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SHORT COMMUNICATION

ISUP Group 4 – a Homogenous Group of Prostate Cancers?

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Abstract The International Society of Urological Pathology (ISUP) and the World Health Organisation have adopted a five-tiered prognostic grade group for prostate cancer in 2014. Grade group 4 is comprised of Gleason patterns 4 + 4, 3 + 5 and 5 + 3. Recent articles have suggested heterogeneity in their prognostic outcomes. We aimed to determine whether there was a difference in mortality outcomes within the ISUP 4 grouping, as identified on needle biopsy. A total of 4080 men who were diagnosed with non-metastatic (N0 M0) prostate cancer on biopsy with Gleason scores of 7, 8 and 9 were included. Multi-variable Cox Regression and Fine and Grey competing risk analysis were used to determine the All-Cause Mortality (ACM) and the Prostate Cancer Specific Mortality (PCSM) as a function of Gleason Scores (Gleason 3 + 4, 4 + 3, 4 + 4, 3 + 5/5 + 3, 9). Gleason score 4 + 4 was utilized as the referent. The 60 months' prostate cancer specific mortality with Gleason patterns 4 + 4 and 3 + 5/5 + 3 were 17% and 20% respectively ($P < 0.01$). Patients with 3 + 5/5 + 3 disease, had no statistically significant difference in the ACM (adjusted hazard ratio [aHR] 0.99, 95% confidence interval [Cl] 0.68–1.4, $p = 0.99$) and PCSM risk (aHR 0.77, 95% Cl 0.47–1.2, $p = 0.31$) when compare with the referent group of patients. Patients with Gleason patterns 4 + 3 and 9 had statistically significant difference in their PCSM risk (aHR 0.70, 95% CI 0.54–0.91, $P < 0.001$ and aHR 1.5, 95% Cl 1.2–1.9, $P < 0.001$) when compared to the referent group. Our analysis suggest that ISUP group 4 is homogenous in terms of the all-cause mortality and the prostate cancer specific morality risk as differentiated by the presence of Gleason 5 score.

Keywords Prostate cancer · Gleason score · Grade group 4 · Biopsy · Prostate cancer specific mortality

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Introduction

The Gleason score is used to stratify prostate cancer into risk and treatment groups, but is also a powerful prognostic indicator. It is a combination of primary and secondary patterns. Recently the International Society of Urological Pathology (ISUP) has recommended a new prognostic grading system with five tiers [1]. The ISUP grade groups reflect a behavioural distinction within prostate cancers with Gleason score 7, separating 3 + 4 into group 2, and 4 + 3 into group 3 (Fig. 1).

The ISUP grade group 4 is equivalent to prostate cancer with a total Gleason score of 8, comprising of 4 + 4, 3 + 5 and 5 + 3. It is considered a homogenous entity. Recent literature published has raised questions about whether Gleason score 8, or ISUP grade group 4 is a heterogeneous entity

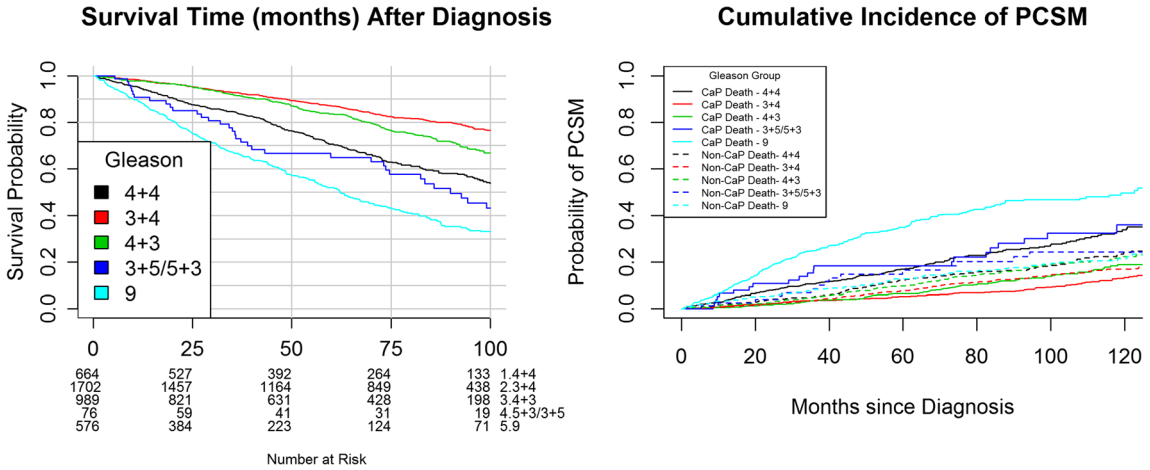

Fig. 1 Kaplan Meier Curve for ACM and the Cumulative Incidence Plot for PCSM by Gleason score (GS) among all patients with N0 M0 Gleason score 7, 8 or 9

prognostically, and hence whether there is merit in the reclassification of grade group 4 into separate grade groups.

