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Prognosis of Gleason Score 9–10 Prostatic Adenocarcinoma in Needle Biopsies: A Nationwide Population-based Study

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Abstract

Background: Since 2014, prostate cancer is reported using five-tier grouping of Gleason scores. Studies have suggested prognostic heterogeneity within the groups.
Objective: We assessed the risk of prostate cancer death for men diagnosed with Gleason scores 4 + 5, 5 + 4, and 5 + 5 on needle biopsy in a population-based cohort.
Design, setting, and participants: We used the data from Prostate Cancer data Base Sweden (PCBaSe) 4.0 for a survival analysis. Among 199 620 men reported to have prostate cancer in 2000–2020, 172 112 were diagnosed on needle biopsy. The primary treatment was classified as androgen deprivation therapy (66%), deferred treatment (5%), radical prostatectomy (7%), or radical radiotherapy (21%).
Outcome measurements and statistical analysis: The risks of death from prostate cancer in men with Gleason score 9–10 at 5 and 10 yr were used as endpoints. Multivariable Cox regression models controlling for socioeconomic factors and primary treatment were used for time-to-event analyses of death from prostate cancer and death from any causes.
Results and limitations: A total of 20 419 (12%) men had a Gleason score of 9–10, including Gleason scores of 4 + 5, 5 + 4, and 5 + 5 in 14 333 (70%), 4223 (21%), and 1863 (9%) men, respectively. The risks of prostate cancer death for men with Gleason scores 4 + 5, 5 + 4, and 5 + 5 at 10 yr of follow-up were 0.45 (confidence interval [CI] 0.44–0.46), 0.56 (0.55–0.58), and 0.66 (0.63–0.68), respectively. The risks of death of any cause for men with Gleason scores 4 + 5, 5 + 4, and 5 + 5 at 10 yr were 0.73 (CI 0.72–0.74), 0.81 (0.80–0.83), and 0.87 (0.85–0.89), respectively.
Conclusions: We demonstrate in the largest and most complete cohort analyzed to date that collapsing the Gleason scores by grouping results in loss of prognostic information in men with Gleason score 9–10 cancer.
Patient summary: Survival of prostate cancer patients with the highest tumor grades varies depending on grade composition.

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1. Introduction

One of the benefits of the Gleason grading system for prostate cancer is that it takes into account the grade heterogeneity that is so prevalent in this tumor. In 2014, an International Society of Urological Pathology (ISUP) consensus conference suggested that Gleason scores be grouped into five ISUP grades (also known as ISUP grade groups) [1]. It has, however, been argued that this grouping may lead to a loss of granularity in the reporting of prostatic adenocarcinomas [2]. Studies have investigated the prognostic differences between different compositions of Gleason scores 8 (3 + 5, 4 + 4, and 5 + 3) [3–7] and 9–10 (4 + 5, 5 + 4, and 5 + 5) [8–12]. The results of most of these studies have indicated prognostic heterogeneity across the grades. We here used a nationwide population-based cohort in Sweden for an analysis of survival of men with Gleason score 9–10 cancer diagnosed by core needle biopsy. The National Prostate Cancer Register (NPCR) is a population-based registry that allows linking to other registries, for example, the National Death Registry. This enabled us to study the risk of prostate cancer death in the entire group of Gleason score 9–10 cancers in the largest and most complete cohort analyzed to date.

2. Patients and methods

Histopathological and clinical data and primary treatment of newly diagnosed prostate cancers in Sweden are reported to the NPCR since 1998 [13]. The coverage has been estimated to be >96% of all prostate cancer cases diagnosed in Sweden [14]. Men diagnosed in 2000–2020 with acinar adenocarcinoma of the prostate with Gleason score 9–10 in needle biopsies were included in the study. Cases with incomplete or inconsistent data entries (missing Gleason score or negative follow-up) were excluded. Data were extracted on biopsy Gleason score, age, clinical tumor-node-metastasis (TNM) categories, serum prostate-specific antigen, and Charlson Comorbidity Index at diagnosis. The primary treatment was classified as androgen deprivation therapy, deferred treatment, radical prostatectomy, or radical radiotherapy.

In Prostate Cancer data Base Sweden (PCBaSe), data in the NPCR have been linked to other nationwide population-based health care registers and demographic databases including the Cause of Death Register, Patient Register, and Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), a socioeconomic database by the use of the unique Swedish personal identity number. Deaths were classified as death from prostate cancer or death from other causes. Comorbidity was assessed by use of the Charlson Comorbidity Index, which was calculated based on discharge diagnoses from hospitalizations and specialist outpatient visits, extracted from the Patient Register for the 10-yr period preceding the prostate cancer diagnosis [15].

Data on education level (grouped in three levels: elementary school, upper secondary, and university) were retrieved from the LISA of Statistics Sweden [16]. PCBaSe 5.0 has been approved by the Research Ethics Authority.

2.1. Statistical analysis

Multivariable Cox regression models were used for time-to-event analyses of death from prostate cancer and death from any cause. Multivariable analyses included Gleason score, age, TNM staging categories, Charlson Comorbidity Index, primary treatment, period of diagnosis, and education level.

Prostate cancer–specific mortality (PCSM) and all-cause mortality (ACM) were calculated at 5 and 10 yr, using cumulative incidence functions that considered competing events (death from causes other than prostate cancer) for PCSM using the nonparametric Aalen-Johansen estimator. The time interval from diagnosis to death was registered. The last death record was from March 2023. Follow-up was calculated from the date of diagnosis to the date of death, date of emigration, or last date of follow-up on April 1, 2023, whichever came first. Graphs were generated for PCSM and ACM. A p value of <0.05 was considered significant.

