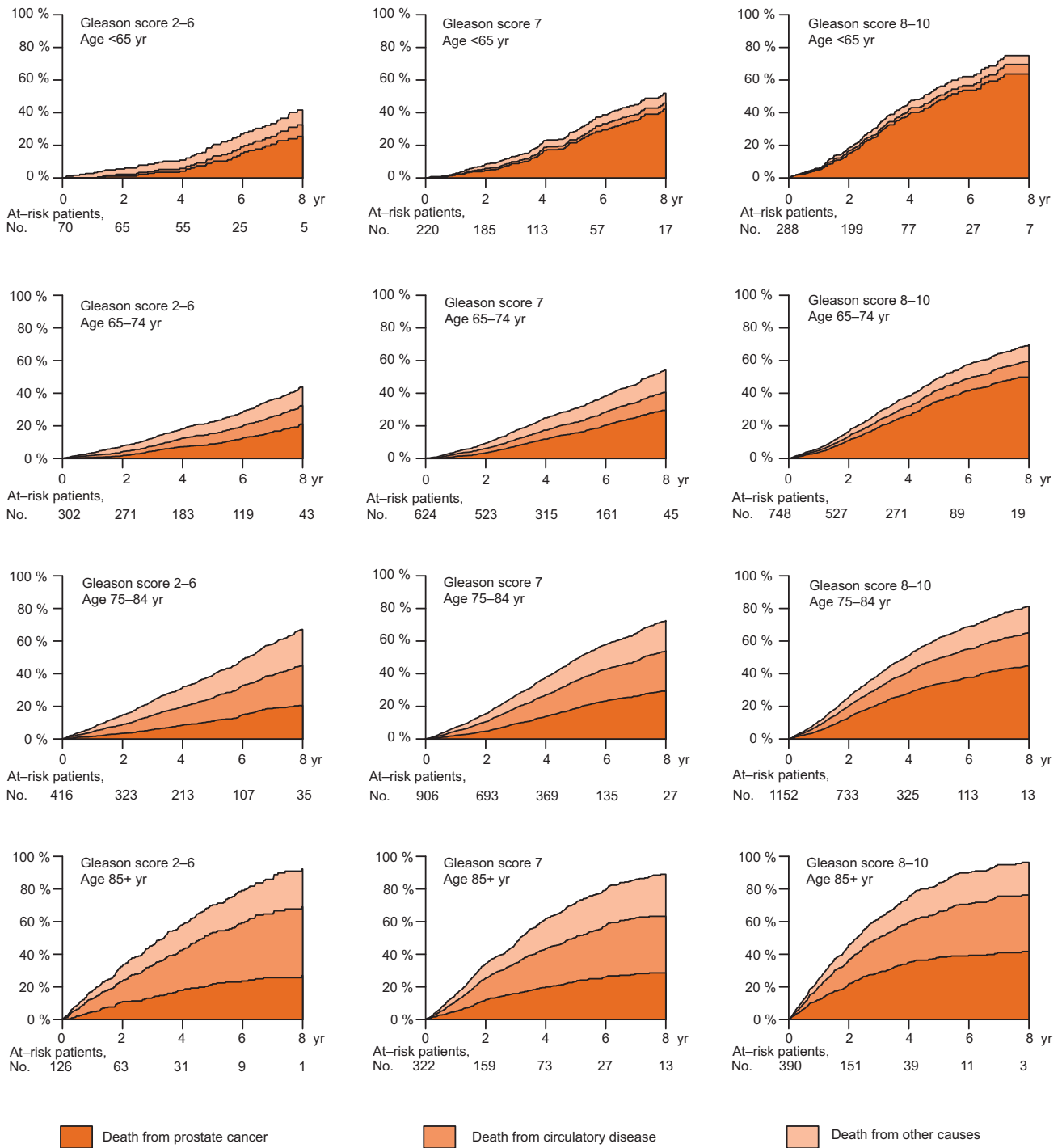


Fig. 1 – Cumulative mortality from prostate cancer and other causes after diagnosis of locally advanced prostate cancer, stratified by age and Gleason score.

has been constructed by grouping of International Classification of Diseases (ICD) codes, as previously described [13,14].

