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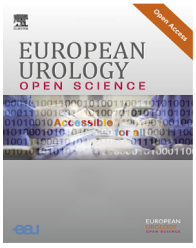

European Association of Urology

Prostate Cancer

Prostate Cancer Tumor Volume and Genomic Risk

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Abstract

Background: Despite the historic association of higher prostate cancer volume with worse oncologic outcomes, little is known about the impact of tumor volume on cancer biology.
Objective: To characterize the relationship between tumor volume (measured by percent positive cores [PPC]) and cancer biology (measured by Decipher genomic risk classifier [GC]) in men who underwent prostate biopsy.
Design, setting, and participants: Prostate biopsies from 52 272 men profiled with Decipher captured in a population-based prospective tumor registry were collected from 2016 to 2021.
Outcome measurements and statistical analysis: The degree of distribution and correlation of PPC with a GC score across grade group (GG) strata were examined using the Mann-Whitney U test, Pearson correlation coefficient, and multivariable linear regression controlled for clinicopathologic characteristics.
Results and limitations: A total of 38 921 (74%) biopsies passed quality control (14 331 GG1, 16 159 GG2, 5661 GG3, 1775 GG4, and 995 GG5). Median PPC and GC increased with sequentially higher GG. There was an increasingly positive correlation (r) between PPC and GC in GG2–5 prostate cancer (r [95% confidence interval {CI}]: 0.07 [0.5, 0.8] in GG2, 0.15 [0.12, 0.17] in GG3, 0.20 [0.15, 0.24] in GG4, and 0.25 [0.19, 0.31] in GG5), with no correlation in GG1 disease (r = 0.01, 95% CI [–0.001, 0.03]). In multivariable linear regression, GC was significantly associated with higher PPC for GG2–5 (all $p < 0.05$) but was not significantly associated with PPC for GG1. Limitations include retrospective design and a lack of final pathology from radical prostatectomy specimens.
Conclusions: Higher tumor volume was associated with worse GC for GG2–5 prostate cancer, whereas tumor volume was not associated with worse GC for GG1 disease. The finding that tumor volume is not associated with worse cancer biology in GG1 disease encourages active surveillance for most patients irrespective of tumor volume.
Patient summary: We studied the relationship between prostate cancer tumor volume and cancer biology, as measured by the Decipher genomic risk score, in men who underwent prostate biopsy. We found that tumor volume was not associated

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with worse cancer biology for low-grade prostate cancer. Our findings reassuringly support recent guidelines to recommend active surveillance for grade group 1 prostate cancer in most patients, irrespective of tumor volume.

1. Introduction

Tumor volume has widely been incorporated in staging classification systems for solid malignancies as it reflects cancer progression, strongly correlates with prognosis, and is a critical component in assessing the objective treatment response [1–4]. Tumor volume is thought to contribute to the biologic aggressiveness of prostate cancer with early landmark studies ushering in tumor volume as a commonly accepted predictor of worse oncologic outcomes, which continues to be prominently featured in contemporary guidelines [5–8].

However, subsequent studies have not reached consensus on whether tumor volume, measured either as percent positive biopsy cores (PPC) or tumor volume on radical prostatectomy specimen, represents a true independent predictor of worse outcomes for any Gleason grade group (GG). While some studies demonstrated that higher tumor volume on radical prostatectomy specimen is associated with biochemical recurrence [7,9], regional metastasis [10], and adverse pathologic features [11], other series demonstrated tumor volume to offer minimal independent prognostic information, with some arguing that tumor volume should not be measured routinely [12–15]. The controversial relationship between tumor volume and cancer aggressiveness is further complicated by evidence demonstrating that high PPC is prognostic of worse outcomes in low-, intermediate-, and high-risk prostate cancer [16–18]. Importantly, the majority of these studies included the original Gleason system in which many pattern 3 morphologies would today be considered pattern 4 [19] and predate contemporary, routine use of genomic risk classifiers (GCs). Despite the conflicting evidence, the recently updated National Comprehensive Center Network (NCCN) guidelines on prostate cancer include tumor volume and genomic risk as factors associated with worse outcomes, such as biopsy reclassification on active surveillance (AS) and increased probability of adverse pathologic features on radical prostatectomy pathology [6].