3. Results

A total of 199 620 men with newly diagnosed prostate cancer were reported to the NPCR in 2000–2020. After exclusion of 8520 cases of cancer (4%) diagnosed in transurethral resection or transvesical enucleation specimens, 5917 (3%) were diagnosed by fine needle aspiration cytology and cases with incomplete data entries (Supplementary Fig. 1), 172 112 men with prostate cancer diagnosed on needle biopsy remained for analysis. Among them, 20 419 (12%) were diagnosed with a Gleason score of 9–10, including Gleason scores of 4 + 5, 5 + 4, and 5 + 5 in 14 333 (70%), 4223 (21%), and 1863 (9%) men, respectively. Of all cancers diagnosed in 2000–2005, 2006–2010, 2011–2015, and 2016–2020, the proportions of cancers that were assigned a Gleason score of 9–10 were 9% (3146/35 665), 9% (3946/41 889), 12% (5729/46 028), and 16% (7598/48 530), respectively (Supplementary Fig. 2). The mean ages at diagnosis were 73.7, 74.3, and 74.7 yr in men with Gleason scores of 4 + 5, 5 + 4, and 5 + 5, respectively. The median prostate-specific antigen values were 32, 40, and 35 ng/ml in men with Gleason scores of 4 + 5, 5 + 4, and 5 + 5, respectively. Other descriptive data are shown in Table 1. The most common primary treatment was androgen deprivation therapy (66%), followed by radical radiotherapy (21%), radical prostatectomy (7%), and deferred therapy (5%). Of all men with a Gleason score of 9–10, 34% were alive at the end of follow-up, while 43% died of prostate cancer and 23% died of other causes.

The median follow-up time was 8.1 yr (Q1 = 5.1, Q3 = 12.1). PCSM and ACM after 5 and 10 yr are shown in Table 2. PCSM for men with Gleason scores 4 + 5, 5 + 4, and 5 + 5 at 5 yr of follow-up were 0.30 (95% confidence interval [CI] 0.29–0.31), 0.43 (0.41–0.44), and 0.56 (0.54–0.58), respectively, and at 10 yr of follow-up, these were 0.44 (95% CI 0.44–0.46), 0.56 (0.55–0.58), and 0.66 (0.63–

Table 1 – Descriptive data of men diagnosed with Gleason score 4 + 5, 5 + 4, and 5 + 5 prostate cancer in Prostate Cancer data Base Sweden 4.0 in 2000–2020

		All GS 9–10 *n* (%)	GS 4 + 5 *n* (%)	GS 5 + 4 *n* (%)	GS 5 + 5 *n* (%)
Total		20 419 (100.0)	14 333 (70.2)	4223 (20.7)	1863 (9.1)
Age (yr)	≤70	6967 (34.1)	5038 (35.1)	1378 (32.6)	551 (29.6)
	71–80	5068 (24.8)	3414 (23.8)	1132 (26.8)	522 (28.0)
	>80	8384 (41.1)	5881 (41.0)	1713 (40.6)	790 (42.4)
Education	Low (elementary school)	8278 (40.5)	5673 (39.6)	1792 (42.4)	813 (43.6)
	Intermediate (high school)	7850 (38.4)	5558 (38.8)	1612 (38.2)	680 (36.5)
	High (university)	4291 (21.0)	3102 (21.6)	819 (19.4)	370 (19.9)
Civil status	Married	12 366 (61.5)	8747 (61.7)	2525 (60.9)	1094 (60.8)
	Unmarried	2462 (12.2)	1769 (12.5)	472 (11.4)	221 (12.3)
	Divorced	2900 (14.4)	2057 (14.5)	589 (14.2)	254 (14.1)
	Widower	2389 (11.9)	1599 (11.3)	560 (13.5)	230 (12.8)
Income	Q1	6477 (33.5)	4543 (33.1)	1345 (33.9)	589 (35.6)
	Q2	5746 (29.7)	4032 (29.4)	1206 (30.4)	508 (30.7)
	Q3	3973 (20.5)	2844 (20.7)	799 (20.1)	330 (19.9)
	Q4	3158 (16.3)	2313 (16.8)	616 (15.5)	229 (13.8)
Year of diagnosis	2000–2005	3146 (15.4)	1924 (13.4)	786 (18.6)	436 (23.4)
	2006–2010	3946 (19.3)	2625 (18.3)	902 (21.4)	419 (22.5)
	2011–2015	5729 (28.1)	4111 (28.7)	1122 (26.6)	496 (26.6)
	2016–2020	7598 (37.2)	5673 (39.6)	1413 (33.5)	512 (27.5)
S-PSA (ng/ml)	0–3	341 (1.7)	199 (1.4)	62 (1.5)	80 (4.4)
	3.1–10	3670 (18.2)	2726 (19.2)	642 (15.4)	302 (16.5)
	10.1–20	3412 (16.9)	2463 (17.3)	679 (16.3)	270 (14.8)
	>20	12 778 (63.3)	8808 (62.0)	2793 (66.9)	1177 (64.4)
T category	T1c	2696 (13.2)	2062 (14.4)	455 (10.8)	179 (9.6)
	T2	6346 (31.1)	4758 (33.2)	1168 (27.7)	420 (22.5)
	T3	8670 (42.5)	5912 (41.2)	1953 (46.2)	805 (43.2)
	T4	2299 (11.3)	1340 (9.3)	561 (13.3)	398 (21.4)
	TX	408 (2.0)	261 (1.8)	86 (2.0)	61 (3.3)
N category	N0	5648 (27.7)	4336 (30.3)	982 (23.3)	330 (17.7)
	N1	3011 (14.7)	2018 (14.1)	665 (15.7)	328 (17.6)
	NX	11 760 (57.6)	7979 (55.7)	2576 (61.0)	1205 (64.7)
M category	M0	10 948 (53.6)	8219 (57.3)	1977 (46.8)	752 (40.4)
	M1	6396 (31.3)	4142 (28.9)	1530 (36.2)	724 (38.9)
	MX	3075 (15.1)	1972 (13.8)	716 (17.0)	387 (20.8)
Charlson Comorbidity Index	0	13 777 (67.5)	9819 (68.5)	2772 (65.6)	1186 (63.7)
	1	4167 (20.4)	2848 (19.9)	913 (21.6)	406 (21.8)
	2+	2475 (12.1)	1666 (11.6)	538 (12.7)	271 (14.5)
Treatment	Androgen deprivation therapy	13 586 (66.5)	9033 (63.0)	3091 (73.2)	1462 (78.5)
	Deferred treatment	1044 (5.1)	734 (5.1)	209 (4.9)	101 (5.4)
	Radical prostatectomy	1509 (7.4)	1230 (8.6)	211 (5.0)	68 (3.7)
	Radical radiotherapy	4280 (21.0)	3336 (23.3)	712 (16.9)	232 (12.5)
Death status	Alive	6831 (33.5)	5418 (37.8)	1078 (25.5)	335 (18.0)
	Death from prostate cancer	8853 (43.4)	5517 (38.5)	2174 (51.5)	1162 (62.4)
	Death from other causes	4735 (23.2)	3398 (23.7)	971 (23.0)	366 (19.6)