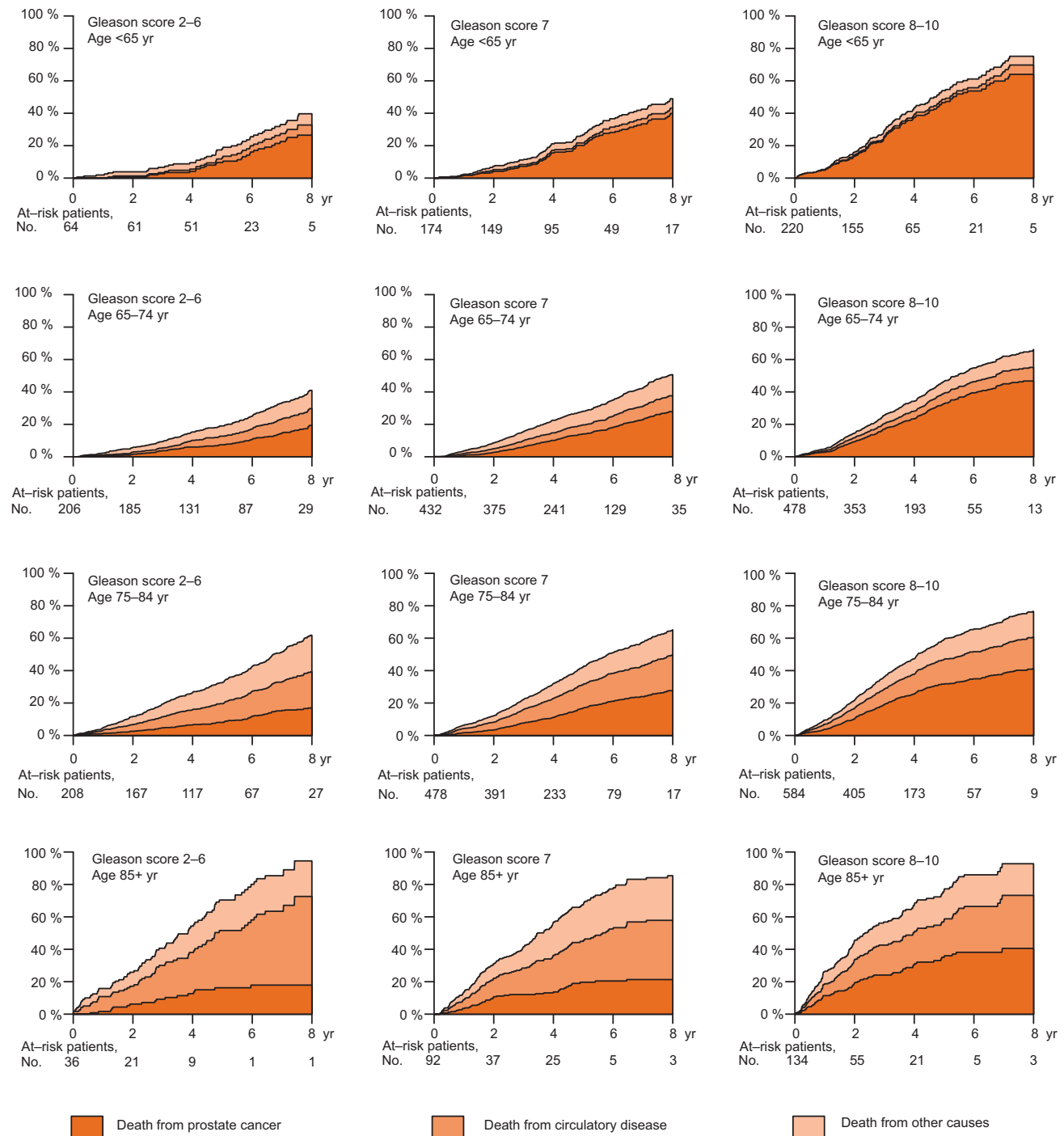
**2.2. The cohort**

The PCBaSe project was approved by the Central Research Ethical Board (EPN 14-2007). We defined locally advanced PCa as clinical local stage T3 or T4. Men with T2 tumors without evidence of metastatic disease and serum PSA between 50 ng/ml and 99 ng/ml were also included. The reason for including this group of men with T2 tumors was that digital