While a high genomic risk [20–22] mediates worse outcomes via more aggressive disease, higher tumor volume has not been associated with more aggressive cancer biology or adverse genomic features. Consequently, uncertainty regarding the management of men with a high tumor burden may be allayed with a better understanding of the relationship between tumor volume and cancer biology. Decipher, a 22-gene GC, is validated to improve patient selection for AS [23,24], predicts early metastasis after prostatectomy [25] and use of androgen deprivation therapy with radiation [26], correlates with worse tumor biology [20,27], and has recently been endorsed by the NCCN to improve risk stratification after prostate biopsy [6]. Therefore, we aimed to characterize the relationship between tumor volume (measured by PPC) and cancer biology (measured by GC). Our hypothesis is that higher PPC is associated with worse GC, and thereby worse cancer biology.

2. Patients and methods

2.1. Data source

We retrieved prostate biopsy characteristics and GC results from the Decipher Genomic Resource for Intelligent Discovery (GRID) database, a prospectively maintained genome-wide expression registry (NCT02609269), as described previously [28]. Deidentified transcriptome profiles, and basic demographic and clinicopathologic data—age at biopsy, self-reported race, prebiopsy prostate-specific antigen (PSA), clinical stage, continuous GC scores (0–1), and International Society of Urologic Pathology Gleason GG—were collected from clinical use of the Decipher prostate genomic classifier (Veracyte, Inc., San Diego, CA, USA). A waiver of informed consent was obtained (WIRB #20172337).

2.2. Study design

We performed a retrospective study of all men who underwent prostate biopsy captured by the GRID registry from February 2016 to November 2021. Of the 52 272 men with a Decipher biopsy genomic risk score, 38 921 met our selection criteria (Supplementary Fig. 1). Men with incomplete clinicopathologic data or with results not reported due to assay quality control failure were excluded (n = 13 351). Our primary outcome was PPC on prostate biopsy, defined as the total number of cores that contain cancer divided by the total number of cores obtained. To facilitate discussion, we defined low-, intermediate-, and high-volume prostate cancer as fewer than three, between three and six, and six or more positive biopsy cores, respectively. Continuous GC scores (generated on a scale of 0–1) were calculated based on a previously described commercially available GC model [29].

2.3. Statistical analysis

Summary statistics were reported as medians (interquartile ranges [IQRs]) and counts (percentages) for continuous and categorical clinicopathologic variables, respectively. The statistical significance of differences in continuous and categorical variables across PPC strata was assessed via the two-sided Kruskal-Wallis and chi-squared tests, respectively. Pairwise comparisons of continuous variables across GG strata were performed via the Mann-Whitney U test. Pearson correlation coefficients with 95% confidence intervals (CIs) between PPC and GC were reported by GG. Univariable and multivariable linear regression models were used to investigate the relationships between PPC and GC and clinicopathologic variables, which included continuous GC scores (0–1), age at biopsy, race, prebiopsy PSA, clinical stage, and GG; in a post hoc manner, the multivariable linear model was fit to include an interaction term between GC and GG to account for the increasingly positive correlation between these variables.

As a secondary analysis, we evaluated differences in GC between the highest-volume PPC strata (>83%) of one GG with the lowest-volume PPC strata (<17%) of the subsequent GG with the Mann-Whitney U test. We considered p values of <0.05 to indicate statistical significance. All analyses were performed in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The median age was 68 yr (IQR 62–73). The median pre-biopsy PSA was 6.2 (IQR 4.7–8.6). Most men were not Black (97.3%) and had cT1 disease (84.3%), <50% PPC (73.0%), and GG1 (36.8%) or GG2 (41.5%) disease (Table 1). For men with GG1 prostate cancer, less than half (41.0%) had intermediate- or high-volume disease; there was no statistically significant difference in the distribution or median GC across PPC strata (p = 0.172; Supplementary Table 1).

In our study population, the median PPC was 25.0% for GG1 (IQR 14.3–37.5), 33.3% for GG2 (IQR 16.7–50.0), 36.8% for GG3 (IQR 23.1–53.8), 41.7% for GG4 (IQR 25.0–65.7), and 64.3% for GG5 (IQR 41.7–91.7). Similarly, median GC was 0.32 for GG1 (IQR 0.21–0.48), 0.46 for GG2 (IQR 0.29–0.66), 0.61 for GG3 (IQR 0.41–0.82), 0.76 for GG4 (IQR 0.53–0.92), and 0.88 for GG5 (IQR 0.69–0.97; Table 2 and Fig. 1). There was a statistically significant difference in both median PPC and GC between GG strata sequentially (all p < 0.001).

