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Original Article

Gleason pattern 5 is associated with an increased risk for metastasis following androgen deprivation therapy and radiation: An analysis of RTOG 9202 and 9902

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ABSTRACT

Background/purpose: Stratification of Gleason score (GS) into three categories (2–6, 7, and 8–10) may not fully utilize its prognostic discrimination, with Gleason pattern 5 (GP5) previously identified as an independent adverse factor.

Materials/methods: Patients treated on RTOG 9202 ($n = 1292$) or RTOG 9902 ($n = 378$) were pooled and assessed for association of GS and GP5 on biochemical failure (BF), local failure (LF), distant metastasis (DM), and overall survival (OS). Fine and Gray's regression and cumulative incidence methods were used for univariate and multivariate analyses.

Results: With median follow-up of 9.4 years, patients with GS 8–10 with GP5 had worse outcome than GS 4 + 4 for DM on both RTOG9202 ($p = 0.038$) and RTOG9902 ($p < 0.001$) with a trend toward worse OS ($p = 0.059$ and $p = 0.089$, respectively), but without differences in BF or LF. At 10-years DM was higher by 11% (RTOG 9202) and 18% (RTOG 9902) with GP5 compared to GS 4 + 4. On multivariate analysis restricted to long-term androgen deprivation therapy the presence of GP5 substantially increased distant metastasis (HR = 0.43, 95%CI: 0.24–0.76, $p = 0.0039$) with a trend toward worse OS (HR:0.74, 95% CI:0.54–1.0, $p = 0.052$) without association with LF (HR:0.55, 95%CI:0.28–1.09, $p = 0.085$) or BF (HR:1.15, 95% CI:0.84–1.59, $p = 0.39$). We did not observed substantial differences between Gleason 3 + 5, 5 + 3, or Gleason 9–10.

Conclusions: These results validate GP5 as an independent prognostic factor which is strongest for DM. As a result GP5 should be considered when stratifying patients with GS 8 and may be a patient population in which to evaluate newly approved systemic therapies or additional local treatments.

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The Gleason score (GS) is key for counseling men about treatment, clinical trial enrollment, and comparison of treatment modalities [1]. However, growing evidence has suggested that the commonly utilized method of categorizing the GS into 3-groups (2–6, 7, 8–10) [2] over-simplifies stratification leading to heterogeneity, particularly in the Gleason 8–10 sub-group [3–

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6]. A 2014 consensus statement by the International Society of Urologic Pathologists (IUSP) adopted a modified grade grouping which considers Gleason 8–10 as two separate entities: Gleason 8 and Gleason 9–10 [7]. However, previous analyses are limited by differences in treatment which may have been influenced by the Gleason score and as such may limit the conclusions about the impact of Gleason score where grade potentially confounded treatment.

Therefore, we conducted a secondary analysis of two multi-institutional phase 3 trials performed in the 1990s with external beam radiation therapy (RT) for higher risk prostate cancers: NRG Oncology Radiation Therapy Oncology Group (RTOG) 9202 and RTOG 9902 [8,9].

Materials and methods

Patient, treatment, follow-up

Eligible patients from RTOG 9202 and RTOG 9902 were analyzed [8,9]. For RTOG 9202 patients had locally advanced prostate cancer (T2c-T4), and prostate-specific antigen (PSA) <150 ng/mL. All received external-beam RT to the whole pelvis (WP) followed by a boost to the prostate to a total dose of 67.5–70 Gy using fractions of 1.8–2.0 Gy. Patients were randomly assigned to receive short-term androgen deprivation therapy (STAD) for 4 months starting 2 months prior to RT or to the same with an additional 2 years of ADT (LTAD). For RTOG 9902 patients had localized prostate cancer without metastasis with either PSA 20–100 ng/mL and GS $\geq$ 7 (any T-stage) or clinical T-stage $\geq$ T2 and GS $\geq$ 8 (PSA $\leq$ 100). All patients received WPRT followed by a boost to the prostate to a total dose of 70.2 Gy. Patients were randomly assigned to receive 24-months ADT or to the same with four cycles of Paclitaxel, Estramustine, and Etoposide starting 28 days after completion of RT.

Study endpoints

Although not initially part of the planned protocols, biochemical failure (BF) was defined here by the Phoenix definition: Nadir + 2 ng/mL, clinical progression (including metastasis), or initiation of salvage ADT [10]. Overall survival (OS) was defined as death by any cause. Local failure (LF) was defined as: tumor recurrence (positive re-biopsy at least 2 years after study entry) or by tumor regrowth by at least 50% or tumor never cleared by digital rectal exam. Distant metastasis (DM) was defined as the documentation of clinical evidence of lymph nodal, osseous or visceral spread. All event times were measured from the date of randomization.