GS = Gleason score; S-PSA = serum prostate-specific antigen.

0.68), respectively. ACM values for men with Gleason scores 4 + 5, 5 + 4, and 5 + 5 at 10 yr of follow-up were 0.73 (95% CI 0.72–0.74), 0.81 (0.80–0.83), and 0.87 (0.85–0.89), respectively. Plots of PCSM and ACM of all men with a Gleason score of 9–10 are shown in Figure 1.

The PCSM of men with a Gleason score of 5 + 4 tended to be higher than that of those with a Gleason score of 4 + 5 after both 5 and 10 yr, regardless of the primary treatment (radical prostatectomy, radical radiotherapy, androgen deprivation therapy or deferred treatment; Table 2). The same was mostly true for men with a Gleason score of 5 + 5 versus 5 + 4. In the entire group of men with Gleason score 9–10 cancers, the survival rate at 5 and 10 yr was higher after radical prostatectomy or radical radiotherapy than after androgen deprivation therapy or deferred therapy (Table 2). Plots of PCSM and ACM after these treatment options are shown in Figure 2. Plots of PCSM and ACM of all Gleason score 9–10 cancers diagnosed during the time periods of 2000–2005, 2006–2010, 2011–2015, and 2016–2020 are shown in Figure 3.

In a multivariable Cox analysis including Gleason score, age, TNM categories, Charlson Comorbidity Index, primary treatment, period of diagnosis, and education level, Gleason scores 5 + 4 and 5 + 5 remained significant predictors of PCSM at 10 yr of follow-up with hazard ratios of 1.34 (95% CI 1.27–1.41) and 1.80 (95% CI 1.68–1.92), respectively, using Gleason score 4 + 5 as a referent (Table 3).

4. Discussion

In this study, we demonstrate, utilizing the largest cohort reported to date, that there are prognostic differences between Gleason scores 4 + 5, 5 + 4, and 5 + 5, regardless of the primary treatment. Although prostate cancer with these grades is associated with a poor outcome, the progno-

Table 2 – Prostate cancer-specific mortality and all-cause mortality at 5 and 10 yr