The aim of this study was to determine in men having a prostate biopsy with a ISUP grade group 4 prostate cancer, whether there is a difference in mortality outcomes between 4 + 4 and 3 + 5/5 + 3. A sensitivity analysis was conducted with radical prostatectomy patients only, and then separating 3 + 5 and 5 + 3 Gleason patterns.

Methods

Patients and Data Collection

The South Australian Prostate Cancer Clinical Outcomes Collaboration (SA-PCCOC) is a registry that prospectively collects diagnosis, treatment and outcome data relating to men with prostate cancer diagnosed in South Australia, Australia. The registry contains more than 10,000 patients. The study cohort consisted of 4080 men from this database who were diagnosed between 1998 and 2015 with non-metastatic prostate cancer with Gleason scores of 7, 8 and 9 from biopsy. Patients were excluded if data on age of diagnosis, date of diagnosis were missing, or either the Gleason score or the primary and secondary patterns were missing.

The primary independent variable in this study was Gleason score at biopsy. Patients were stratified as follows: Gleason Score 3 + 4 = 7, 4 + 3 = 7, 4 + 4 = 8, 3 + 5 = 8 with 5 + 3 = 8, and 9. Assignment of biopsy grade was undertaken by a range of pathologists (including specialist uropathologists and non-specialist pathologists) servicing both the public and private sector, reflecting the multi-institutional community-based nature of the cohort. Clinical T stage was determined per guidelines set by the American Joint Commission on Cancer (AJCC) and was recorded in the database. Age at diagnosis was included as a continuous variable. PSA was defined by categories; PSA <4, 4–10, 10–20, >20 or missing. Treatment received was classified according to the intent, as either with intention for cure or palliation. Clinical stage was defined by categories also; T1, T2, T3–4.

Baseline patient characteristics were summarised (Table 1). Univariable and multivariable cox regression (adjusting for age, PSA, intent of cure, clinical T stage) were undertaken to examine differences in all-cause mortality (ACM) according to Gleason score (3 + 4 = 7, 4 + 3 = 7, 4 + 4 = 8, 3 + 5 = 8/5 + 3 = 8 and 9). Similarly, univariable and multivariable competing risk regression analyses (fine and grey) were used to determine risk of prostate cancer specific mortality across grade score categories. GS 4 + 4 = 8 was utilised as the baseline referent pattern for these analyses. Cox regression and Fine and Gray methods were utilised to generate survival and cumulative incidence curves respectively. .

P values of 0.05 were considered statistically significant for all analyses. STATA and R were independently utilised to perform the same data analysis. Ethics approval has been granted to the SA – PCOCC registry including analyses of de-identified data sets, a condition met by this study.

Results

Baseline Characteristics

A total of 4080 patients were analysed in the study. The number of patients with primary and secondary Gleason patterns of; 3 + 4, 4 + 3, 4 + 4, 5 + 3/3 + 5 and 9 are 1702, 1062, 664, 76 and 576 patients respectively. The mean age of each group was within 1 SD of each other. Men with Gleason score 9 had the highest percentage of cancers with PSA > 20 (54.2%) and the lowest percentage of patients who were treated with curative intent (38.5%).

Table 1 Baseline demographics for patients with N0 M0 with gleason 7, 8 or 9 prostate cancer

