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МОРФОЛОГИЧЕСКАЯ ГЕТЕРОГЕННОСТЬ В ГРУППАХ ГЛИСОНА: ПИЛОТНАЯ КОМПЛЕКСНАЯ ОЦЕНКА АГРЕССИВНОСТИ ОПУХОЛИ ПРИ МУЛЬТИСАЙТОВОМ ИССЛЕДОВАНИИ РАКА ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

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MORPHOLOGICAL HETEROGENEITY WITHIN GLEASON GRADE GROUPS: A PILOT COMPOSITE AGGRESSIVENESS SCORE FOR MULTI-SITE PROSTATE CARCINOMA ASSESSMENT

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Резюме. Система Глисона не отражает морфологическую гетерогенность опухоли простаты при мультибиопсии. Данное пилотное исследование предлагает комплексную оценку агрессивности (КОА) на основе семи H&E-параметров (криброзная архитектура, ВПК-ПЖ, ЛВИ, стромальная реакция, скученность желёз, распространённость, воспаление), применённую к 50 образцам от 5 пациентов.

Ключевые слова: рак предстательной железы, оценка Глисона, морфологическая гетерогенность, криброидная архитектура, внутрипротоковая карцинома, сложный показатель агрессивности.

Resume. The Gleason grading system assigns a single score to prostate tumors, missing morphological heterogeneity across multi-site biopsies. This pilot study develops a Composite Aggressiveness Score (CAS) integrating seven H&E-observable parameters (cribriform architecture, intraductal carcinoma [IDC-P], lymphovascular invasion [LVI], stromal reaction, gland crowding, tumor extent, inflammation) applied to 50 specimens from 5 patients.

Keywords: prostate carcinoma, Gleason grading, morphological heterogeneity, cribriform architecture, intraductal carcinoma, composite aggressiveness score.

Relevance. Prostate cancer is the second most common malignancy in men worldwide, with approximately 1.4 million new diagnoses annually [4]. The Gleason grading system and its modern refinement which is the ISUP Grade Group system, remain the cornerstone of risk stratification. However, both systems assign a single score to a tumor that is, by nature, morphologically heterogeneous: different biopsy sites from the same patient can exhibit markedly divergent architectural features under standard H&E staining yet receive an identical grade. The Gleason score is based on how prostate cancer cells arrange themselves into glands under the microscope, and ISUP grouping simplifies Gleason scores into 5 prognostic categories [1]. Emerging supplementary tools including the CR/IDC+ binary classification % pattern 4 reporting, the cGrade system, and the Irani inflammation score [6] each address only a single feature in isolation. No validated instrument currently combines the full panel of aggressive H&E morphological markers into

a per-specimen composite score applied across multi-site specimens within the same patient and Gleason grade group. This gap represents the direct clinical and scientific rationale for the present study.

Aim: to develop and pilot a Composite Aggressiveness Score (CAS) based on routinely observable H&E slide-level morphological features, and to evaluate whether significant intra-patient, intra-Gleason-grade heterogeneity in this score exists across multi-site prostate carcinoma specimens.

Objectives:

1. To develop the CAS framework integrating seven H&E-observable morphological parameters as a supplementary tool to Gleason grading.

2. To evaluate intra-grade and intra-patient morphological heterogeneity across multi-site prostate carcinoma specimens and determine whether CAS captures clinically meaningful severity variation missed by Gleason alone.

3. To identify which morphological features most strongly associate with composite aggressiveness and propose CAS as a pilot framework for future outcome-linked validation in larger cohorts.

Material and methods. A purely morphological, observational cross-sectional pilot study was conducted on 50 H&E-stained prostate carcinoma histological slides obtained from 5 patients (10 slides per patient), representing multi-site sampling across Gleason Grade Groups 3, mixed 3+4, and Grade Group 4. Each slide was evaluated independently for nine morphological parameters: cribriform architecture, intraductal carcinoma (IDC-P), lymph vascular invasion (LVI), stromal reaction, gland crowding, tumor extent, inflammation, and predominant gland morphology. Binary and semi-quantitative scoring was applied to produce a per-slide CAS (range 0–11). Statistical analysis was performed in R using linear regression to quantify the proportion of CAS variance explained by Gleason grade alone.

Results and their discussion. Linear regression of Gleason grade against CAS across all 50 specimens yielded $R^2 = 0.22$, confirming that Gleason grade accounts for only 22% of morphological severity variation. The remaining 78% is driven by features outside the grading system; the central statistical proof of this study's hypothesis. CAS scores ranged from 3 to 9 across the cohort, and specimens within the same Gleason grade group showed overlapping CAS ranges: Grade Group 3 spanned CAS 3-7, mixed 3+4 spanned 4-9, and Grade Group 4 spanned 4-9.

A specimen with CAS 6 could belong to any of the three Gleason groups, demonstrating that identical grades can mask profoundly different morphological risk profiles. Feature distribution analysis revealed a consistent three-feature pattern across severity tiers.