Statistical methods

The Chi-square test for categorical variables, and an ANOVA *F*-test for continuous variables was used to compare pretreatment characteristics across GS group while the Kaplan-Meier method [11] and log-rank test was used to estimate the rates for OS [12]. The cumulative incidence method [13] was used to estimate time to BF, LF, DM, and disease-specific survival (DSS) with Gray's test utilized to compare the cumulative incidence rates over time between GS groups [14]. Death without an event was a competing risk for BF, LF, and DM while death from other causes was a competing risk for DSS. Multivariate analysis utilized Cox proportional hazard regression analyses [15] for OS and Fine and Gray's regression analysis [16] for LF and DM. The following covariates were considered for the combined data of RTOG 9202 and 9902: Age (continuous), GS (2–6 (Reference Level [RL]), 7, 8 (without GP5), and 8–10 (with GP5)), PSA (continuous and dichotomized as $\leq$30 ng/mL (RL) vs. >30 ng/mL), clinical stage (T1/T2 (RL) vs. >T3/4), comorbid illness (none (RL) vs. any), and Study (RTOG 9202 (RL) vs. RTOG 9902). All statistical comparisons were two-sided and a *p*-value <0.05 was statistically significant. All analyses were conducted using SAS ® Version 9.4 of the SAS System for Windows.

Results

Patient characteristics

A total of 1670 patients are included in this analysis: RTOG 9202 ((77.4%) and RTOG 9902 (22.6%)). Median follow-up was 9.4-years (Range: 0.04–22.0). There have been 1161 deaths of which 1021 (88%) were on RTOG 9202 and 140 (12%) were on RTOG 9902. On RTOG 9202 prostate cancer death increased with increasing Gleason grade: 12.6% (66/524) of Gleason 2–6 patients, 19.2% (86/449) for Gleason 7, 20.8% (21/101) for Gleason 8 (without GP5), and 34.9% (76/218) for Gleason 8–10 (with GP5). Cause of death was not ascertained on RTOG 9902.

Demographics are provided for the combined analysis (Table 1, Supplemental Tables 1 and 2). No difference was found for age or performance status based upon Gleason score. Mean PSA was 30.1 ng/mL (Range: 0.12–250) and was higher for those with GS 7 (35.6 (Standard deviation [STD]:25.8) than those with GS 2–6, 8 with No GP5, and 8–10 (with GP5) (26.6 STD:17.5, 28.2 STD:17.0, 27.6 STD:18.0, respectively; $p < 0.0001$). Clinical tumor stage was T1-T2 in 51% and T3 in 46% with 3.5% of men with T4 disease and did differ by GS ($p < 0.001$). GP 5 (either primary or secondary) was found in 22% (363/1670) men overall which was 17% (218/1292) for RTOG 9202 and 38% (145/378) for RTOG 9902. Combined pre-treatment characteristics are also provided based upon Gleason 4–4 ($n = 209$), Gleason 3 + 5 ($n = 65$), Gleason 5 + 3 ($n = 28$), and Gleason 9–10 ($n = 270$) (Supplemental Table 3) where there were no differences in any demographic features between these sub-groupings.

Clinical end-points as a function of Gleason score – bivariate analysis

On RTOG 9202, higher GS associated with increased biochemical recurrence ($p < 0.0001$, Fig. 1A, Table 2); however, there was no difference between GS 8 (without GP5) vs. GS 8–10 (with GP5) with 10-year rates of BF 59.3% and 58.0%, respectively (HR:1.05, 95% Confidence Interval [CI]:0.78–1.43, $p = 0.73$). Similarly, LF (Supplemental Fig. 1A) was higher with GS 8–10 (25.1% without GP5 and 22.7% with GP5) compared to GS 2–6 (14.5%) or GS 7 (15.6%, $p = 0.01$), but not based upon GP 5 ($p = 0.66$). Unlike BF and LF, however, DM was greater both with increasing GS ($p < 0.0001$) and with the presence of GP5 with 10-year rates of metastasis of 11.5%, 15.7%, 25.8%, and 37.0% for those with GS 2–6, 7, 8 (No GP5), and 8–10 (GP5), respectively (Fig. 1C, Table 2). The absence of GP5 reduced the risk of DM in those with GS 8 prostate cancer by more than 30% ($p = 0.038$, HR:0.64, 95% CI:0.41–0.98). On RTOG 9202, OS was associated with GS ($p = 0.0001$) with 10-yr survival of 57.8%, 54.2%, 49.3%, and 34.6% as a function of increasing GS (2–6, 7, 8 (No GP5), 8–10 (GP5)), respectively, with the difference between those with and without GP5 approaching but not significant ($p = 0.059$, HR:0.78, 95% CI:0.60–1.01; Fig. 1E, Table 2). In addition, when broken down within Gleason 8–10 (4 + 4, 3 + 5, 5 + 3, or 9–10) there was no difference in any clinical end-point within those with GP5 (3 + 5, 5 + 3 or 9–10) (Supplemental Tables 4–7). At 10-years DM was 25.4% (4 + 4), 36.8% (3 + 5), 35.3% (5 + 3), and 37.2% (Gleason 9–10) which was only statistically different for Gleason 4 + 4 ($p < 0.05$) which paralleled OS at 10-years which was 49.3% (4 + 4), 36.1% (3 + 5),