		Prostate cancer–specific mortality				All-cause mortality			
		All GS 9–10	GS 4 + 5	GS 5 + 4	GS 5 + 5	All GS 9–10	GS 4 + 5	GS 5 + 4	GS 5 + 5
5-yr mortality									
	Total	0.35 (0.35–0.36)	0.30 (0.29–0.31)	0.43 (0.41–0.44)	0.56 (0.54–0.58)	0.52 (0.51–0.52)	0.47 (0.46–0.48)	0.59 (0.58–0.61)	0.71 (0.68–0.73)
Treatment	ADT	0.47 (0.47–0.48)	0.43 (0.42–0.44)	0.53 (0.51–0.55)	0.65 (0.62–0.67)	0.67 (0.66–0.68)	0.63 (0.62–0.64)	0.72 (0.70–0.74)	0.80 (0.78–0.82)
	DT	0.32 (0.29–0.35)	0.27 (0.24–0.31)	0.40 (0.33–0.46)	0.54 (0.44–0.63)	0.59 (0.56–0.62)	0.54 (0.51–0.58)	0.63 (0.56–0.70)	0.87 (0.78–0.92)
	RP	0.05 (0.04–0.06)	0.04 (0.03–0.06)	0.06 (0.03–0.10)	0.13 (0.06–0.22)	0.08 (0.07–0.10)	0.07 (0.06–0.09)	0.09 (0.05–0.13)	0.17 (0.09–0.28)
	RRT	0.07 (0.06–0.08)	0.06 (0.05–0.07)	0.11 (0.08–0.13)	0.12 (0.08–0.16)	0.14 (0.13–0.15)	0.13 (0.12–0.15)	0.17 (0.14–0.20)	0.17 (0.12–0.22)
Year of diagnosis	2000–2005	0.46 (0.44–0.48)	0.41 (0.39–0.43)	0.51 (0.47–0.54)	0.61 (0.56–0.65)	0.64 (0.63–0.66)	0.60 (0.57–0.62)	0.68 (0.65–0.72)	0.79 (0.75–0.82)
	2006–2010	0.42 (0.40–0.43)	0.37 (0.35–0.39)	0.46 (0.43–0.50)	0.60 (0.56–0.65)	0.60 (0.58–0.61)	0.56 (0.54–0.58)	0.64 (0.61–0.67)	0.75 (0.70–0.79)
	2011–2015	0.35 (0.33–0.36)	0.30 (0.29–0.32)	0.43 (0.40–0.46)	0.53 (0.48–0.57)	0.51 (0.49–0.52)	0.46 (0.44–0.47)	0.59 (0.56–0.62)	0.70 (0.66–0.74)
	2016–2020	0.26 (0.25–0.27)	0.22 (0.21–0.23)	0.35 (0.32–0.37)	0.50 (0.46–0.55)	0.42 (0.40–0.43)	0.38 (0.36–0.39)	0.51 (0.48–0.53)	0.60 (0.55–0.64)
10-yr mortality									
	Total	0.50 (0.49–0.50)	0.45 (0.44–0.46)	0.56 (0.55–0.58)	0.66 (0.63–0.68)	0.76 (0.76–0.77)	0.73 (0.72–0.74)	0.81 (0.80–0.83)	0.87 (0.85–0.89)
Treatment	ADT	0.61 (0.60–0.62)	0.58 (0.57–0.59)	0.65 (0.63–0.67)	0.74 (0.71–0.76)	0.90 (0.90–0.91)	0.89 (0.88–0.90)	0.92 (0.91–0.93)	0.95 (0.93–0.96)
	DT	0.44 (0.41–0.48)	0.41 (0.37–0.45)	0.49 (0.42–0.56)	0.58 (0.47–0.67)	0.82 (0.79–0.85)	0.79 (0.75–0.83)	0.88 (0.81–0.93)	0.91 (0.82–0.95)
	RP	0.17 (0.15–0.20)	0.16 (0.13–0.19)	0.24 (0.17–0.31)	0.23 (0.12–0.36)	0.29 (0.26–0.33)	0.28 (0.24–0.32)	0.34 (0.26–0.42)	0.37 (0.22–0.51)
	RRT	0.20 (0.18–0.21)	0.17 (0.15–0.19)	0.26 (0.22–0.30)	0.30 (0.22–0.37)	0.39 (0.37–0.42)	0.38 (0.36–0.41)	0.43 (0.37–0.47)	0.47 (0.38–0.55)
Year of diagnosis	2000–2005	0.59 (0.57–−0.61)	0.56 (0.53–0.58)	0.62 (0.58–0.65)	0.70 (0.65–0.74)	0.85 (0.84–0.86)	0.83 (0.81–0.85)	0.87 (0.84–0.89)	0.92 (0.89–0.94)
	2006–2010	0.55 (0.53–−0.56)	0.51 (0.49–0.53)	0.59 (0.55–0.62)	0.68 (0.64–0.73)	0.82 (0.81–0.83)	0.80 (0.78–0.81)	0.83 (0.81–0.86)	0.89 (0.86–0.92)
	2011–2015	0.47 (0.46–−0.49)	0.43 (0.41–0.45)	0.56 (0.53–0.59)	0.63 (0.58–0.67)	0.73 (0.72–0.74)	0.70 (0.68–0.71)	0.80 (0.77–0.83)	0.85 (0.82–0.88)
	2016–2020	–	–	–	–	–	–	–	–

ADT = androgen deprivation therapy; DT = deferred treatment; GS = Gleason score; RP = radical prostatectomy; RRT = radical radiotherapy.
Cumulative risks with 95% confidence intervals.

sis is not uniformly poor, in particular in men amenable to treatment with curative intent.

The original design of the Gleason system for grading of prostate cancer defined nine Gleason scores through the addition of the two predominant Gleason patterns. It was later realized that the large group of men with a Gleason score of 7 was prognostically heterogeneous, being dependent on the proportion of Gleason pattern 4 present in the biopsy [17–19]. At the 2014 ISUP consensus conference on grading of prostate cancer, it was suggested that for communication purposes, Gleason scores be grouped in five tiers: 2–6, 7 (3 + 4), 7 (4 + 3), 8, and 9–10 [1]. It has, however, been debated whether this grouping leads to a loss of prognostic information contained within each tier [2]. If the outcome of men with Gleason score 7 cancers depends on the balance between the grade components, it could be assumed that the same is true for Gleason score 9 cancers. Grouping of Gleason scores 9–10 may thus cause loss of prognostic discrimination.

