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Interpreting Prostate Needle Biopsy Needle Biopsie
Today's World

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CANCER

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Grading Cancer

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SPECIAL ARTICLE

The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD, William C. Allsbrook, Jr, MD,† Mahul B. Amin, MD,‡ and Lars L. Egevad, MD, PhD,§ and the ISUP Grading Committee‖*

The American Journal of Surgical Pathology: Volume 29. September 2005, p 1228-1242

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The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

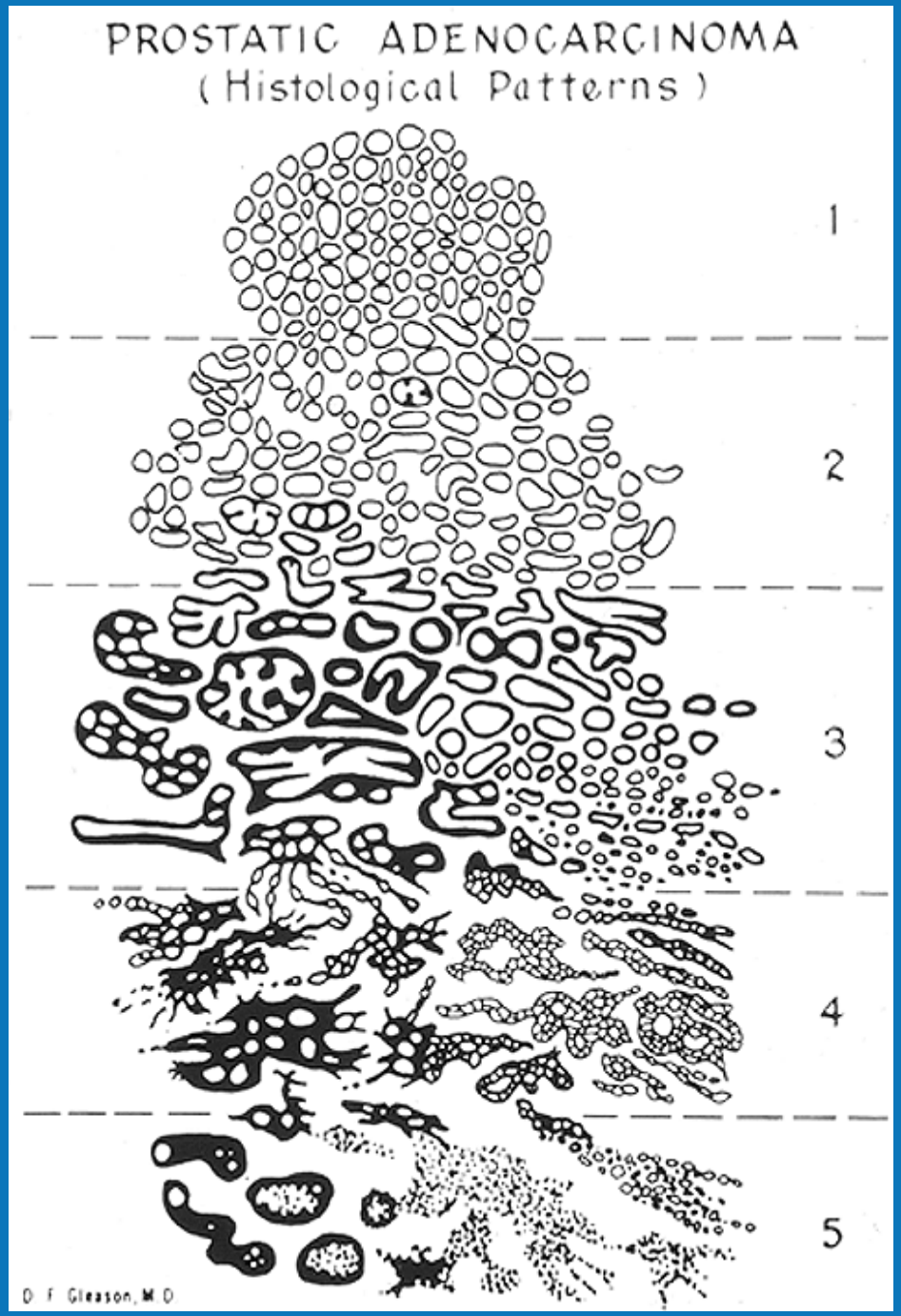
Definition of Grading Patterns and Proposal for a New Grading System