Table 1
Combined RTOG 9202 and RTOG 9902 pretreatment characteristics.

Characteristic	Gleason score				
	2–6 (n = 524) n (%)	7 (n = 574) n (%)	8 (No GP5) (n = 209) n (%)	8 (GP5), 9–10 (n = 363) n (%)	Total (n = 1670) n (%)
Age					
Mean	69.5	68.6	67.9	68.1	68.7
Standard deviation	6.5	6.8	7.5	7.5	7.0
Min – Max	44–86	44–87	43–88	42–88	42–88
p-value*	0.0074				
PSA, ng/mL – Continuous					
Mean	26.6	35.6	28.2	27.6	30.1
Standard deviation	26.9	31.0	29.3	26.7	28.9
Min – Max	0.4–180.3	0.2–250	1.2–172.7	0.123–152	0.123–250
p-value*	<0.0001				
PSA – Dichotomized					
≤30 ng/mL	383 (73.1%)	332 (57.8%)	146 (69.9%)	251 (69.1%)	1112 (66.6%)
>30 ng/mL	141 (26.9%)	242 (42.2%)	63 (30.1%)	112 (30.9%)	558 (33.4%)
p-value**	<0.0001				
KPS/Zubrod					
Zubrod 0, KPS 90–100	481 (91.8%)	533 (92.9%)	184 (88.0%)	334 (92.0%)	1532 (91.7%)
Zubrod 1, KPS 70–80	43 (8.2%)	41 (7.1%)	25 (12.0%)	29 (8.0%)	138 (8.3%)
p-value**	0.1902				
Clinical T-stage					
T1	0 (0.0%)	33 (5.7%)	7 (3.3%)	10 (2.8%)	50 (3.0%)
T2	288 (55.0%)	236 (41.1%)	113 (54.1%)	161 (44.4%)	798 (47.8%)
T3	223 (42.6%)	285 (49.7%)	82 (39.2%)	174 (47.9%)	764 (45.7%)
T4	13 (2.5%)	20 (3.5%)	7 (3.3%)	18 (5.0%)	58 (3.5%)
p-value**	<0.0001				
Study					
9202	524 (100.0%)	449 (78.2%)	101 (48.3%)	218 (60.1%)	1292 (77.4%)
9902	0 (0.0%)	125 (21.8%)	108 (51.7%)	145 (39.9%)	378 (22.6%)
p-value**	<0.0001				

