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Brief Correspondence

Gleason Score 3 + 5 or 5 + 3 versus 4 + 4 Prostate Cancer: The Risk of Death

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Abstract

The International Society of Urological Pathology recommends that Gleason score (GS) 8 prostate cancer (PC) is one prognostic category, yet heterogeneity in cancer control potentially exists amongst men with GS 3 + 5/5 + 3 versus GS 4 + 4 PC. We compared PC-specific mortality (PCSM) and all-cause mortality (ACM) risk among men with GS 3 + 5/5 + 3 versus GS 4 + 4 PC using competing-risks and Cox regression analyses, adjusting for age, known PC prognostic factors, treatment, and a treatment propensity score. Between 1998 and 2012, 462 men with GS 8 PC were treated using brachytherapy with supplemental external-beam radiation therapy and/or androgen deprivation therapy at the Chicago Prostate Cancer Center. After a median follow-up of 7.6 yr, 118 men died, 26 of PC. PCSM (adjusted hazard ratio [AHR] 2.77, 95% confidence interval [CI] 1.13–6.80; $p = 0.026$) and ACM (AHR 1.75, 95% CI 1.06–2.87; $p = 0.028$) were significantly higher for men with GS 3 + 5/5 + 3 PC than for men with GS 4 + 4 PC. Subcategorizing GS 8 into PC with or without grade 5 should be considered as a stratification factor in randomized trials.
Patient summary: Long-term success rates for men with Gleason score 8 prostate cancer vary depending on whether the most aggressive type of cancer (grade 5) is present at biopsy.

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Multiple studies have shown that higher Gleason score (GS) is an important prognostic factor across all treatments for prostate cancer (PC) [1]. Using data on prostate-specific antigen (PSA) recurrence, the International Society of Urological Pathology (ISUP) has recommended a five-tiered prognostic staging system [2], including: group 1, GS $\leq$6; group 2, GS 3 + 4 = 7; group 3, GS 4 + 3 = 7; group 4, GS 8; and group 5, GS 9–10 [3]. However, the known negative prognostic significance of Gleason grade 5 compared to Gleason grade 4 [4] raises the concern that prognostic group 4 (GS 8) is subject to heterogeneity with respect to long-term PC outcomes, including PC-specific mortality (PCSM) and all-cause mortality (ACM). Specifically, men with GS 3 + 5, GS 5 + 3, and GS 4 + 4 would be grouped into a single category but may have distinct outcomes given the known negative prognostic significance of Gleason grade 5 compared to grade 4 PC [4].

Therefore, the purpose of this study was to use a prospectively assembled database to ascertain whether men with GS 3 + 5 or 5 + 3 had a higher risk of PCSM and ACM compared to men with GS 4 + 4 after adjusting for age, known prognostic PC factors, treatment, and a treatment propensity score.

Between January 6, 1998 and May 18, 2012, 462 men (median age 72.08 yr) with 2002 American Joint Commission on Cancer (AJCC) tumor (T) category[5] 1c-3 and high-risk PC

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based on the highest biopsy GS being 8 (3 + 5 or 4 + 4 or 5 + 3) from at least one core formed the prospectively assembled study cohort. The biopsy GS was assigned by a pathologist with expertise in genitourinary cancers. Men were treated using prostate brachytherapy and additional supplemental therapies, including neoadjuvant external-beam radiation therapy (EBRT, 45 Gy; $n = 63$) or androgen deprivation therapy (ADT; $n = 117$) or both ($n = 157$), at the Chicago Prostate Cancer Center. At the time of PSA failure, defined as PSA nadir +2 ng/ml, salvage ADT was administered.

Univariate and multivariate Cox [6] and Fine-Gray [7] regression models were used to assess whether men with GS 3 + 5/5 + 3 versus GS 4 + 4 were at higher risk of ACM or PCSM respectively, adjusting for age, PSA, T category, treatment, and treatment propensity score. Cox regression [6] was used for ACM given all deaths are considered events, whereas competing-risks regression [7] was used for PCSM and other-cause mortality (OCM) given that 92 of the 118 deaths were from other causes.

Age-adjusted ACM, defined as 1 – [Kaplan-Meier estimates [8] of overall survival (OS)], and cumulative incidence [9] estimates of PCSM and OCM were calculated for men with GS 3 + 5/5 + 3 versus GS 4 + 4.

SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for all calculations apart from the Fine-Gray regression and cumulative incidence estimates, for which R version 3.0.1 (R Project for Statistical Computing, Vienna, Austria) was used.

After a median follow-up of 7.6 yr (interquartile range [IQR] 5.6–10.5 yr), 118 of the 462 men died, 26 of PC. There was significantly higher risk of PCSM (adjusted hazard ratio [AHR] 2.77, 95% confidence interval [CI] 1.13–6.80; $p = 0.026$) and ACM (AHR 1.75, 95% CI 1.06–2.87; $p = 0.028$) but not OCM (AHR 1.37, 95% CI 0.79–2.40; $p = 0.26$) among men with GS 3 + 5/5 + 3 compared to GS 4 + 4 PC after adjusting for treatment and known PC prognostic factors (Table 1). When looking at the individual terms of GS 5 + 3/3 + 5 versus GS 4 + 4, the higher risk for both PCSM and ACM remained, although this was only significant for PCSM among men with GS 5 + 3 compared to GS 4 + 4 (Table 1), justifying collapse of these two GS subgroups into one cohort for illustration in Figure 1. Increasing age was also significantly associated with higher ACM risk (AHR 1.07, 95% CI 1.02–1.12; $p = 0.004$) but did not reach statistical significance for PCSM (AHR 1.08, 95% CI 0.999–1.17; $p = 0.054$).