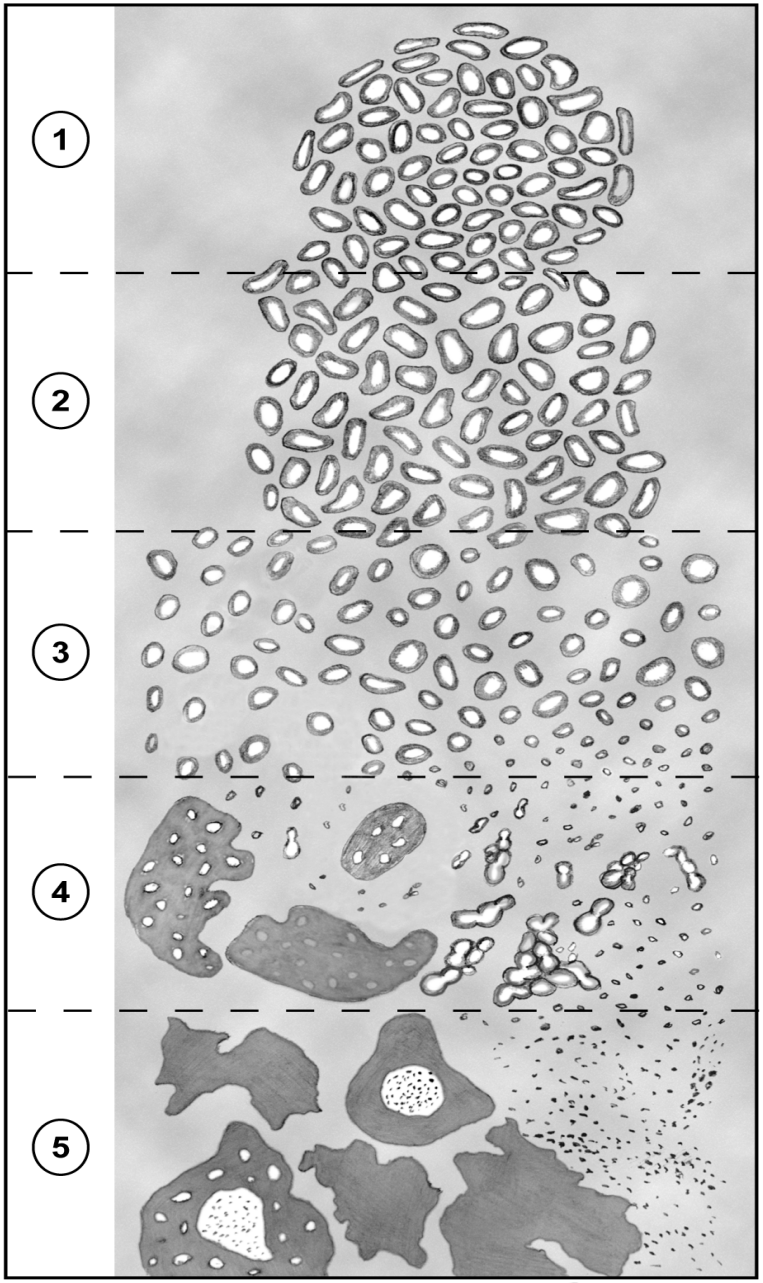
Jonathan I. Epstein, MD, Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srigley, MD,‖ Peter A. Humphrey, MD, PhD,¶ and the Grading Committee*