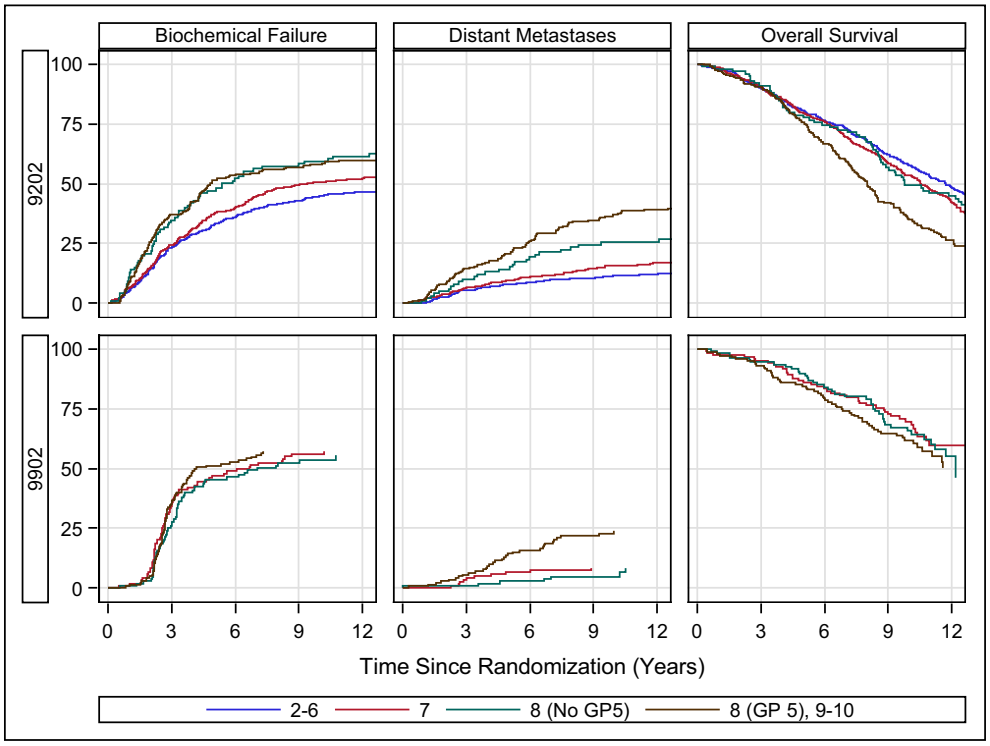

Fig. 1. Outcomes by study. Biochemical failure and distant metastasis plots are cumulative incidence estimator. Overall survival plot is Kaplan-Meier estimator.

41.2% (5 + 3), and 33.9% (Gleason 9–10) with only Gleason 4 + 4 being statistically different ($p < 0.05$).

For RTOG 9902 GS 2–6 patients were not enrolled, and there was no difference in BF ($p < 0.76$) or LF ($p < 0.29$) as a function of GS (Fig. 1B, Table 3). However, DM was strongly associated with GS ($p = 0.0002$) with 10-yr DM rates of 8.4%, 4.7%, and 23.8% for GG 7, 8 (No GP5), and 8–10 (GP5), and a lack of GP5 was favorable ($p = 0.001$, HR:0.26, 95% CI:0.12–0.58; Fig. 1D, Table 3). Overall sur-

Table 2
Influence of Gleason score and Gleason pattern 5 on clinical events for RTOG 9202.

	Biochemical failure		Distant metastasis		Local failure		Overall survival	
	5-year	10-year	5-year	10-year	5-year	10-year	5-year	10-year
Gleason 2–6	32.8% (28.7–32.6)	44.7% (40.3–49.0)	7.7% (5.8–10.4)	11.5% (8.9–14.4)	12.7% (9.8–15.5)	14.5% (11.5–17.5)	80.7% (77.1–83.9)	57.8% (53.4–62.2)
Gleason 7	37.4% (40.0–49.3)	50.8% (46.0–55.4)	9.4% (6.9–12.4)	15.7% (12.3–19.1)	13.0% (9.9–16.1)	15.6% (12.2–19.0)	79.5% (75.8–83.3)	54.2% (49.4–59.0)
Gleason 8 (No GP5)	47.0% (36.9–56.4)	59.3% (48.8–68.3)	14.1% (8.1–21.7)	25.8% (17.3–34.4)	23.0% (15.3–31.7)	25.1% (17.0–34.0)	78.7% (70.6–86.8)	49.3% (39.0–58.8)
Gleason 8–10 (GP5)	51.6% (44.7–58.0)	58.0% (51.0–64.3)	20.8% (20.3–32.0)	37.0% (30.4–43.4)	18.8% (14.0–24.3)	22.7% (17.3–28.5)	75.8% (70.1–81.5)	34.6% (28.0–41.2)
p-value (Overall)*	<0.0001		<0.0001		0.01		0.0001	
p-value for Gleason pattern 5**	0.73 HR: 1.05 (0.78–1.43)		0.0382 HR: 0.64 (0.41–0.98)		0.66 HR: 1.1 (0.69–1.79)		0.0586 HR 0.78 (0.60–1.01)	

Table 2: Cumulative Incidence (and 95% confidence intervals) of events at 5- and 10-years from randomization for RTOG 9202. *p-value from Gray's test for the influence of Gleason score overall (2–6, 7, 8 (without Gleason pattern 5), or 8–10 (with Gleason pattern 5) or ** just when comparing Gleason 8–10 with or without Gleason pattern 5. HR: hazard ratio (and 95% confidence interval); GP: Gleason pattern.

Table 3
Influence of Gleason score and Gleason pattern 5 on clinical events for RTOG 9902.