While there was no correlation between PPC and GC for GG1 prostate cancer (r = 0.01, 95% CI [−0.001, 0.03]), there was an increasingly positive correlation between PPC and Decipher risk score in GG2 (r = 0.07, 95% CI [0.05–0.08]),

Table 1 – Clinical characteristics of the analytic cohort stratified by percentage positive cores

	Percent positive cores (PPC)							Overall	p value
	<17%	18–25%	26–3%	34–50%	51–66%	67–83%	>84%		
N	11 955 (30.7)	5743 (14.8)	2004 (5.1)	12 085 (31.1)	2320 (6.0)	2482 (6.4)	2332 (6.0)	38 921 (100.0)	
Age at biopsy									
Median (Q1, Q3)	67 (62, 72)	68 (62, 73)	68 (63, 73)	68 (62, 73)	68 (62, 73)	68 (62, 73)	68 (62, 74)	68 (62, 73)	<0.001[a]
Race									
Black	271 (2.3)	139 (2.4)	38 (1.9)	324 (2.7)	69 (3.0)	75 (3.0)	79 (3.4)	995 (2.6)	0.004[b]
Not Black	11 684 (97.7)	5604 (97.6)	1966 (98.1)	11 761 (97.3)	2251 (97.0)	2407 (97.0)	2253 (96.6)	37 926 (97.4)	
PSA									
Median (Q1, Q3)	5.94 (4.5, 8.19)	6 (4.66, 8.16)	6.11 (4.6, 8.5)	6.2 (4.8, 8.46)	6.5 (4.92, 9)	6.71 (5.07, 10)	7.7 (5.4, 13.3)	6.2 (4.7, 8.6)	<0.001[a]
PSA <4	1869 (15.6)	776 (13.5)	279 (13.9)	1362 (11.3)	206 (8.9)	231 (9.3)	209 (9.0)	4932 (12.7)	<0.001 [b]
4 ≤ PSA < 10	8225 (68.8)	4124 (71.8)	1390 (69.4)	8738 (72.3)	1652 (71.2)	1625 (65.5)	1300 (55.7)	27 054 (69.5)	
10 ≤ PSA < 20	1624 (13.6)	736 (12.8)	297 (14.8)	1681 (13.9)	373 (16.1)	456 (18.4)	467 (20.0)	5634 (14.5)	
PSA ≥20	237 (2.0)	107 (1.9)	38 (1.9)	304 (2.5)	89 (3.8)	170 (6.8)	356 (15.3)	1301 (3.3)	
Clinical stage									
T1	10 769 (90.1)	5016 (87.3)	1691 (84.4)	10 010 (82.8)	1785 (76.9)	1885 (75.9)	1661 (71.2)	32 817 (84.3)	<0.001 [b]
T2a	812 (6.8)	450 (7.8)	206 (10.3)	1114 (9.2)	282 (12.2)	268 (10.8)	223 (9.6)	3355 (8.6)	
T2b/c	351 (2.9)	255 (4.4)	102 (5.1)	883 (7.3)	232 (10.0)	293 (11.8)	346 (14.8)	2462 (6.3)	
T3/4	23 (0.2)	22 (0.4)	5 (0.2)	78 (0.6)	21 (0.9)	36 (1.5)	102 (4.4)	287 (0.7)	
ISUP grade group									
1	6159 (51.5)	2303 (40.1)	633 (31.6)	3782 (31.3)	504 (21.7)	530 (21.4)	420 (18.0)	14 331 (36.8)	<0.001 [b]
2	4281 (35.8)	2395 (41.7)	947 (47.3)	5488 (45.4)	1108 (47.8)	1077 (43.4)	863 (37.0)	16 159 (41.5)	
3	1160 (9.7)	763 (13.3)	300 (15.0)	2006 (16.6)	447 (19.3)	510 (20.5)	475 (20.4)	5661 (14.5)	
4	293 (2.5)	220 (3.8)	98 (4.9)	568 (4.7)	152 (6.6)	202 (8.1)	242 (10.4)	1775 (4.6)	
5	62 (0.5)	62 (1.1)	26 (1.3)	241 (2.0)	109 (4.7)	163 (6.6)	332 (14.2)	995 (2.6)	
GC score									
Median (Q1, Q3)	0.39 (0.25, 0.58)	0.41 (0.25, 0.62)	0.43 (0.27, 0.66)	0.45 (0.28, 0.68)	0.52 (0.31, 0.75)	0.52 (0.302, 0.77)	0.61 (0.35, 0.88)	0.43 (0.27, 0.67)	<0.001 [a]