Galeason score	7	4 + 4	5 + 3	3 + 5	9	P
Number of patients	2764	664	21	55	576	
Mean age (SD)*	68.39 (9.00)	72.42 (9.03)	74.81 (7.17)	73.56 (8.32)	74.42 (9.14)	<0.001
PSA value (SD)*	27.29 (153.94)	103.15 (376.85)	137.02 (373.83)	105.37 (385.65)	198.15 (940.15)	<0.001
Percentage of positive cores (SD)*	49.53 (27.57)	54.64 (31.22)	78.00 (28.07)	61.28 (28.14)	73.78 (26.40)	<0.001
Tumor volume (SD)*	4.77 (5.22)	4.69 (6.29)	13.27 (NA)	3.86 (3.81)	9.82 (7.11)	NA
Survival months (SD)*	73.15 (42.34)	65.89 (42.40)	66.30 (57.10)	68.79 (49.04)	48.90 (39.04)	<0.001
Treatment year >2005 (%)	2375 (85.9)	519 (78.2)	11 (52.4)	30 (54.5)	438 (76.0)	<0.001
PSA (%)						<0.001
< 4	136 (4.9)	27 (4.1)	0 (0.0)	0 (0.0)	23 (4.0)	
4–10	1093 (39.5)	171 (25.8)	4 (19.0)	15 (27.3)	91 (15.8)	
10–20	618 (22.4)	151 (22.7)	5 (23.8)	15 (27.3)	93 (16.1)	
> 20	383 (13.9)	214 (32.2)	8 (38.1)	20 (36.4)	263 (45.7)	
Missing	534 (19.3)	101 (15.2)	4 (19.0)	5 (9.1)	106 (18.4)	
Treatment group (%)						<0.001
Chemotherapy	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hormones	245 (8.9)	174 (26.2)	7 (33.3)	21 (38.2)	217 (37.7)	
Observation	145 (5.2)	14 (2.1)	0 (0.0)	2 (3.6)	11 (1.9)	
Other	343 (12.4)	110 (16.6)	4 (19.0)	8 (14.5)	130 (22.6)	
Radical prostatectomy	1147 (41.5)	157 (23.6)	3 (14.3)	8 (14.5)	60 (10.4)	
Radiation therapy	883 (31.9)	209 (31.5)	7 (33.3)	16 (29.1)	158 (27.4)	
Curative intent (%)	2075 (75.1)	371 (55.9)	10 (47.6)	24 (43.6)	222 (38.5)	<0.001
Clinical stage (%)						<0.001
T1	473 (29.7)	77 (18.9)	1 (12.5)	3 (10.7)	32 (9.6)	
T2	963 (60.5)	236 (57.8)	5 (62.5)	17 (60.7)	168 (50.5)	
T3-T4	156 (9.8)	95 (23.3)	2 (25.0)	8 (28.6)	133 (39.9)	
Prostate cancer specific death (%)	262 (42.5)	160 (59.0)	9 (81.8)	13 (46.4)	218 (70.8)	<0.001

*Data are given in mean

Gleason Score, ACM and PCSM

The median follow-up time in our study is 60 months. The 60 month PCSM mortality for 3 + 4 = 7, 4 + 3 = 7, 4 + 4 = 8, 3 + 5/5 + 3 = 8 and 9 are respectively 4.3%, 6.1%, 16.1%, 20% and 32% respectively. On univariable analysis (Table 2) we found no significant difference in the ACM of the 3 + 5/5 + 3 group when compared to the 4 + 4 referent group (crude hazard ratio [cHR] 1.17, 95% confidence interval [CI] 0.84–1.6, $p = 0.22$). Repeating the analysis to account for other variables including PSA, clinical stage, age and intention for cure, patients with Gleason pattern 4 + 4 had no statistically significant difference in the ACM when compared to the patients with 3 + 5/5 + 3 (Adjusted hazard ratio [aHR] 0.99, 95% CI 0.68–1.4, $p = 0.99$). Furthermore, the PCSM of pattern 4 + 4 was not statistically different than 3 + 5/5 + 3 group when adjusted for the above variables (aHR 0.77 95% CI 0.47–1.2, $p = 0.31$).

Patients with 4 + 3 = 7 disease had significantly lower PCSM (aHR 0.70, CI 0.54–0.91 $p < 0.001$) than the referent 4 + 4 group, whilst Gleason group 9 had significantly higher ACM (aHR 1.3, CI 1.13–1.6, $p = 0.001$) and PCSM (aHR 1.5, CI 1.2–1.9, $p < 0.001$) after adjusting for PSA, age and intention for cure.