One of the challenges in studying the prognostic impact of cancers with a biopsy Gleason score 9–10 is the difficulty in collecting a sufficiently large group of patients. In a small study, Lim et al. [8] showed that lymph node metastases and biochemical recurrence were more common in 22 men with Gleason score 5 + 4 cancer in their radical prostatectomy specimens than in 58 men with Gleason score 4 + 5 cancer. Moschini et al. [9] later analyzed a series of men who underwent radical prostatectomy after a needle biopsy diagnosis of Gleason score 4 + 4, 4 + 5, or 5 + 4 cancer. The outcome measures of 347 men with a preoperative Gleason score of 4 + 5 and 119 men with a Gleason score of 5 + 4 were rather similar with 10-yr cancer-specific survival rates of 70% and 73%, respectively. Tilki et al. [10] analyzed 922 men who underwent radical prostatectomy at the Martini Clinic in Hamburg between 1992 and 2014 after a biopsy with a Gleason score of 9–10. In this series, men with a primary versus secondary Gleason pattern of 5 had 5-yr metastasis-free survival rates of 80.4% and 86.9%, respectively.

Recently, several registry studies have addressed this issue [11,12,20]. All of them have been based on the data from the Surveillance, Epidemiology and End Results database, including the periods 2004–2015, 2005–2015, and 2004–2016. The number of men with Gleason score 9–10 cancer who were analyzed in these studies varied from 17 263 [11] to 18 640 [12]. The studies included patients who underwent radical prostatectomy or radical radiotherapy. The current study is, to our knowledge, the first registry study that has analyzed the entire group of Gleason score 9–10 cancers, including patients treated with androgen deprivation therapy, deferred treatment, radical prostatectomy, or radical radiation therapy.

Another difference compared with previous registry studies is that we have been able to analyze a population-based cohort with a very high coverage. More than 96% of all newly diagnosed prostate cancers in Sweden are reported to the NPCR [14]. The endpoints used in the current study are more robust than other endpoints based on, for example, biochemical recurrence. We have

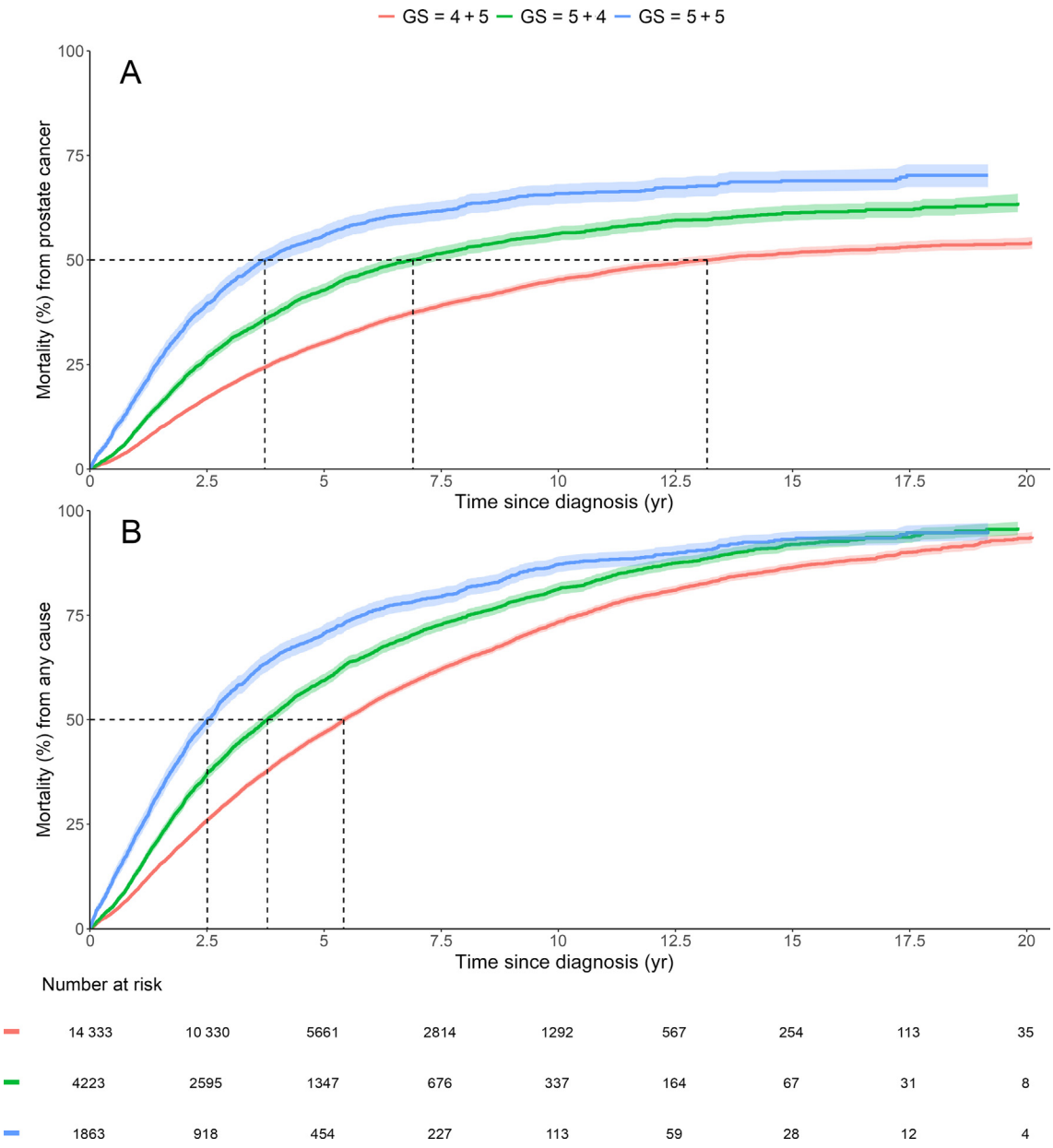

Fig. 1 – (A) Prostate cancer–specific mortality of men with Gleason scores (GSs) 4 + 5, 5 + 4, and 5 + 5. (B) All-cause mortality of men with GSs 4 + 5, 5 + 4, and 5 + 5. Curves are truncated at the time point of the last event.

also been able to control for socioeconomic data and primary treatment.