GC = genomic risk classifier; ISUP = International Society of Urological Pathology; PPC = percent positive cores; PSA = prostate-specific antigen; Q1 = quartile 1; Q3 = quartile 3.
[a] Kruskal-Wallis test.
[b] Chi-squared test.

Table 2 – Median (with interquartile ranges) percent positive cores and genomic risk classifier by grade group, with Pearson correlations and slope estimates (with 95% confidence intervals) derived from linear regressions between percent positive cores and genomic risk classifier by grade group

	ISUP grade group				
	1	2	3	4	5
N (%)	14 331 (36.8)	16 159 (41.5)	5661 (14.5)	1775 (4.6)	995 (2.6)
Median PPC (Q1, Q3)	25 (14.3, 37.5)	33.3 (16.7, 50)	36.8 (23.1, 53.8)	41.7 (25, 65.7)	64.3 (41.7, 91.7)
Median GC (Q1, Q3)	0.32 (0.21, 0.48)	0.46 (0.29, 0.66)	0.61 (0.41, 0.82)	0.76 (0.53, 0.92)	0.88 (0.69, 0.97)
Pearson correlation (95% CI)	0.01 (−0.00, 0.03)	0.07 (0.05, 0.08)	0.15 (0.12, 0.17)	0.20 (0.15, 0.24)	0.25 (0.19, 0.31)
Slope (95% CI)	0.12 (−0.05, 0.30)	0.61 (0.47, 0.76)	1.34 (1.11, 1.57)	1.74 (1.32, 2.16)	2.88 (2.25, 3.52)

CI = confidence interval; GC = genomic risk classifier; ISUP = International Society of Urological Pathology; PPC = percent positive cores; Q1 = quartile 1; Q3 = quartile 3.