The American Journal of Surgical Pathology: Volume 40. September 2016, p 244-52

Gleason Pattern 3

- Individual well-formed discrete glands


PROSTATIC ADENOCARCINOMA
(Histological Patterns)
1
2
3
4
5
D. F. Gleason, M.D.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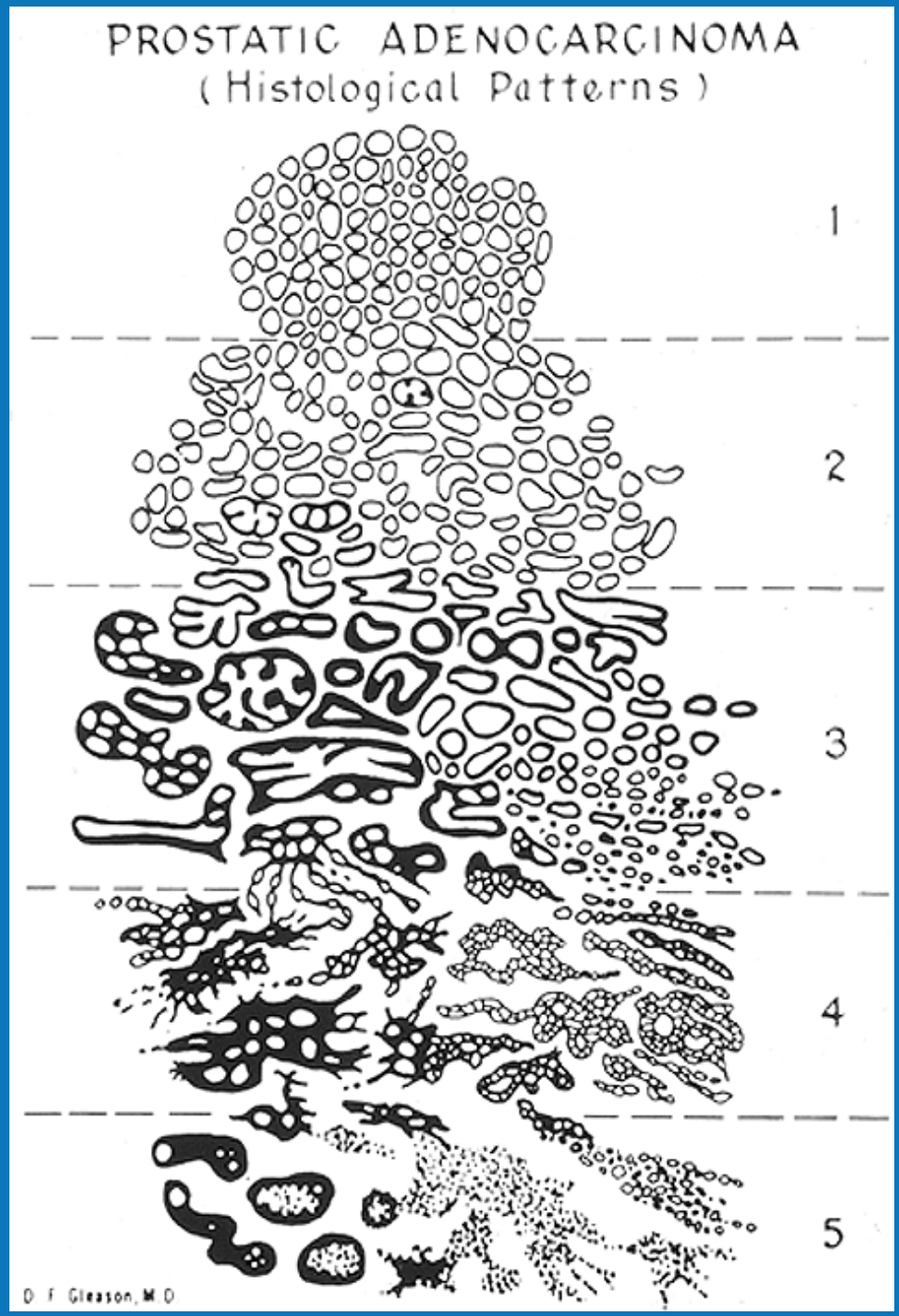
Brumbaugh