A sensitivity analysis was conducted separating 3 + 5/5 + 3 which showed no statistically significant ACM difference between the groups 4 + 4, 3 + 5 and 5 + 3. The PCSM could not be analysed due to insufficient numbers. Similarly, adjustment was made by treatment groups which showed no statistical

Table 2 Cox regression and competing risk regression for the ACM and PCSM among patients with N0 M0 gleason 7, 8 or 9

Characteristic	All cause mortality *		Prostate cancer specific mortality*	
	HR (95% CI)	P value	SHR (95% CI)	P value
Gleason score				
3 + 4	0.78 (0.65–0.93)	<0.001	0.58 (0.45–0.75)	<0.001
4 + 3	0.93 (0.77–1.13)	0.011	0.70 (0.54–0.91)	<0.001
4 + 4	1.0	BASE	1.0	BASE
5 + 3/3 + 5	0.99 (0.68–1.4)	0.99	0.77 (0.47–1.2)	0.31
9	1.3 (1.13–1.6)	0.001	1.5 (1.2–1.9)	<0.001

All data are 2 significant figures

*Multivariable analyses adjusting for PSA, Clinical Stage, Age, and Intention for Cure

difference between 4 + 4 and 3 + 5/5 + 3. Another sensitivity analysis was run only with radical prostatectomy patients. The number of the 3 + 5/5 + 3 cohort was only 11 patients, insufficient to reach a statically significant result.

Discussion

In our study of 4080 men with N0 M0 prostate cancer with Gleason score of 3 + 4, 4 + 3 = 7, 4 + 4 = 8, 3 + 5/5 + 3 = 8 and 9, we found no significant difference in the PCSM between 4 + 4 = 8 and 3 + 5/5 + 3 = 8. However, there was significant difference in the PCSM with 4 + 3 = 7 having a lower hazard ratio than 3 + 5/5 + 3 and 4, and Gleason 9 having a significantly higher ACM and PCSM than 3 + 5/5 + 3 and 4.

The current literature looking at the homogeneity of Gleason score 8 has differed in respect to the comparator groups used. The combination of 3 + 5/5 + 3 = 8 has previously been used in two studies [2, 3]. Gleason score 3 + 5 = 8 was used as the sole comparator in two studies [4, 5], and one study looked at 4 + 4 vs. 3 + 5 vs. 5 + 3 [6]. Previous reports provide evidence that Gleason pattern 5 is the strongest pathologic predictor of recurrence, metastasis and prostate cancer specific death [7, 8]. Our study therefore separated the independent variables into Gleason score 8 with and without pattern 5 (4 + 4) and those with pattern 5 (3 + 5/5 + 3). This also follows methodology precedence from previous studies [2, 3].

The five tiered ISUP prognostic grade groups was recently adopted by the WHO and published in the 2016 Pathology and Genetics of Tumour of the Urinary System and Male Genital Organs. There are now officially five grade groups encompassing the spectrum of prostate cancer. This provides simplification in risk stratification, from nine Gleason scores to five prognostic grade groups. Gleason score 3 + 3 = 6 is traditionally the lowest score reported on biopsy and has an excellent prognosis with very rare potential for lymph node metastasis. A Gleason score of six out of 10 may be interpreted by patients as suggestive of medium aggressiveness, but in reality, a scale of six confers good prognosis and may be better represented by group one, out of five grades. This has been proposed to contribute to a reduction of patient anxiety and consequently over diagnosis and overtreatment [1, 9]. The new grading groups have also been further validated both using biochemical free progression and survival in multi-institutional, large cohort studies [10]. It received 90% support at the Chicago grading meeting in 2014, an international expert consultation conference on Gleason grading.

Potential limitations of the study include a retrospective observational design, low numbers of 5 + 3 in our cohort, high percentage of men with PSA data missing at diagnosis which may affect the multivariable analysis and the non-uniform treatment choice. Furthermore this study did not have expert urologist pathology review of the study slides, though this does provide a valuable insight into pathology at a population or community level rather than in specialised centres only. Although consistent with previous literature, due to low 5 + 3 numbers and as Gleason 5 is the strongest predictor of mortality, the combination of 3 + 5/5 + 3 is still a potential limitation as our study did not possess sufficient power to determine if there is difference in mortality outcomes between 3 + 5 and 5 + 3.

Conclusion

From the survival analysis, using a sample of patients from SA PCOCC, we found no statistical significant difference in prostate specific mortality risk between Gleason groups 4 + 4 = 8 and 3 + 5/5 + 3 = 8. Our analysis suggest that Gleason score 8 or ISUP grouping 4 as differentiated by the presence of Gleason 5 pattern, is a reasonably homogenous group in terms of all-cause and disease specific mortality risk.

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Compliance with Ethical Standards

Conflict of Interest Nil

Ethical Approval All data utilised in the study was attained from the South Australian Prostate Cancer Clinical Outcomes Collaboration. Ethical approval is provided for analyses using de-identified data, a condition which this study met.

Informed Consent The South Australian Prostate Cancer Clinical Outcomes Collaboration database operates under an ethically approved opt-out consent model.

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