	Biochemical failure		Distant metastasis		Local failure		Overall survival	
	5-year	10-year	5-year	10-year	5-year	10-year	5-year	10-year
Gleason 2–6	NA	NA	NA	NA	NA	NA	NA	NA
Gleason 7	47.1% (33.0–50.5)	55.8% (46.6–64.3)	6.6% (3.1–12.0)	8.4%% (4.3–14.2)	6.7% (3.1–12.1)	10.1% (5.5–16.4)	85.9% (78.2–91.0)	65.5% (53.5–77.4)
Gleason 8 (No GP5)	45.4% (35.7–54.5)	53.4% (43.4–62.5)	2.8% (0.7–7.3)	4.7% (1.7–10.0)	3.7% (1.2–8.6)	6.2% (2.5–12.3)	89.7% (83.9–95.5)	65.3% (49.1–81.4)
Gleason 8–10 (GP5)	51.1% (42.5–59.1)	57.2% (48.5–65.0)	14.3% (9.1–20.6)	23.8% (16.9–31.3)	4.3% (1.8–8.6)	10.3% (5.9–16.0)	84.4% (78.4–90.4)	54.4% (37.8–71.1)
p-value (Overall)*	<0.76		0.0002		0.32		0.18	
p-value for Gleason pattern 5**	0.49 HR: 0.89 (0.64–1.24)		0.001 HR: 0.26 (0.12–0.58)		0.12 HR: 0.48 (0.19–1.22)		0.089 HR 0.84 (0.56–1.26)	

Table 3: Cumulative Incidence (and 95% confidence intervals) of events at 5- and 10-years from randomization for RTOG 9902. *p-value from Gray's test for the influence of Gleason score overall (2–6, 7, 8 (without Gleason pattern 5), or 8–10 (with Gleason pattern 5) or ** just when comparing Gleason 8–10 with or without Gleason pattern 5. HR: hazard ratio (and 95% confidence interval); GP: Gleason pattern.

vival was not substantially worse based upon GS with 10-year OS of 69.5%, 65.3%, and 54.4% for GS 7, 8 (No GP5), and 8–10 (GP5), these rates were not different either overall ($p = 0.18$) or in the subset analysis of GP5 ($p = 0.089$) (Fig. 1F, Table 3). In addition, when broken down within Gleason 8–10 there was no difference in any clinical end-point within those with GP5 (3 + 5, 5 + 3 or 9–10) except BF was higher in those with Gleason 5 + 3 (HR:2.3 (95% CI:1.4–4.1), $p = 0.002$) when compared to those with Gleason 9–10. In addition, although DM did not differ by sub-groups within Gleason 8–10 the lack of differences may be due to small sample sizes with DM at 10-years of 4.7% (4 + 4), 13.3% (3 + 5), 10% (5 + 3), and 26.2% (Gleason 9–10) which was only statistically different for Gleason 4 + 4 ($p = 0.04$) vs. Gleason 9–10 (Supplemental Tables 4–7).

Impact of Gleason pattern 5 on RT plus long-term ADT

Given that LTAD has become the standard of care when added to RT in men with GS 8–10 prostate cancer an exploratory analysis was performed specifically looking at the impact of GP5 in those with GS 8–10 prostate cancers treated with LTAD. When pooling the experimental arm from RTOG 9202 (excluding those treated with STAD) with the standard arm of 9902 (excluding those treated with LTAD plus chemotherapy) there were a total of 279 men with GS 8–10 treated with LTAD on these two trials. In this group the presence of GP5 as compared to no GP5 had borderline association with OS (Fig. 2A, 10-yr: 63.5% (95%CI:53.0–72.2) vs. 47.7% (95% CI:39.8–52.8); HR:0.74 (95% CI:0.54–1.0), $p = 0.052$) and was associated with higher DM (Fig. 2B, 10-yr: 10.7% (95%CI:5.6–17.6) vs. 29.1% (95%CI:23.1–36.2), HR = 0.43 (95%CI: 0.24–0.76), $p = 0.0039$). The presence of GP5 resulted in numerically higher but not statistically different rates of LF (Fig. 2C, 10-yr: 10.5% (95%CI:5.6–17.4) vs. 17.3% (95%CI:12.0–23.4); HR:0.55 (95% CI:0.28–1.09), $p = 0.085$) with no difference in BF (Fig. 2D, 10-yr: 55.2%, (95%CI:45.0–64.3) vs. 50.8% (95%CI:42.9–58.2); HR:1.15, 95%CI:0.84–1.59, $p = 0.39$).