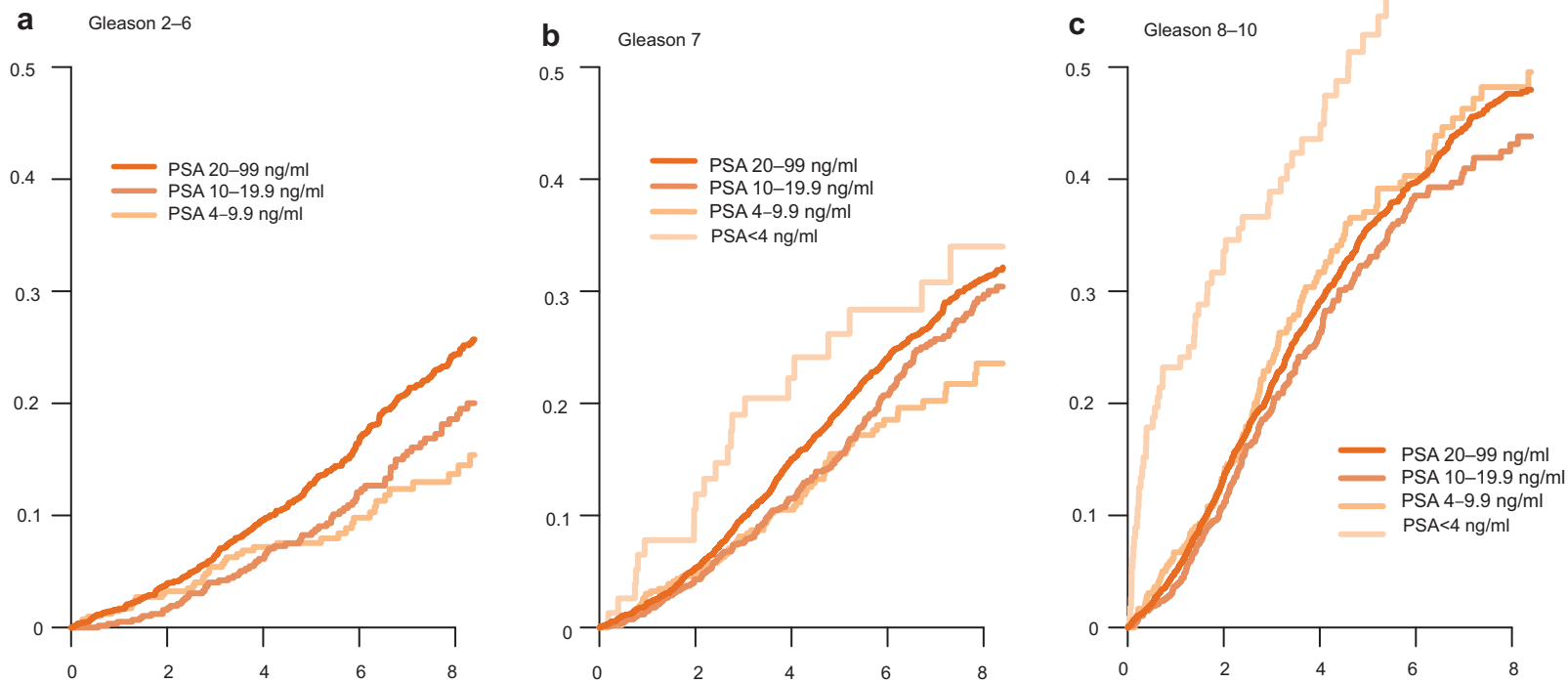
rectal examination often underestimates tumor extension [15]. Men with confirmed (by bone scan) metastatic disease (M1) or PSA  $\geq 100$  ng/ml were excluded ( $n = 13\ 611$ ).

**2.3. Data analysis**

The men were followed until death, emigration, or to December 31, 2007, whichever occurred first. We categorized the primary cause of death as PCa, other cancer, cardiovascular diseases, or other cause, using the codes in the ICD-10. World Health Organization (WHO) grade 1 tumors



**Fig. 2 – Cumulative mortality from prostate cancer and other causes, excluding those with unknown metastasis status at diagnosis. Graphs are stratified by age and Gleason score.**



Patients at Risk

No.	PSA<4 ng/ml	PSA4-9.9 ng/ml	PSA 10-19.9 ng/ml	PSA 20-99 ng/ml											
	-	-	-	-	-	77	56	31	16	6	112	52	25	8	4
PSA<4 ng/ml	409	343	237	142	67	464	362	215	106	41	358	242	109	51	18
PSA 10-19.9 ng/ml	588	499	341	217	101	957	758	445	247	109	679	468	248	99	38
PSA 20-99 ng/ml	1635	1309	902	544	228	3532	2740	1601	829	318	2739	1852	920	406	136

Fig. 3 – Cumulative mortality from prostate cancer during 8 yr of follow-up, stratified by Gleason score and prostate-specific antigen (PSA) category.