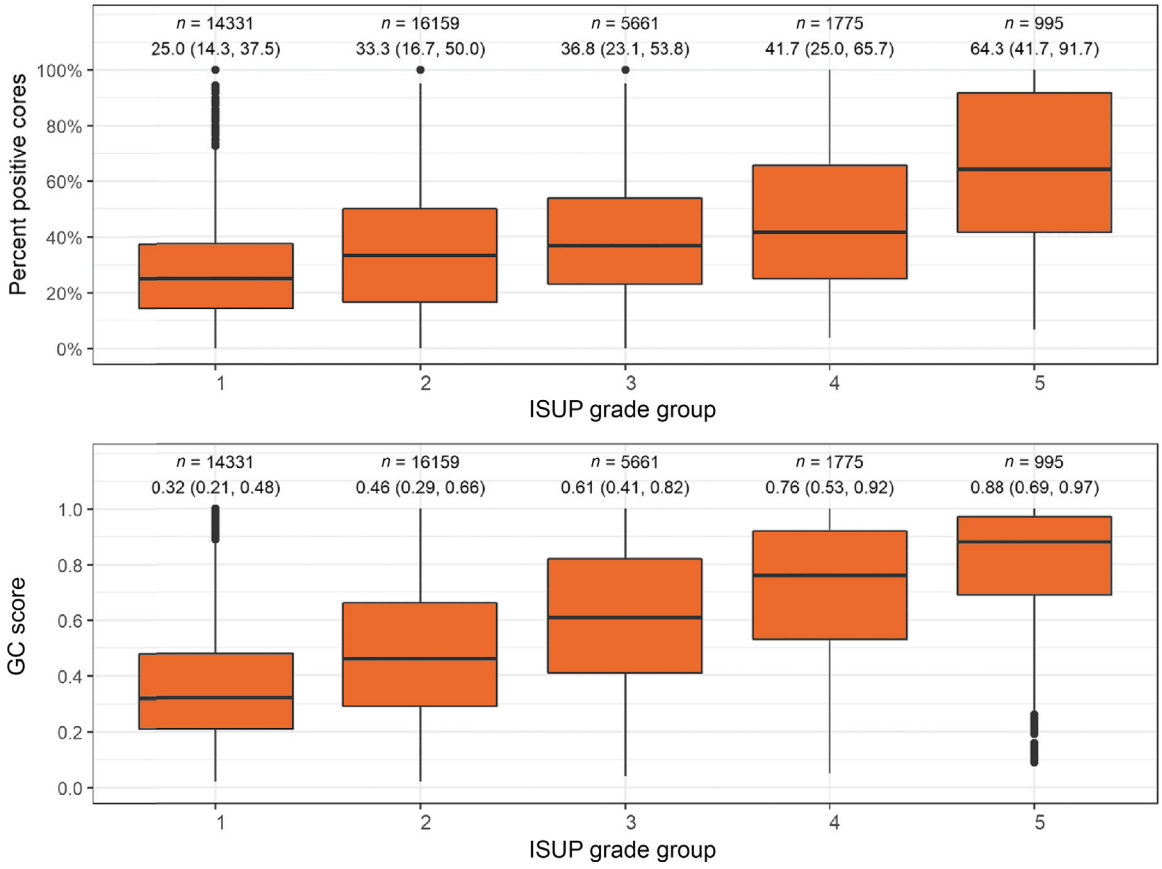

Fig. 1 – Boxplots of percent positive cores and genomic risk classifier (GC) by International Society of Urological Pathology (ISUP) grade group. Sample sizes with medians (first quartile, third quartile) are superimposed above each boxplot.

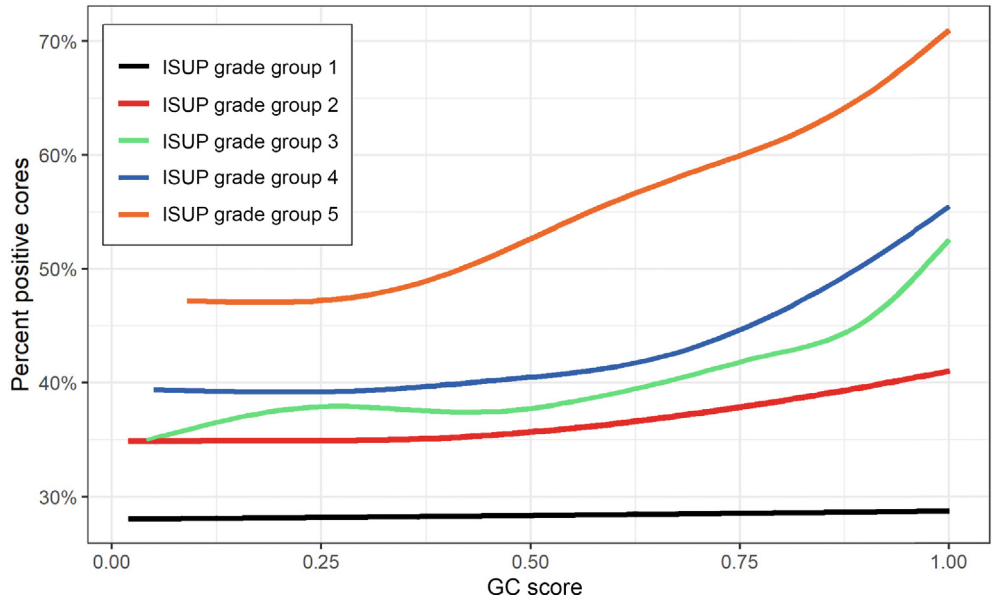

Fig. 2 – Smoothed generalized additive model fits for percent positive cores by genomic risk classifier (GC) stratified by International Society of Urological Pathology (ISUP) grade group.

GG3 (r = 0.15, 95% CI [0.12–0.17]), GG4 (r = 0.20, 95% CI [0.15–0.24]), and GG5 disease (r = 0.25, 95% CI [0.19–0.31]; Table 2 and Fig. 2).