The strengths of registry studies are that these are population based and may include very large datasets. An important feature of the NPCR is the possibility to link the data to other registries for endpoints such as cause of death and for covariates such as education level. Limitations of registry studies in pathology include the lack of a central review of tumor classification and grade, which would be impossible with datasets of this size. However, despite the lack of precision, the massive amount of data provides the best source to determine whether or not there are differences between groups.

The survival in high-grade prostate cancer improved over the 20-yr study period. The 5-yr PCSM in all men with Gleason score 9–10 cancer has decreased from 0.46 in 2000–2005 to 0.26 in 2016–2020. There are several possible explanations for this shift. Changes in the use of detection methods including more extensive serum prostate-specific antigen testing and the introduction of modern imaging techniques have led to earlier detection and, hence, a prolonged lead time, which gives a false impression of an improved outcome. In addition, more active treatment of high-grade cancer may have contributed to this improvement. However, changed grading practices have probably also affected the outcome data. The percentage of newly

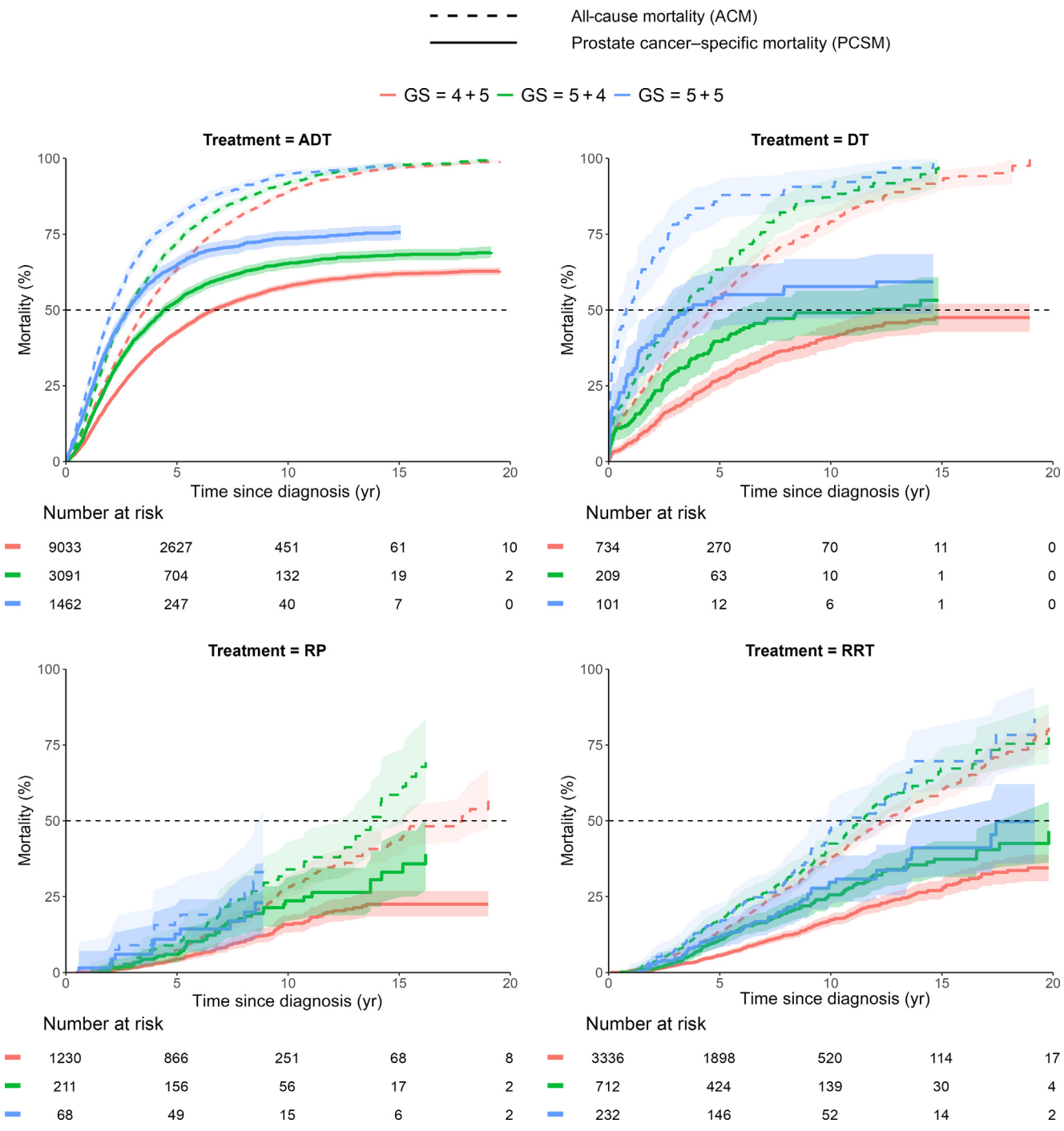

Fig. 2 – Prostate cancer–specific mortality and all-cause mortality of men with Gleason score 9–10 prostate cancer managed by androgen deprivation therapy (ADT), deferred therapy (DT), radical prostatectomy (RP), or radical radiotherapy (RRT). All-cause survival was marked with dashed lines. Curves are truncated at the time point of the last event. GS = Gleason score.