**Table 3 – Hazard ratios for the risk of dying from prostate cancer**

	Entire cohort			Clinical T3–4 tumor		
	Crude HR	Adjusted <sup>a</sup> HR (95% CI)		Crude HR	Adjusted <sup>a</sup> HR (95% CI)	
Age, yr						
<65	1.26	1.38	(1.20–1.59)	1.27	1.39	(1.20–1.60)
65–69	0.91	0.96	(0.84–1.10)	0.89	0.94	(0.81–1.08)
70–74	0.89	0.98	(0.87–1.09)	0.90	0.97	(0.87–1.09)
75–79	1	1	(Reference)	1	1	(Reference)
79–84	1.31	1.20	(1.08–1.33)	1.30	1.19	(1.06–1.33)
≤85	2.07	1.74	(1.54–1.96)	2.14	1.79	(1.58–2.03)
Tumor stage						
2	0.89	0.90	(0.80–1.02)	NA	NA	–
3	1	1	(Reference)	1	1	(Reference)
4	2.32	1.82	(1.64–2.02)	2.31	1.81	(1.63–2.00)
Metastasis status						
M0	0.66	0.71	(0.65–0.76)	0.68	0.73	(0.67–0.79)
Mx	1	1	(Reference)	1	1	(Reference)
PSA, ng/ml						
<4	2.31	1.79	(1.41–2.28)	2.32	1.77	(1.39–2.26)
4–9.9	1	1	(Reference)	1	1	(Reference)
10–19.9	1.11	1.07	(0.92–1.25)	1.10	1.07	(0.92–1.25)
20–99	1.40	1.22	(1.07–1.40)	1.47	1.20	(1.05–1.38)
Gleason score <sup>b</sup>						
2–6	0.63	0.68	(0.59–0.78)	0.63	0.68	(0.59–0.79)
7	1	1	(Reference)	1	1	(Reference)
8	1.58	1.45	(1.28–1.64)	1.59	1.45	(1.27–1.65)
9–10	2.64	2.32	(2.07–2.61)	2.64	2.33	(2.06–2.63)
Charlson comorbidity index						
0	1	1	(Reference)	1	1	(Reference)
1	1.12	1.08	(0.98–1.18)	1.15	1.11	(1.01–1.22)
2	1.18	1.10	(0.98–1.24)	1.20	1.13	(1.00–1.29)
≥3	1.26	1.11	(0.96–1.30)	1.30	1.16	(1.01–1.52)
Primary treatment						
Watchful waiting	0.48	0.62	(0.55–0.69)	0.44	0.58	(0.51–0.65)
AA	0.66	0.78	(0.68–0.90)	0.67	0.80	(0.69–0.94)
GnRH	1	1	(Reference)	1	1	(Reference)
Orchiectomy	1.29	1.13	(1.02–1.25)	1.26	1.1	(0.99–1.23)
Other conservative treatment	1.18	1.19	(0.98–1.46)	1.24	1.23	(1.01–1.52)

HR = hazard ratio; CI = confidence interval; NA = not applicable; Mx = unknown distant metastasis status; PSA = prostate-specific antigen; AA = antiandrogen treatment; GnRH = gonadotropin-releasing hormone.

<sup>a</sup> Adjusted mutually exclusive for age, T stage, M stage, PSA, Gleason score, and treatment. Models were run stratified by calendar year of diagnosis.

<sup>b</sup> The estimates for Gleason score were derived from a model including exclusively subjects with complete Gleason score information.

were merged with Gleason score (GS) 2–6, WHO 2 with GS 7, and WHO 3 with GS 8–10. Patients were considered to be free from metastasis (M0) at diagnosis if they were confirmed M0 through bone scan ( $n = 4462$ ) or had a PSA <20 ng/ml ( $n = 2599$ ).