Different Types of Pattern 4

- Poorly-Formed Glands
- Fused Glands
- Cribriform Glands (From the Latin word for sieve)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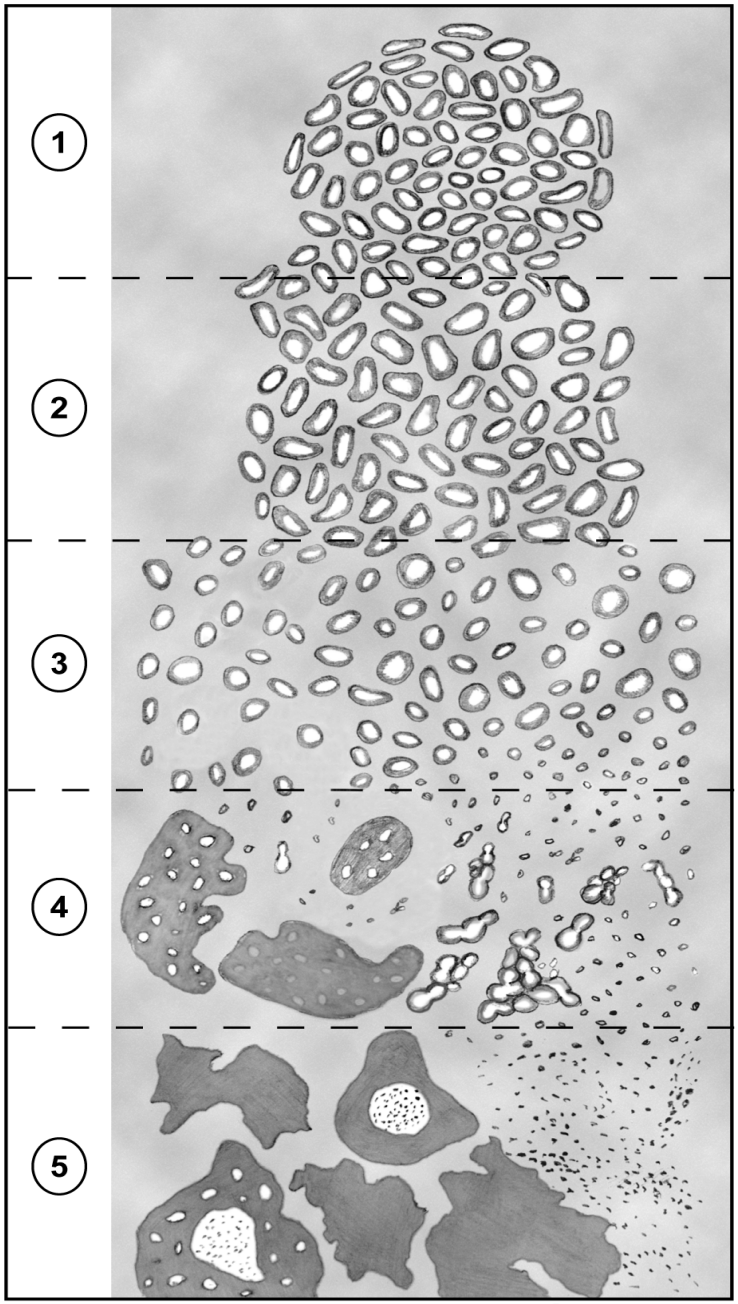