As shown in Figure 1A–C, cumulative incidence estimates of PCSM ($p = 0.02$), OCM ($p = 0.18$) and age-adjusted ACM ($p = 0.01$), were significantly higher, not significantly different, and significantly higher respectively for GS 3 + 5/5 + 3 compared to GS 4 + 4.

We observed that the risks of both PCSM and ACM were significantly higher in men with GS 3 + 5/5 + 3 compared to those with GS 4 + 4 PC. This observation was noted after adjusting for treatment received, a treatment propensity score, known PC prognostic factors, and age. The clinical significance of this finding is that the ISUP proposal [3] to classify men with GS 8 in a single category (prognostic group 4) may not be optimal given the difference in long-term PCSM and ACM outcomes we observed between GS 5 + 3/3 + 5 and GS 4 + 4 groups. Specifically, our results provide evidence supporting subdivision of men with GS 8 PC into two prognostic groups: those with and without Gleason grade 5 PC. Prospective and adequately powered studies are warranted to validate our results in the contemporary era of 12-core prostate needle biopsy and post-2005 ISUP recommendations [10] and within individual treatment modalities to ensure generalizability across treatment modalities for patients presenting today.

Table 1 – Unadjusted and adjusted hazard ratios for overall mortality [6] and prostate cancer–specific mortality [7] for each clinical factor

Clinical factor	Men	ACM					PCSM				
	(*n*)	Deaths	Univariable		Multivariable		PC	Univariable		Multivariable	
		(*n*)	HR (95% CI)	*p* value	AHR (95% CI)	*p* value	deaths (*n*)	HR (95% CI)	*p* value	AHR (95% CI)	*p* value
Gleason score [a]											
4 + 4	421	99	1.0 (reference)	–	1.0 (reference)	–	20	1.0 (reference)	–	1.0 (reference)	–
3 + 5 or 5 + 3	41	19	1.91 (1.17–3.13)	0.01	1.75 (1.06–2.87)	0.028	6	2.92 (1.17–7.27)	0.021	2.77 (1.13–6.80)	0.026
Log PSA (ng/ml)	462	118	1.20 (0.98–1.48)	0.08	1.19 (0.84–1.68)	0.33	26	1.45 (0.84–2.50)	0.18	1.11 (0.48–2.57)	0.80
Age (yr)	462	118	1.06 (1.04–1.09)	<0.0001	1.07 (1.02–1.12)	0.004	26	1.04 (0.97–1.10)	0.26	1.08 (0.999–1.17)	0.054
Clinical tumor category [b]											
T1	223	43	1.0 (reference)	–	1.0 (reference)	–	5	1.0 (reference)	–	1.0 (reference)	–
T2–3	239	75	1.74 (1.20–2.54)	0.004	1.53 (0.88–2.66)	0.13	21	4.05 (1.53–10.70)	0.005	2.60 (0.73–9.19)	0.14
Treatment											
Other	305	80	1.0 (reference)	–	1.0 (reference)	–	14	1.0 (reference)	–	1.0 (reference)	–
BT + ADT + EBRT	157	38	0.86 (0.58–1.26)	0.43	0.86 (0.56–1.33)	0.50	12	1.60 (0.74–3.45)	0.23	1.22 (0.53–2.79)	0.64
Treatment propensity score	462	118	1.0 (0.99–1.01)	0.68	1.01 (0.98–1.03)	0.56	26	1.02 (0.998–1.04)	0.08	1.02 (0.98–1.06)	0.28

ACM = all-cause mortality; PC = prostate cancer; PCSM = PC-specific mortality; HR = hazard ratio; CI = confidence interval; AHR = adjusted HR; GS = Gleason score; PSA = prostate-specific antigen; BT = brachytherapy; ADT = androgen deprivation therapy; EBRT, external beam radiation therapy.

[a] GS 5 + 3 versus GS 4 + 4: AHR 3.39 (95% CI 1.15–9.99; $p = 0.027$) for PCSM; AHR 1.76 (95% CI 0.80–3.83; $p = 0.16$) for ACM. GS 3 + 5 versus GS 4 + 4: AHR 2.36 (95% CI 0.67–8.32; $p = 0.18$) for PCSM; AHR 1.74 (95% CI 0.95–3.22; $p = 0.07$) for ACM. GS 3 + 5/5 + 3 versus GS 4 + 4: AHR 1.37 (95% CI 0.79–2.40; $p = 0.26$) for other-cause mortality (OCM). None of the other covariates in the multivariable model reached statistical significance; however, the result for increasing age was AHR 1.05 (95% CI 0.996–1.11; $p = 0.067$). Patient characteristics at study entry are listed in Supplementary Table 1. Results for all covariates from the univariate and multivariate analyses for OCM are reported in Supplementary Table 2.

[b] According to the American Joint Cancer Center 2002 [5].

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