Clinical end-points as a function of Gleason score – multivariate analysis

Finally, a pooled multivariate analysis was performed of both RTOG 9202 and RTOG 9902 as a function of the presence or absence of GP 5 (Table 4). After controlling for clinical variables those without GP5 had significantly lower BF ($p = 0.0038$, HR: 0.78 (95%CI:0.66–0.92)), DM ($p < 0.0001$, HR:0.38 (95%CI:0.30–0.48)), and all-cause mortality ($p < 0.0001$, HR:0.73 (95% CI:0.63–0.85)). Younger age ($p < 0.0001$), higher PSA ($p < 0.0001$), and higher T-stage ($p = 0.0056$) were all associated with an increased risk for BF, while comorbid illness ($p = 0.8$) and study ($p = 0.54$) were not. For DM, in addition to GP5 younger age ($p < 0.0001$), higher PSA ($p = 0.015$), higher T-stage ($p < 0.0001$), and treatment on RTOG 9202 ($p < 0.0001$) were each associated with increased

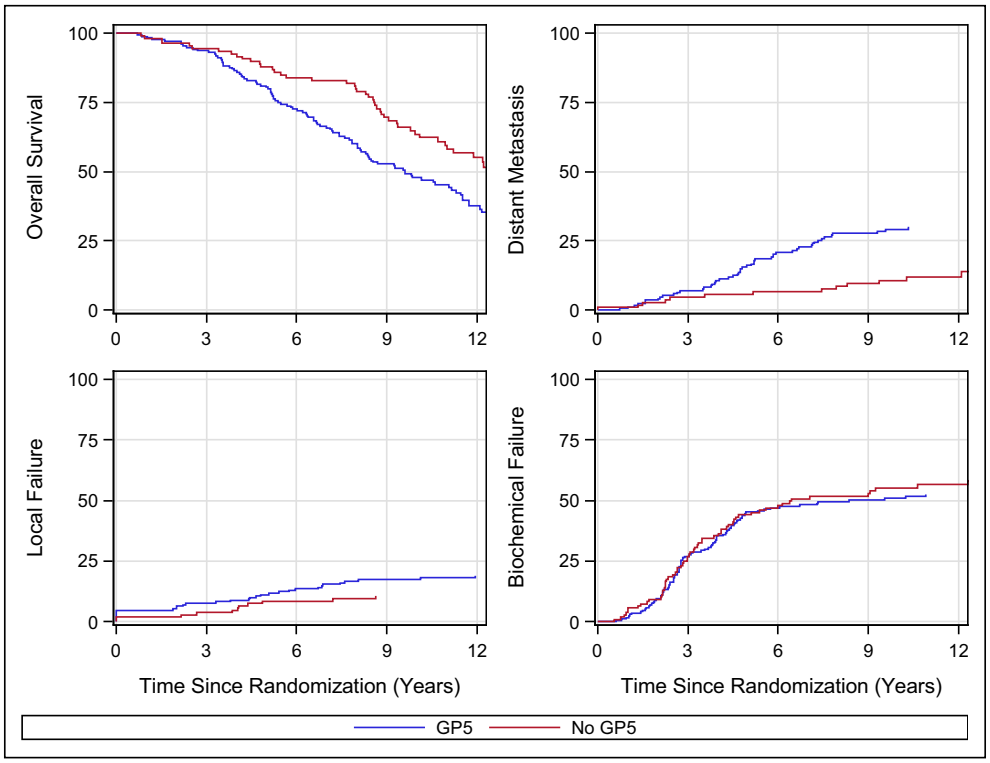

Fig. 2. Outcomes for men with GS 8–10 who received the current standard of care, the experimental arm from RTOG 9202 (excluding those treated with STAD) with the standard arm of 9902 (excluding those treated with LTAD plus chemotherapy). Overall survival plot is Kaplan-Meier estimator. Biochemical failure, local failure, and distant metastasis plots are cumulative incidence estimator.

Table 4
Cox proportional hazards models.

		Overall survival		Biochemical failure		Distant metastases	
Covariate	Comparison	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gleason (grouped)	GP5 (RL) vs No GP5	0.73 (0.63, 0.85)	<0.0001	0.78 (0.66, 0.92)	0.0038	0.38 (0.30, 0.48)	<0.0001
Age	Continuous	1.05 (1.04, 1.06)	<0.0001	0.97 (0.96, 0.98)	<0.0001	0.96 (0.94, 0.97)	<0.0001
PSA	<30 (RL) vs ≥30	1.03 (0.91, 1.16)	0.6673	1.49 (1.30, 1.71)	<0.0001	1.33 (1.06, 1.66)	0.0148
Intercurrent disease	No (RL) vs Yes	1.07 (1.01, 1.14)	0.0326	0.99 (0.89, 1.09)	0.7958	0.85 (0.67, 1.09)	0.1947
T-Stage	T1/T2 (RL) vs T3/T4	1.15 (1.02, 1.29)	0.0181	1.21 (1.06, 1.38)	0.0056	1.70 (1.35, 2.13)	<0.0001
Study	9202 (RL) vs 9902	0.78 (0.64, 0.94)	0.0100	0.95 (0.80, 1.12)	0.5369	0.48 (0.34, 0.66)	<0.0001

GP = Gleason pattern, RL = reference level, HR = hazard ratio, CI = confidence interval
Patients with unknown intercurrent disease were excluded from the model.