Investigations for lymph node metastases were performed in only 6.4% of the study population and this variable was excluded from further analysis. We calculated cumulative mortality from date of diagnosis until date of death from PCA, cardiovascular disease, or other causes. A previous validation study reported agreement of 86% (95% CI, 85–87%) between the Cause of Death Register and an assigned end point committee [12]. Although that agreement is fairly good, we complemented cause-specific mortality with an estimation of relative survival, defined as the ratio of observed survival to the expected survival of an age-standardized group from the general population. The expected relative survival was estimated using the Ederer II method [16] based on Swedish population data stratified by age, sex, and calendar time.

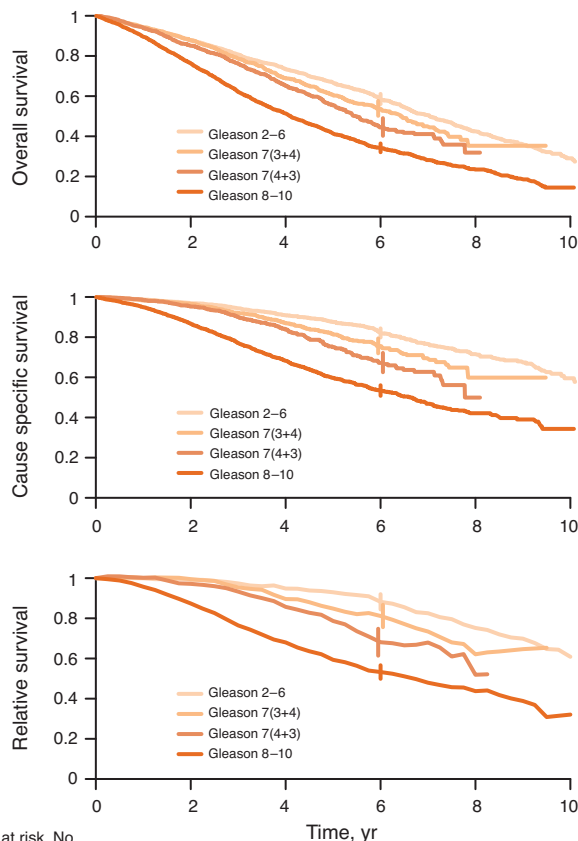
We also estimated the relative risk of dying from PCA through Cox proportional hazards regression models calculating hazard ratios (HRs) and 95% CIs. The models were stratified by calendar year of diagnosis to account for stage and grade migration that may have occurred [17]. All  $p$  values come from two-tailed tests. Statistical significance was set at 0.05.

### 3. Results

Among the 80 079 men in Sweden with PCA during the study period, 14 908 had locally advanced, nonmetastatic PCA. Of those men, 2724 (18%) were treated curatively and thus excluded, leaving 12 184 men for analysis. During ≤11 yr of follow-up, 3075 patients (25.2%) died of PCA and 3396 (27.7%) died of other causes (Table 1).

Men excluded due to primary curative treatment were considerably younger and had less advanced disease than the conservatively treated study cohort (Table 2), and the overall mortality was lower in this group.

A substantial proportion of the observed mortality came from PCA in all age groups and GS already at 4 yr of follow-up; the 4-yr cumulative mortality from PCA was 9% (95% CI, 8–11%) for GS 2–6, 15% (95% CI, 14–17%) for GS 7, 25% (95% CI, 23–28%) for GS 8, and 39% (95% CI, 36–42%) for GS 9–10 (Fig. 1; data not tabulated). At 8 yr of follow-up, the corresponding GS-specific mortalities were 28% (95% CI, 25–32%) for GS 2–6, 41% (95% CI, 38–44%) for GS 7, 52% (95%



Patients at risk, No.	0	2	4	6	8	10
Gleason 2–6	2037	1656	1099	628	239	41
Gleason 7(3+4)	1267	993	515	205	5	0
Gleason 7(4+3)	1109	810	393	120	2	0
Gleason 8–10	3103	2075	973	391	115	15

**Fig. 4 – Cumulative survival after diagnosis of prostate cancer by Gleason score category. The bars at 6 yr of follow-up indicate 95% confidence intervals.**

CI, 47–57%) for GS 8, and 64% (95% CI, 59–69%) for GS 9–10. Restriction of the cohort to M0 only led to marginal changes in the absolute risks of dying from PCa, with the exception of lower cumulative PCa-specific mortality in the oldest age group with GS 2–6 or GS 7 tumors (Fig. 2). The analysis of relative risks was virtually unaffected by the restriction to M0 patients (data not shown).