diagnosed prostate cancers assigned a Gleason score of 9–10 increased from 9% to 16% from 2000–2005 to 2016–2020 (Supplementary Fig. 2). It is very unlikely that the biology of prostate cancer will have altered during this period, although the use of magnetic resonance imaging in the most recent years may have contributed to an increased detection rate of high-grade cancers. Magnetic resonance imaging–guided prostate biopsies were introduced in Sweden in 2014 but were very rarely used in the first years. A prostate biopsy was preceded by magnetic resonance imaging in only 7% of cases in 2016 [21]. Yet, an increasing number of cancer cases were diagnosed to have a Gleason score of 9–10 already before 2016 (Supplementary Fig. 2). Prostate cancer grading has been the subject of a large number of changes over the past decades. Some of these revisions have fueled a dramatic inflation of prostate cancer grading

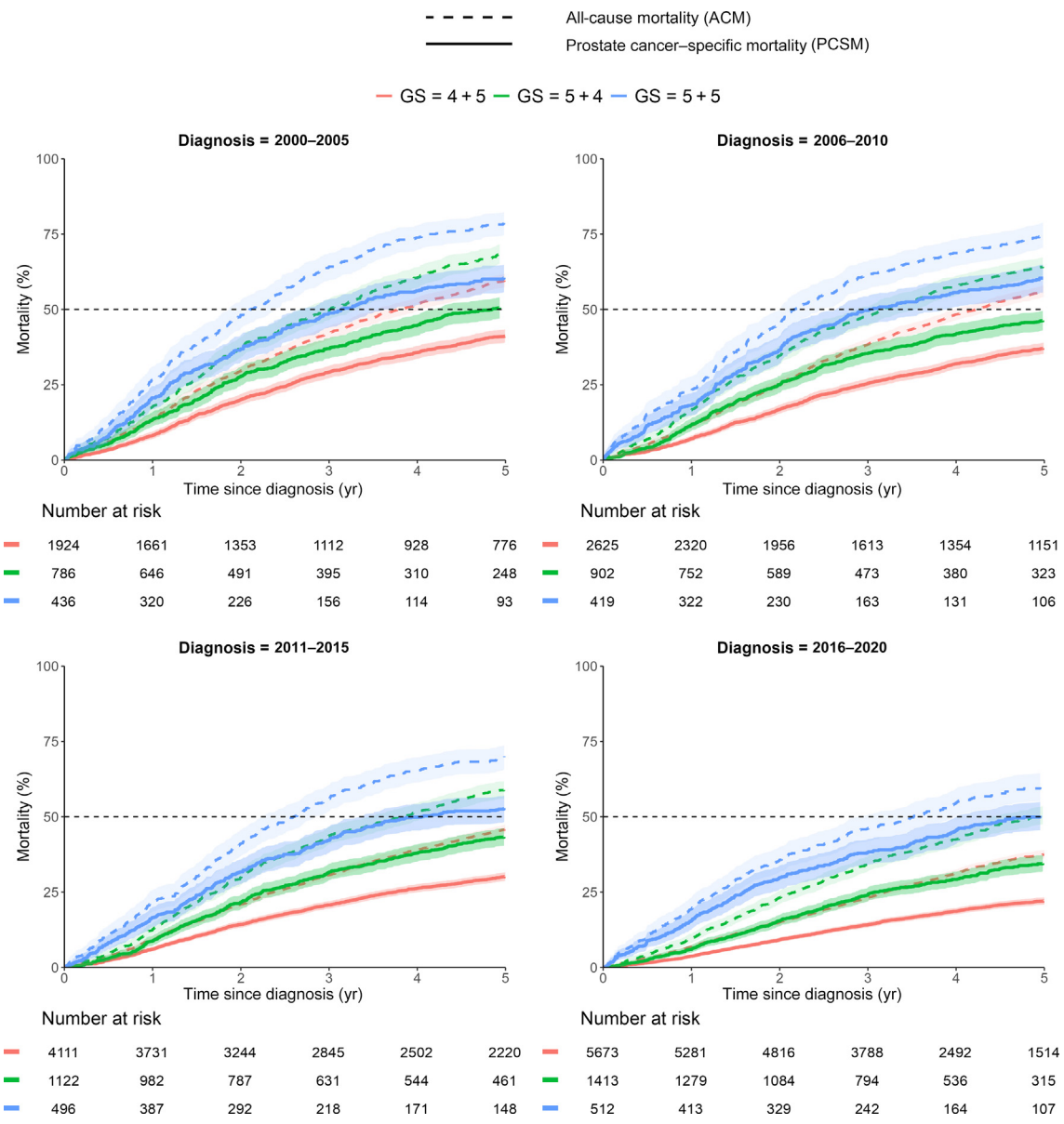

Fig. 3 – Prostate cancer–specific mortality and all-cause mortality of men with Gleason score 9–10 prostate cancer diagnosed in 2000–2005, 2006–2010, 2011–2015, and 2016–2020. Curves are truncated at the time point of the last event. GS = Gleason score.