In univariable analyses, age, Black race, clinical stage, PSA, GC, and GG were associated with higher PPC (all p < 0.05). In multivariable analyses including an interaction

Table 3 – Univariable and multivariable linear regression (with and without interaction term between genomic classifier and grade group) for percent positive cores

Regression term	Univariable		Multivariable		Multivariable + interaction	
	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value
(Intercept)	–	–	31.9 (29.9, 33.8)	<0.001	33.9 (31.9, 35.9)	<0.001
GC (per 0.1)	1.8 (1.7, 1.9)	<0.001	0.7 (0.6, 0.8)	<0.001	0.1 (–0.1, 0.3)	0.177
Age at biopsy (per 5 yr)	0.4 (0.3, 0.5)	<0.001	–0.8 (–0.9, –0.6)	<0.001	–0.8 (–0.9, –0.6)	<0.001
Race: Black	2.7 (1.3, 4.2)	<0.001	1.2 (–0.1, 2.6)	0.079	1.3 (0.0, 2.7)	0.056
4 ≤ PSA < 10 vs >4	3.6 (2.9, 4.3)	<0.001	3.6 (2.9, 4.2)	<0.001	3.6 (2.9, 4.2)	<0.001
10 ≤ PSA < 20 vs >4	7.2 (6.3, 8.1)	<0.001	5.3 (4.4, 6.1)	<0.001	5.2 (4.4, 6.1)	<0.001
PSA ≥20 vs >4	23.6 (22.2, 25.0)	<0.001	15.0 (13.7, 16.4)	<0.001	14.6 (13.2, 15.9)	<0.001
ISUP grade group 2 vs 1	7.9 (7.4, 8.4)	<0.001	6.9 (6.4, 7.4)	<0.001	5.2 (4.1, 6.2)	<0.001
ISUP grade group 3 vs 1	12.7 (12.0, 13.3)	<0.001	10.0 (9.3, 10.7)	<0.001	4.1 (2.4, 5.7)	<0.001
ISUP grade group 4 vs 1	17.7 (16.6, 18.8)	<0.001	12.8 (11.7, 14.0)	<0.001	3.5 (0.3, 6.7)	0.030
ISUP grade group 5 vs 1	34.8 (33.4, 36.2)	<0.001	27.4 (25.9, 28.8)	<0.001	7.9 (2.5, 13.2)	0.004
Clinical stage T2b/c vs T1-T2a	13.6 (12.7, 14.5)	<0.001	9.8 (8.9, 10.7)	<0.001	9.8 (8.9, 10.6)	<0.001
Clinical stage T3/4 vs T1-T2a	27.7 (25.1, 30.3)	<0.001	15.0 (12.5, 17.6)	<0.001	14.6 (12.0, 17.1)	<0.001
GC (per 0.1): ISUP grade 2 vs 1	–	–	–	–	0.5 (0.3, 0.7)	<0.001
GC (per 0.1): ISUP grade 3 vs 1	–	–	–	–	1.2 (0.9, 1.5)	<0.001
GC (per 0.1): ISUP grade 4 vs 1	–	–	–	–	1.6 (1.2, 2.1)	<0.001
GC (per 0.1): ISUP grade 5 vs 1	–	–	–	–	2.8 (2.1, 3.4)	<0.001

CI = confidence interval; GC = genomic risk classifier; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen.

term, all variables that were statistically significant in univariable analyses remained so, except race; furthermore, there was no association between GC and PPC for men with GG1 and a statistically significant increase in the degree of association between GC and GG from GG1 to GG2, GG2 to GG3, and GG4 to GG5, with similar parameter estimates between GC and GG between GG3 and GG4 (Table 3).

In a secondary analysis, the mean GC for high-volume GG1 was statistically significantly lower than that for low-volume GG2 (0.37 vs 0.47, $p < 0.001$), and the mean GC for high-volume GG2 was statistically significantly lower than that for low-volume GG3 (0.52 vs 0.57, $p < 0.001$). Conversely, the mean GC for high-volume GG3 was not statistically significantly different from that for low-volume GG4 (0.69 vs 0.67, $p = 0.232$), and the mean GC for high-volume GG4 was statistically significantly higher than that for low-volume GG5 (0.79 vs 0.71, $p = 0.02$; Fig. 3). Using a cutoff proposed previously as a very–low-risk threshold for metastatic progression, 26% of high-volume GG1 and 12% of low-volume GG2 had GC <0.2 [30].