DM while comorbid illness had no impact ($p = 0.19$). Adverse risk factors for OS included older age ($p < 0.0001$), pre-existing comorbid illness ($p = 0.033$), more advanced T-stage ($p = 0.018$), and treatment on RTOG 9202 ($p = 0.01$), but not PSA level ($p = 0.67$).

Additional analyses were performed to more fully ascertain the prognostic significant of higher Gleason grade. First, in a pooled multivariate analysis Gleason score was broken-up to assess potential differences between Gleason 4 + 4, 3 + 5, 5 + 3, or Gleason 9–10. These results mirrored those seen in the individual trials where compared to Gleason 9–10 there was reduced risk of all-cause mortality with Gleason 4 + 4 (HR:0.75 (95%CI:0.59–0.95, $p = 0.015$) but not with either Gleason 3 + 5 ($p = 0.97$) or Gleason 5 + 3 ($p = 0.21$) (Supplemental Table 12). Similarly distant metastasis was lower with Gleason 4 + 4 (HR:0.49 (95%CI:0.33–0.72), $p = 0.003$) but not with Gleason 3 + 5 ($p = 0.36$) or Gleason 5 + 3 ($p = 0.38$) (Supplemental Table 13). However, there was no difference in BF between any of the pathologic sub-groups contained within Gleason 8–10 (Supplemental Table 14). Finally, given the discordance between BF and DM, BF was further assessed based upon the PSA rise portion of the Phoenix definition with clinical failure (local or distant) or initiation of ADT considered competing events. Of 332 BF events in 572 men with Gleason 8–10 a rise in

PSA alone was the cause in 88% (292/332) and there was no difference in BF by rising PSA within the Gleason 8–10 sub-groupings (Supplemental Table 15, all $p > 0.10$).

Discussion

More than 50-years ago Donald Gleason proposed the eponymous grading system for prostate cancer which bears his name [1]. He identified 5 histologic patterns (from most well differentiated (Gleason pattern 1) to least differentiated (GP 5)) and noted that when combined with stage this system was prognostic for overall survival. It is notable that Dr. Gleason suggested the use of this system in a continuous fashion without grouping. Over the years this system was largely adopted and different risk stratification schemes were later developed that incorporated the GS to facilitate comparisons between studies or treatment modalities. For ease of use most of these systems have historically grouped GS into 2–6 (low-risk), 7 (intermediate-risk), and 8–10 (high-risk) with other factors such as T-stage, PSA, and the volume of cancer often included [2].

Studies suggested that this 3-tiered grouping does not capture the full stratification potential of the GS. Johns Hopkins noted after radical prostatectomy those with GS 9–10 where more than 2.8 fold more likely to have biochemical recurrence than those with GS of 8 [17,18]. Sabolch et al studied men treated with dose-escalated EBRT and found substantially worse clinical outcome in those with GS 8–10 prostate cancer who had either primary or secondary GP5 with the 5-year prostate cancer mortality of 9% (±4%) in those with GS 8 prostate cancer (without GP5) compared to 36% (±7%) in those with GS 8–10 with GP5 ($p < 0.0001$, HR:3.6 (95%CI:2.0–6.5)) [3]. Population based data using the Surveillance Epidemiology and End Results (SEER) Program data also noted increasing prostate cancer specific mortality with increasing GS (2–6, 3 + 4, 4 + 3, 4 + 4, 8 with GP5, 9–10) both for patients treated with RT [19] and even in men with metastatic disease [20]. The finding in patients with metastasis at diagnosis is intriguing as it may suggest a shorter time to castrate resistance in those with GP5. Mahal et al. also suggested that Gleason 5 + 3 = 8 should be considered differently from Gleason 3 + 5 with those with Gleason 5 + 3 having twice the risk of death from prostate cancer from Gleason 4 + 4 or 3 + 5 ($p < 0.001$, HR:2.2 (95%CI:2.0–2.4)) [21], a finding mirrored by others [22]. These and similar reports led to the new ISUP Grade Grouping for Prostate Cancer that uses a 5 compartment model (Grade groups 1 through 5) instead of the more commonly utilized 3 compartment groupings [7]; although Grade Group 4 includes all Gleason 8 prostate cancers regardless of GP5. Notably we were not able to adopt the ISUP grade grouping approach (as primary and secondary GP was not always recorded for GS 7 prostate cancer) and looked at the presence of GP 5 (primary or secondary) as the primary variable of interest. Upon further analysis we were also not able to identify substantial differences between Gleason 3 + 5 or 5 + 3 as compared to Gleason 9–10 while Gleason 4 + 4 had lower rates of DM and all-cause mortality when compared to either any GP5 or explicitly to Gleason 9–10. Although exploratory and limited by sample size these results are suggestive that the presence of GP5 alone should be considered a significant risk factor and as such not all Gleason 8 scores (ISUP grade group 4) should be considered the same.