Tbl. 1. Gleason grade group, CAS range and features

Patient	Gleason grade group	CAS range	Notable features
1	3,4	3-6	1 specimen with cribriform pattern, No IDC, no LVI

Continuation of the table 1

2	3,4	4-8	cribriform present, IDC present, LVI present
3	3,4	4-9	cribriform present, IDC present, LVI present
4	3,4	6-9	cribriform present, IDC present, LVI present
5	3,4	4-8	cribriform present, IDC present, LVI present

Cribriform architecture was entirely absent in all 14 low-severity specimens (CAS ≤5) and present in 14 of 15 high-severity specimens (CAS ≥8), establishing 100% specificity for non-low severity. IDC-P showed an identical low-severity distribution (0/14) and was present in 93% of high-severity cases. LVI, though less prevalent overall (8/50 specimens), was exclusively observed in medium or high severity specimens, never in low severity. Together, these three features constitute what we call ***the Aggressive Triad*** . Any positive specimen for even one triad feature can be excluded from low-severity classification. This finding is consistent with modern literature. [2,3,5]. Intra-patient analysis revealed substantial CAS variation across the 10 biopsy sites per patient. Patient 3 showed a range of CAS 4–9 across their specimens; Patient 4 ranged from CAS 6–9. This five-point intra-patient spread within an identical Gleason grade group demonstrates that a single biopsy site may fundamentally misrepresent the global aggressiveness of a tumor. A critical clinical implication for urologists and oncologists is that a solitary biopsy site may inadequately represent the comprehensive morphological grade and underlying aggressive potential of the whole tumor.

Tbl. 2. Distribution of Cribriform Pattern, Intraductal Carcinoma, and Lymphovascular Invasion

Severity Group	**Cribriform Pattern**	**Intraductal Carcinoma (IDC)**	**Lymphovascular Invasion (LVI)**
Low severity (CAS ≤5)	14 cases without 0 cases with	14 cases without 0 cases with	14 cases without 0 cases without
Medium severity (CAS 5–8	7 without 14 with (Mixed)	16 without 5 with (Mixed)	17 without 4 with (Mixed)
High severity (CAS ≥8)	1 without 14 with	1 without 14 with	11 without 4 with

Tbl. 3 Proof of heterogeneity

Patient	1	2	3	4	5
CAS=3	1	0	0	0	0
CAS=4	2	1	1	0	4
CAS=5	5	0	0	0	2
CAS=6	2	5	4	2	0
CAS=7	0	3	2	2	0
CAS=8	0	1	1	3	4
CAS=9	0	0	2	3	0

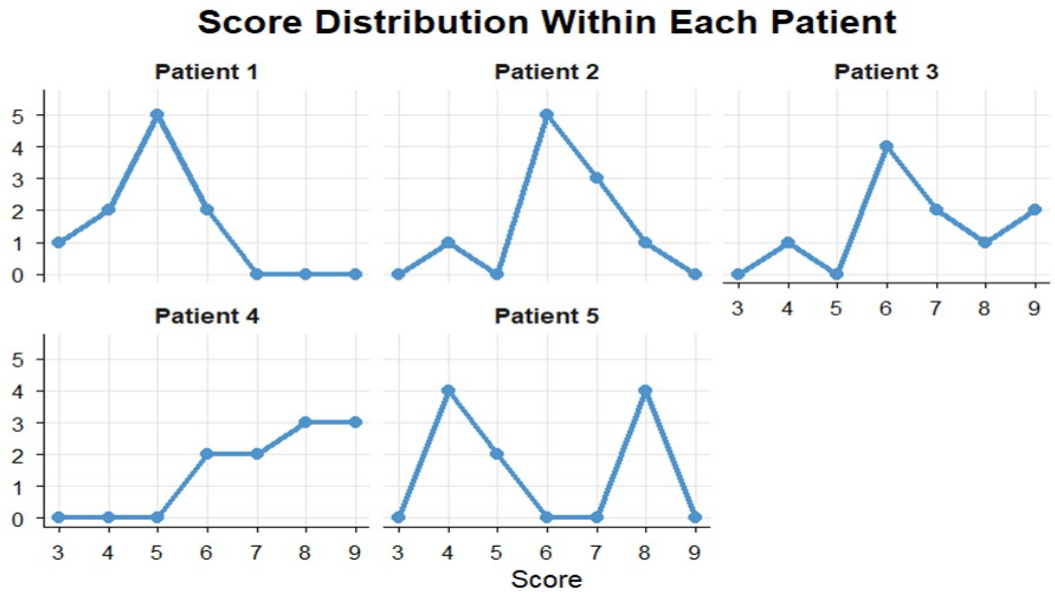

Fig. 1 – Score distribution within each patient

Conclusions:

CAS is an entirely H&E-based tool requiring no immunohistochemistry, molecular testing, or additional technology, making it immediately applicable in any pathological anatomy laboratory including resource-limited settings.

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