4. Discussion

In this novel, population-based study of Decipher biopsy genomic risk assay, we found that higher tumor volume was associated with a higher genomic risk for men with GG2–5 prostate cancer, with stronger interactions associated with progressively higher GGs. However, higher tumor volume was *not* associated with higher GC for GG1 prostate cancer. We demonstrate that higher-volume GG2–5 prostate cancer is more biologically aggressive than low-volume GG2–5 tumor, whereas GG1 prostate cancer has a similar genomic risk regardless of tumor volume. In other words, in contrast to GG1 prostate cancer, tumor volume is associated with worse tumor biology for GG2–5 disease. Additionally, our secondary analysis suggests that high-volume GG3 and GG4 may have similar biologic aggressiveness to low-volume GG4 and GG5, respectively.

The natural history of prostate cancer is largely indolent, and better prediction of tumor biology may obviate treatment in older men. This is the impetus for improving prognostic

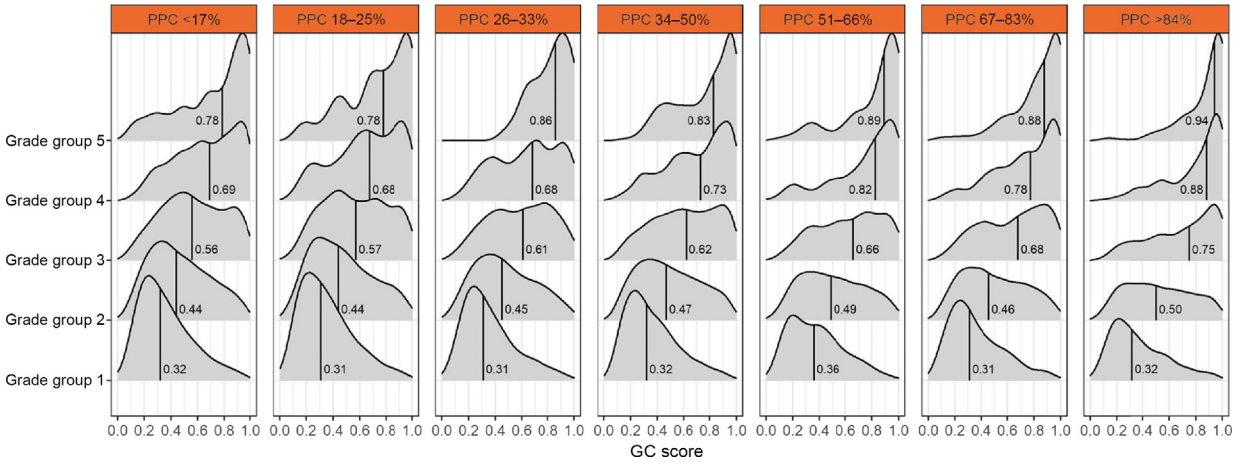

Fig. 3 – Smoothed genomic risk classifier (GC) score densities by grade group and percent positive cores (PPC) strata. The value and solid vertical line within each density represent the median GC score.

models to predict a long-term oncologic outcome after diagnosis with localized prostate cancer. This led to the development of criteria (eg, those by Epstein et al [8]), risk grouping systems (eg, NCCN and D'Amico), risk assessment scoring systems (eg, Cancer of the Prostate Risk Assessment [CAPRA]), and nomograms that have been refined to improve prognostic performance by including variables such as PPC and primary Gleason pattern [16]. Despite this, existing models do not currently reflect recent advancements in our understanding of prostate cancer as a complex, tremendously heterogeneous disease with a unique genomic landscape [20] that may explain the relatively poor performance of the above classification systems in predicting metastasis and cancer-specific mortality [31]. For instance, that a small, but statistically significant, proportion of low-risk prostate cancer is associated with a high genomic risk may provide an explanation for why some men may harbor occult intermediate- or high-risk disease [18,32] and experience worse outcomes [20].