Among men with GS ≤7, increasing PSA was associated with higher mortality (Fig. 3). Among men with GS 2–6, a PSA level of 4–10 ng/ml was associated with an HR of 0.51 (95% CI, 0.37–0.70), compared with PSA 20–100 ng/ml. By contrast, for men with GS 8–10, PSA had less prognostic value; although very low levels were associated with an increased mortality, a PSA value of 4–10 was associated with an HR of 0.94 (95% CI, 0.86–1.25), compared with PSA 20–100 ng/ml.

High GS was the factor most strongly associated with death from PCa. In a multivariable model, the HR for PCa death among men with GS ≥9 was 2.32 (95% CI, 2.07–2.61) compared to those with GS 7, whereas HR was 0.71 (95% CI, 0.63–0.79) for those with GS ≤6 (Table 3). After adjustment for other factors, Charlson comorbidity index was weakly and nonsignificantly associated with PCa-specific mortality.

To assess the accuracy of our translation from WHO grade to GS, we restricted the data to those with known GS and found no differences in the relative risks. Cumulative mortality appeared similar, but due to shorter follow-up among those with GS, this restriction led to less precise estimates during the later years of follow-up.

In Figure 4, GS 7 was divided into grades 3 + 4 and 4 + 3. The prognosis differed significantly between these subgroups: The adjusted HR for PCa death was 1.31 (95% CI, 1.09–1.58) for GS 3 + 4 versus GS 2–6, and the corresponding HR for GS 4 + 3 was 1.70 (95% CI, 1.41–2.05). The graphs for cancer-specific and relative survival were similar, indicating that the excess cancer-specific mortality in the cohort was correctly assigned to death from PCa.

The HR for PCa death among patients with a PSA between 20 ng/ml and 49 ng/ml was 1.22 (95% CI, 1.06–1.39), compared with PSA between 4 ng/ml and 9.9 ng/ml. At the other extreme, men with a PSA <4 ng/ml were at higher risk of dying of cancer (HR: 1.79; 95% CI, 1.41–2.28).

#### 4. Discussion

In this nationwide study in Sweden of men with locally advanced PCa managed with noncurative intent, the PCa-specific mortality ranged from 28% to 64% at 8 yr after diagnosis. This finding is in stark contrast to a previously reported mortality estimate of 3% among men with localized, low- or intermediate-risk tumors from the same database [18]. In particular, high GS were associated with high risk of dying from PCa and men age >80 yr were no exception.

To our knowledge, this is the largest follow-up study of locally advanced PCa to date. The large number of events allowed us to stratify the patients according to age, serum PSA, and specific GS at diagnosis. PSA is an established prognostic factor in PCa [19], but in our cohort the prognostic value of PSA was strongly attenuated by the introduction of GS into the regression model. The prognostic value of high PSA was strong among men with tumors with GS ≤7 but not among those with higher GS. In the same vein, we found a marked worse prognosis for men with locally advanced disease and PSA <4 ng/ml, in accordance with what has been reported previously [20]. High GS have consistently been associated with poor prognosis, and our data support that GS is the most important predictor of tumor progression in PCa also in locally advanced PCa [21–23].

The large size of the present study also enabled us to evaluate prognosis among men with GS 8 separated from those with GS 9–10, and we found that the latter group fared considerably worse. In fact, the difference between GS 9–10 and 8 was greater than between GS 8 and GS 7. A difference in risk of dying between patients with tumors of GS 3 + 4 = 7 and GS 4 + 3 = 7 has previously been reported for localized tumors [23], but not for locally advanced tumors.

Our data were obtained from standard clinical care in a population-based cohort encompassing all hospitals in Sweden and reflect the intensity of work-up that was considered to be appropriate for each patient; consequent-

ly, information on lymph node status and distant metastases were absent for a substantial proportion of men. As much as 42% of the cohort was of unknown distant metastasis status (Mx), when we restricted the dataset to M0 patients, there were only marginal changes in the relative risks of dying and no substantial differences in cumulative mortality other than a moderate decrease in the absolute risk of dying from PCa among the oldest. Therefore, our data seem generalizable to patients with known metastasis status. The lack of information on lymph node status is a less significant issue because treatment decisions for men with locally advanced PCa are commonly taken without known node status.