The pooled analysis of both studies also indicated that for high-risk prostate cancer a lack of GP5 led to decreased BF (HR: 0.78 (95%CI:0.66–0.92)), distant metastasis (HR:0.38 (95%CI:0.30–0.48)), and overall mortality (HR:0.73 (95%CI:0.63–0.85)) compared to those with GP with the greatest impact on distant metastasis. When BF was evaluated only as rising PSA (excluding local and distance failure as well as starting ADT prior to meeting the nadir + 2 definition) there was no difference in BF between any of the sub-categories of Gleason 8–10 while Gleason 4 + 4 did have lower rates of DM and all-cause mortality compared to the groups including GP5. This would also be consistent with the finding that not all BF events bear equal weight and that some biochemical recurrences, such as earlier events, those happening coincident with metastasis, or with shorter PSA doubling time, may be associated with greater clinical risk [23]. The recent validation of DM as a surrogate for overall survival lends further impact to the adverse weight of GP5 [24].

The results of this analysis must also be interpreted in light of newer agents such as Docetaxel, Abiraterone, and Enzalutamide now playing a role in prostate cancer management [25]. Further, a recent meta-analysis of trials involving RT and ADT suggested that in those with GS 9–10 prostate cancer had greatest benefit from life-long ADT while in GS 8 prostate cancer the optimal duration might be long-term (but not lifelong) ADT [26]. In addition to systemic treatments, local control may still play a part even in those with the highest GS. The ASCENDE-RT trial recently demonstrated that permanent prostate implant with ^{125}I added to external RT in addition to 12-months of ADT was shown to significantly decrease the risk of biochemical failure compared to dose-escalated RT plus ADT but without a significant difference in DM or OS [27]. However, additional retrospective or population based analyses have noted that the greatest benefit of adding a brachytherapy boost might be in those with Gleason 9–10 disease, perhaps as a means to prevent local recurrence which later leads to DM [28–30].

Finally, newer means to assess clinical risk based upon transcriptional or whole genomic profiles have also been developed [31]. These demonstrated added prognostic significance even when including GS. However, most have not independently evaluated GP 5 or GS 9–10 separate from GS 8. Therefore, it remains to be seen how much of these biologic differences might be captured with the more continuous use of GS as presented here or in the ISUP grade grouping scheme.

Conclusion

Given the potential impact of GP5 on the both risk-stratification and treatment it is paramount that design and analysis of future studies should be undertaken accounting for differences in clinical outcome (particularly DM and OS) between those with GS 8–10 prostate cancer without or without GP 5. Notably, for example, in those with high-risk prostate cancer without GP 5 treated as part of RTOG 9902 had a <10% risk of DM at 10-years which was >20% in those with GP pattern 5.

Declaration of Competing Interest

Disclosures: Dr(s). Dominello, D'Souza, Hartford, Horwitz, Jones, Lepor, Peters, Pienta, Pisansky, Rosenthal, and Zeitzer have nothing to disclose. Dr. Feng reports personal fees from Dendreon, personal fees from EMD Serono, personal fees from Janssen Oncology, personal fees from Ferring, personal fees from Sanofi, personal fees from Bayer, personal fees from Blue Earth Diagnostics, personal fees from Celgene, personal fees from Medivation/Astellas, personal fees from Clovis Oncology, other from PFS Genomics, grants from Zenith Epigenetics, grants from NRG Oncology, outside the submitted work; In addition, Dr. Feng has a patent EP3047037 A4 issued. Dr. Gomella reports grants from NCI, personal fees from Janssen, personal fees from Astellas, during the conduct of the study. Dr. Hall reports institutional research support from Elekta AB, Stockholm, Sweden, outside the submitted work. Dr. Hamstra

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.08.020.

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