Our findings may offer a potential explanation for the controversy regarding the relationship between tumor volume and cancer biology by demonstrating that higher PPC is associated with worse GC in GG2–5 disease, while strongly implying that GG1 prostate cancer, which involves the population of most interest regarding the future use of genomic classifiers to confirm candidacy for AS, may represent a distinct biologic entity in which high tumor volume is *not* a hallmark of worse tumor biology. While contemporary studies have shown that men with intermediate- and high-volume GG1 tumors have a higher risk of biopsy reclassification [23] or harbor occult clinically significant disease [18,32], these cohorts did not include GCs, which are currently recommended by professional guidelines [6]. Given recently updated NCCN guidelines recommending that men with low-risk prostate cancer undergo GCs after diagnostic biopsy, our findings have important implications to improve the nuance and accuracy of risk stratification and determining AS candidacy [6]. Indeed, results from early efforts to incorporate novel prognostic commercial tissue-based molecular assays, such as the Decipher genomic classifier, into traditional risk classification systems to generate integrated clinical-genomic risk groups have led to significant prognostic reclassification as well as improved independent prediction over existing prognostic models, which currently include variables such as tumor volume that do not directly measure biologic aggressiveness [20,33].

For example, in our study, 5236 men have intermediate- or high-volume GG1 prostate cancer that may not strictly meet the NCCN "very low" or "low" risk criteria for which AS is a "preferred" option. Based on previously established cutoffs of a low or intermediate (<0.60) Decipher risk score [34], 12 271 men in our study who would potentially be recommended to pursue earlier definitive treatment may have been suitable candidates for surveillance; this potentially includes 2090 men with high-volume GG1 disease—"unfavorable intermediate" risk—who currently would not be deemed suitable AS candidates. Although more study is needed, use of genomic classifiers may support the continued use of AS in some men with high-volume GG1 prostate cancer [35,36].

Separately from tumor volume, GCs may contain other potential avenues to better the management of prostate cancer. Analogous to GG1 disease, genomic classifiers may help identify men with GG2 cancer as candidates for AS and promote the concept of biologic aggressiveness when counseling men with GG3–5 cancer. Its use may help refine the distinction between "favorable intermediate-" and "unfavorable intermediate"-risk disease, which may affect the utilization of androgen deprivation therapy after radiation, and the need for cross-sectional imaging and metastatic evaluation prior to definitive treatment. Genomic classifiers may also improve our current understanding of the prognostic significance of the largest (index) cancer focus as the lesion that determines disease progression, with particular relevance to the emerging field of focal therapy. Furthermore, along with an increasing number of positive biopsy cores that often triggers definitive treatment [37–39], use of repeat genomic analysis on subsequent surveillance prostate biopsies can iteratively inform management for men with intermediate- or high-volume prostate cancer. Future research will integrate prostate biopsy GC with final radical prostatectomy specimen pathology to further validate the use of biomarkers in prostate cancer; this goal has been cited as an important goal by the National Cancer Institute Early Detection Research Network.

Our findings must be interpreted in the context of the study design. First, we did not have a centralized pathology review of biopsy specimens, true of any population-based study, but GRID is representative of both community and academic settings, thus increasing generalizability. Second, because our study did not include characteristics of the radical prostatectomy specimen or long-term follow-up, we were unable to assess the rates of pathologic upgrading, upstaging, metastasis, or mortality. However, given that Decipher is validated for predicting progression, rates of metastasis, and mortality, its use allows for significant prognostic associations between tumor volume and intermediate- and long-term outcomes. Third, the GRID dataset lacks sufficient granularity to enable further analysis based on common racial categories and does not capture information regarding prostate magnetic resonance imaging. Finally, the GRID registry does not capture the maximal cancer core length or percent of cancer within a positive core. However, tumor core length and PPC are closely correlated, with one study stating that the two measures together did not add prognostic information [40].

5. Conclusions

Higher tumor volume was associated with a worse genomic risk score for GG2–5 disease, whereas tumor volume was not associated with a worse genomic risk score for GG1 disease. Therefore, tumor volume has a greater, independent role as a prognostic factor with increasing GG, mediated by more aggressive tumor biology. Our findings support the emerging role of genomic classifiers in the risk stratification of prostate cancer and encourage AS in the majority of men with higher-volume GG1 disease.

***Author contributions*:** Ashwin Ramaswamy 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.

Study concept and design: Ross, Schaeffer, Davicioni, Hu.
Acquisition of data: Proudfoot, Davicioni.
Analysis and interpretation of data: Proudfoot.
Drafting of the manuscript: Ramaswamy, Proudfoot.
Critical revision of the manuscript for important intellectual content: Ramaswamy, Proudfoot, Ross, Schaeffer, Davicioni, Hu.
Statistical analysis: Proudfoot.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.12.002.

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