The exclusion of men managed with curative intent may have biased some of the presented relative- and absolute-risk estimates. Most important, the absolute risk of dying from PCa among the youngest men is likely overestimated due to the exclusion of those with the best prognosis. Similarly, it is likely that part of the associations between conservative treatment modalities and survival are due to confounding by indication; for example, the poor outcome for men on gonadotropin-releasing hormone analogs reflects that this treatment was selected for patients with a perceived poorer prognosis than men treated with antiandrogens or expectancy. Apart from the marked difference in age distribution between the excluded curatively treated men and the study cohort, the differences were modest.

Long-term follow-up studies of men with conservatively treated PCa have previously been conducted mainly on localized PCa [21,24]. The results of those studies may have influenced the perception of prognosis and need for treatment also for men with locally advanced disease. To our knowledge, there are no population-based contemporary data on locally advanced disease with sufficient numbers of outcomes allowing detailed stratification by prognostic variables [2]. Previous studies of locally advanced PCa have been based on smaller single-center series [2,25–27]. Consequently, direct comparisons between older data and our data may be misleading. Our finding of an 8-yr PCa-specific mortality of 40% is in accordance with a 10-yr cancer-specific mortality of around 30% observed in earlier studies, and these mortality rates are an order of magnitude higher than in low- and intermediate-risk localized PCa [2,25–27].

In 2009, Widmark et al [3] reported the results of the Scandinavian Prostate Cancer Study Group (SPCG) 7, a randomized trial of radiotherapy plus monotherapy with antiandrogens versus antiandrogens only for locally advanced disease. The 10-yr PCa specific mortality was 11.9% in the combined arm and 23.9% in the antiandrogen-only arm, corresponding to a 56% decrease in risk. In our nonselected cohort, mortality was markedly higher and only 18% of our cohort received primary curative treatment. Our data suggest that locally advanced tumors carry an entirely different prognosis and that considerably higher stakes may be justified in the choice of treatment. Moreover, risk of incontinence and erectile dysfunction is much less controversial when the risk of

fatal disease within 10 yr is one in two or three instead of one in 30.

## 5. Conclusions

In this nationwide cohort, PCa-specific mortality was high among men with locally advanced disease managed with noncurative intent, even in the oldest age groups. The absolute risks of death from PCa presented here may aid clinical decision making by putting cancer-specific mortality in the perspective of competing risks at different ages and by tumor grade. The poor outcome for these patients in our study suggests a role for a more active treatment for men with locally advanced PCa and a need for randomized studies of multimodal therapy for this group of patients.

**Author contributions:** Olof Akre and Hans Garmo had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Akre, Stattin, Garmo.

*Acquisition of data:* Stattin, Garmo, Lambe, Adolfsson.

*Analysis and interpretation of data:* Akre, Garmo, Stattin, Bratt.

*Drafting of the manuscript:* Akre.

*Critical revision of the manuscript for important intellectual content:* Stattin, Bratt, Adolfsson, Lambe.

*Statistical analysis:* Garmo.

*Obtaining funding:* Stattin.

*Administrative, technical, or material support:* Stattin, Lambe, Adolfsson.

*Supervision:* Stattin.

*Other (specify):* None.

**Financial disclosures:** I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** The Swedish Cancer Society (2008:0731), the Swedish Research Council (2008:5910), the Västerbotten County Council (75171) funded this study. The funding organizations had no role in any part of the process of design, analysis, interpretation, manuscript writing, or approval of the manuscript.

**Acknowledgment statement:** This project was made possible by the continuous work of the National Prostate Cancer Register of Sweden (NPCR) steering group: Pär Stattin, chairman; Anders Widmark; Stefan Carlsson; Magnus Törnblom; Jan Adolfsson; Anna Bill-Axelsson; Jan-Erik Johansson; David Robinson; Bill Pettersson; Jonas Hugosson; Jan-Erik Damber; Ola Bratt; Göran Ahlgren; Lars Egevad; and Roy Ehrnström.