[22]. Despite considerable efforts to standardize prostate cancer grading [23,24], this inflation remains problematic. Importantly, a shift upward of grading will cause a false impression of improved outcome, the so-called Will Rogers phenomenon [25,26].

To control for grade inflation, we repeated the analyses in each investigated time period (Fig. 3) and found similar differences in outcome between Gleason scores 4 + 5, 5 + 4, and 5 + 5 in all four periods. Even though the overall prognosis of high-grade cancer may have improved, the prognostic differences between the grades largely remain.

A comparison of prognosis in cancers managed by different primary treatments suggests a benefit of treatment with curative intent with hazard ratios for PCSM at 10 yr of 0.27–0.28 with radical prostatectomy or radiotherapy, using androgen depravation therapy as a referent. There were no significant differences in PCSM in men who underwent radical prostatectomy or radiotherapy, while omitting locally curative treatment seems to incur a risk of developing metastatic clones. It has recently been shown that cells with the ability to develop into castration-resistant prostate cancer are already present in early, hormone-naïve prostatic carcinoma [27]. Clonal expansion of such cells that are not targeted by local therapy may lead to clinical castration-resistant disease. Yet, only 7% and 21% underwent radical prostatectomy and radiotherapy, respectively, as the primary treatment. Some of the observed prognostic differences between these cancers and those treated with noncurative intent are most likely the result of a selection bias, where men with smaller and more localized tumors with better prognosis tend to be offered radical treatment. However, observational studies have suggested that treatment with

Table 3 – Multivariable Cox analysis of prostate cancer–specific (PCSM) and all-cause mortality (ACM) at 10 yr

	PCSM HR (95% CI)	ACM HR (95% CI)
Gleason score		
4 + 5	Ref	Ref
5 + 4	1.34 (1.27–1.41)	1.23 (1.18–1.28)
5 + 5	1.80 (1.68–1.92)	1.53 (1.45–1.62)
Age (per year increase)	1.01 (1.01–1.01)	1.03 (1.03–1.03)
T category		
T1c	Ref	Ref
T2	1.20 (1.09–1.32)	1.10 (1.02–1.17)
T3	1.59 (1.45–1.74)	1.37 (1.28–1.46)
T4	2.07 (1.87–2.29)	1.67 (1.55–1.81)
TX	1.78 (1.51–2.11)	1.47 (1.29–1.68)
N category		
N0	Ref	Ref
N1	1.34 (1.23–1.46)	1.19 (1.12–1.28)
NX	1.24 (1.16–1.34)	1.18 (1.12–1.25)
M category		
M0	Ref	Ref
M1	2.46 (2.33–2.60)	1.82 (1.74–1.90)
MX	1.15 (1.07–1.23)	1.12 (1.05–1.18)
CCI (per unit increase)	1.10 (1.09–1.11)	1.15 (1.13–1.16)
Treatment		
ADT	Ref	Ref
DT	0.92 (0.83–1.02)	1.06 (0.98–1.14)
RP	0.27 (0.23–0.32)	0.28 (0.25–0.32)
RRT	0.28 (0.25–0.31)	0.34 (0.32–0.37)
Year of diagnosis		
2000–2005	Ref	Ref
2006–2010	0.94 (0.88–1.00)	0.95 (0.90–1.00)
2011–2015	0.82 (0.77–0.88)	0.88 (0.84–0.94)
2016–2020	0.59 (0.55–0.64)	0.69 (0.65–0.74)
Education		
Low	Ref	Ref
Intermediate	0.94 (0.90–0.99)	0.96 (0.93–1.00)
High	0.88 (0.83–0.94)	0.84 (0.80–0.89)

ADT = androgen deprivation therapy; CCI = Charlson Comorbidity Index; CI = confidence interval; DT = deferred treatment; HR = hazard ratio; Ref = reference; RP = radical prostatectomy; RRT = radical radiotherapy. Hazard ratios with 95% confidence intervals.

curative intent is associated with a lower risk of prostate cancer death in men with very-high-risk tumors [28].

5. Conclusions

Whether the prognostic differences between Gleason scores 4 + 5, 5 + 4, and 5 + 5 warrant different treatment remains to be investigated; however, our findings indicate that the information loss by grouping of Gleason scores may obscure important outcome differences and thus possibly lead to over- or under-treatment. Thus, the reporting of Gleason scores including the Gleason pattern components is essential since collapsing the scores into groups entails loss of information. This is the first study to evaluate the long-term outcome of these subgroups of high-grade prostate cancer. The results emphasize the importance of identifying men with Gleason score 9–10 prostate cancer who are amenable to radical treatment that offers a substantial opportunity for cure even for this aggressive subset of cancer.

Author contributions: Lars Egevad had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Garmo, Stattin.
Analysis and interpretation of data: Micoli, Garmo, Eklund, Egevad.
Drafting of the manuscript: Egevad, Delahunt.
Critical revision of the manuscript for important intellectual content: Egevad, Delahunt, Samaratunga.
Statistical analysis: Micoli.
Obtaining funding: Egevad, Stattin.
Administrative, technical, or material support: Garmo, Stattin.
Supervision: Egevad, Eklund.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.11.002.

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