## References

- [1] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. *Eur Urol* 2008;53:68–80.
- [2] Van den Ouden D, Schroder FH. Management of locally advanced prostate cancer. 1. Staging, natural history, and results of radical surgery. *World J Urol* 2000;18:194–203.
- [3] Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009; 373:301–8.

- [4] Carver BS, Bianco Jr FJ, Scardino PT, Eastham JA. Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. *J Urol* 2006;176:564–8.
- [5] Gerber GS, Thisted RA, Chodak GW, et al. Results of radical prostatectomy in men with locally advanced prostate cancer: multi-institutional pooled analysis. *Eur Urol* 1997;32:385–90.
- [6] Hsu CY, Joniau S, Roskams T, Oyen R, Van Poppel H. Comparing results after surgery in patients with clinical unilateral T3a prostate cancer treated with or without neoadjuvant androgen-deprivation therapy. *BJU Int* 2007;99:311–4.
- [7] Van den Ouden D, Hop WC, Schroder FH. Progression in and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. *J Urol* 1998;160:1392–7.
- [8] Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005;95:751–6.
- [9] Freedland SJ, Partin AW, Humphreys EB, Mangold LA, Walsh PC. Radical prostatectomy for clinical stage T3a disease. *Cancer* 2007;109:1273–8.
- [10] Hagel E, Garmo H, Bill-Axelsson A, et al. PCBaSe Sweden: a register-based resource for prostate cancer research. *Scand J Urol Nephrol* 2009;43:342–9.
- [11] Adolfsson J, Garmo H, Varenhorst E, et al. Clinical characteristics and primary treatment of prostate cancer in Sweden between 1996 and 2005. *Scand J Urol Nephrol* 2007;41:456–77.
- [12] Fall K, Stromberg F, Rosell J, Andren O, Varenhorst E. Reliability of death certificates in prostate cancer patients. *Scand J Urol Nephrol* 2008;42:352–7.
- [13] Sundararajan V, Quan H, Halfon P, et al. Cross-national comparative performance of three versions of the ICD-10 Charlson index. *Med Care* 2007;45:1210–5.
- [14] Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57:1288–94.
- [15] Sanchez-Chapado M, Angulo JC, Ibarburen C, et al. Comparison of digital rectal examination, transrectal ultrasonography, and multicoil magnetic resonance imaging for preoperative evaluation of prostate cancer. *Eur Urol* 1997;32:140–9.
- [16] Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. *Natl Cancer Inst Monogr* 1961;6:101–21.
- [17] Albertsen PC, Hanley JA, Barrows GH, et al. Prostate cancer and the Will Rogers phenomenon. *J Natl Cancer Inst* 2005;97:1248–53.
- [18] Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J. Outcomes for men with localized prostate cancer: National Prostate Cancer Register (NPCR) of Sweden. *J Natl Cancer Inst* 2010;102:950–8.
- [19] Fall K, Garmo H, Andren O, et al. Prostate-specific antigen levels as a predictor of lethal prostate cancer. *J Natl Cancer Inst* 2007;99:526–32.
- [20] Sandblom G, Ladgevardi S, Garmo H, Varenhorst E. The impact of prostate-specific antigen level at diagnosis on the relative survival of 28,531 men with localized carcinoma of the prostate. *Cancer* 2008;112:813–9.
- [21] Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005;293:2095–101.
- [22] Cuzick J, Fisher G, Kattan MW, et al. Long-term outcome among men with conservatively treated localised prostate cancer. *Br J Cancer* 2006;95:1186–94.
- [23] Wright JL, Salinas CA, Lin DW, et al. Prostate cancer specific mortality and GS 7 disease differences in prostate cancer outcomes between cases with GS 4 + 3 and GS 3 + 4 tumors in a population based cohort. *J Urol* 2009;182:2702–7.
- [24] Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. *JAMA* 2004;291:2713–9.
- [25] Adolfsson J. Deferred treatment of low grade stage T3 prostate cancer without distant metastases. *J Urol* 1993;149:326–8, discussion 328–9.
- [26] Aus G, Hugosson J, Norlen L. Long-term survival and mortality in prostate cancer treated with noncurative intent. *J Urol* 1995;154:460–5.
- [27] Whitmore Jr WF. Localised prostatic cancer: management and detection issues. *Lancet* 1994;343:1263–7.