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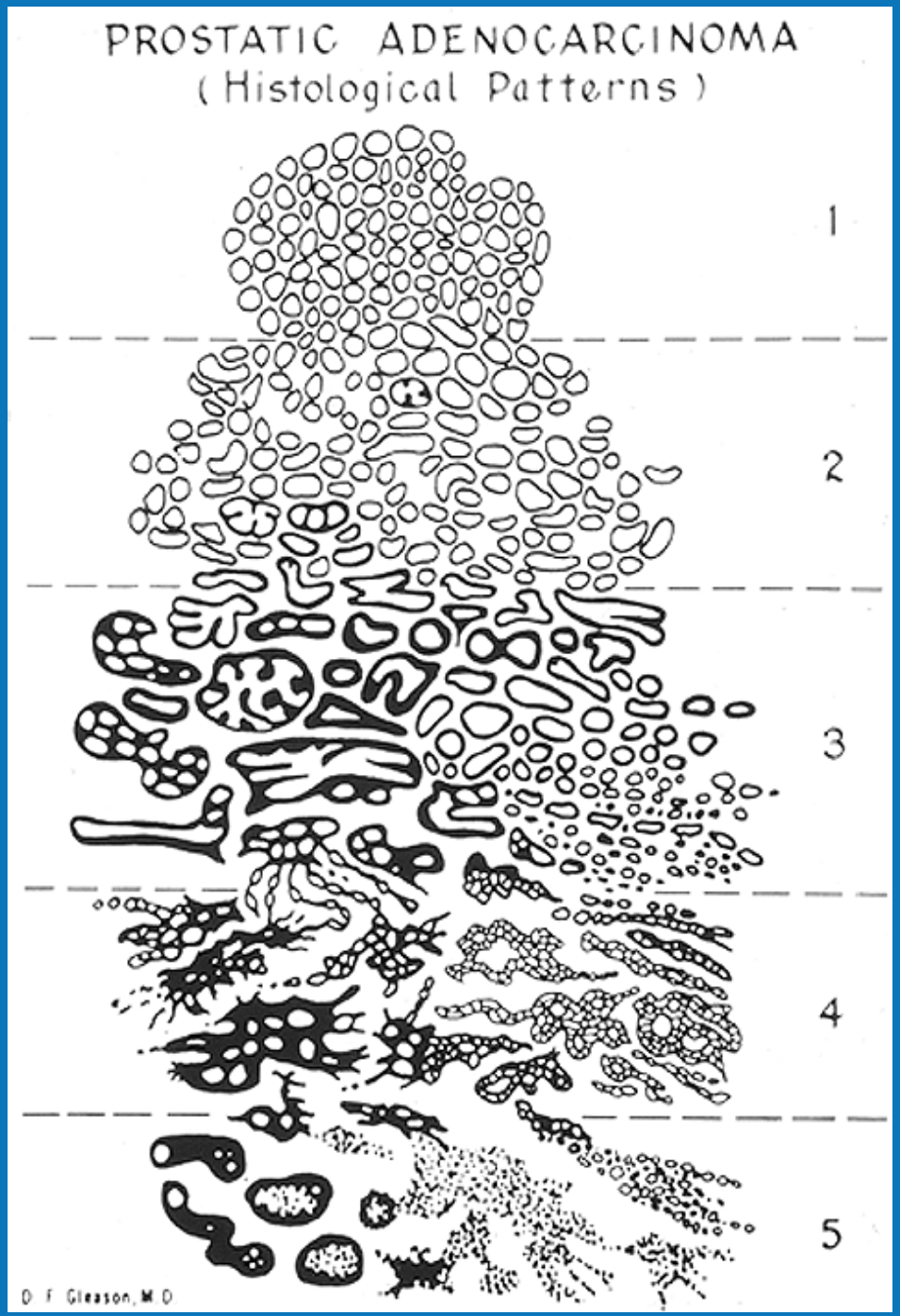
Brumbaugh

Gleason Pattern 5

- No gland formation
- Sheets of cells
- Individual cells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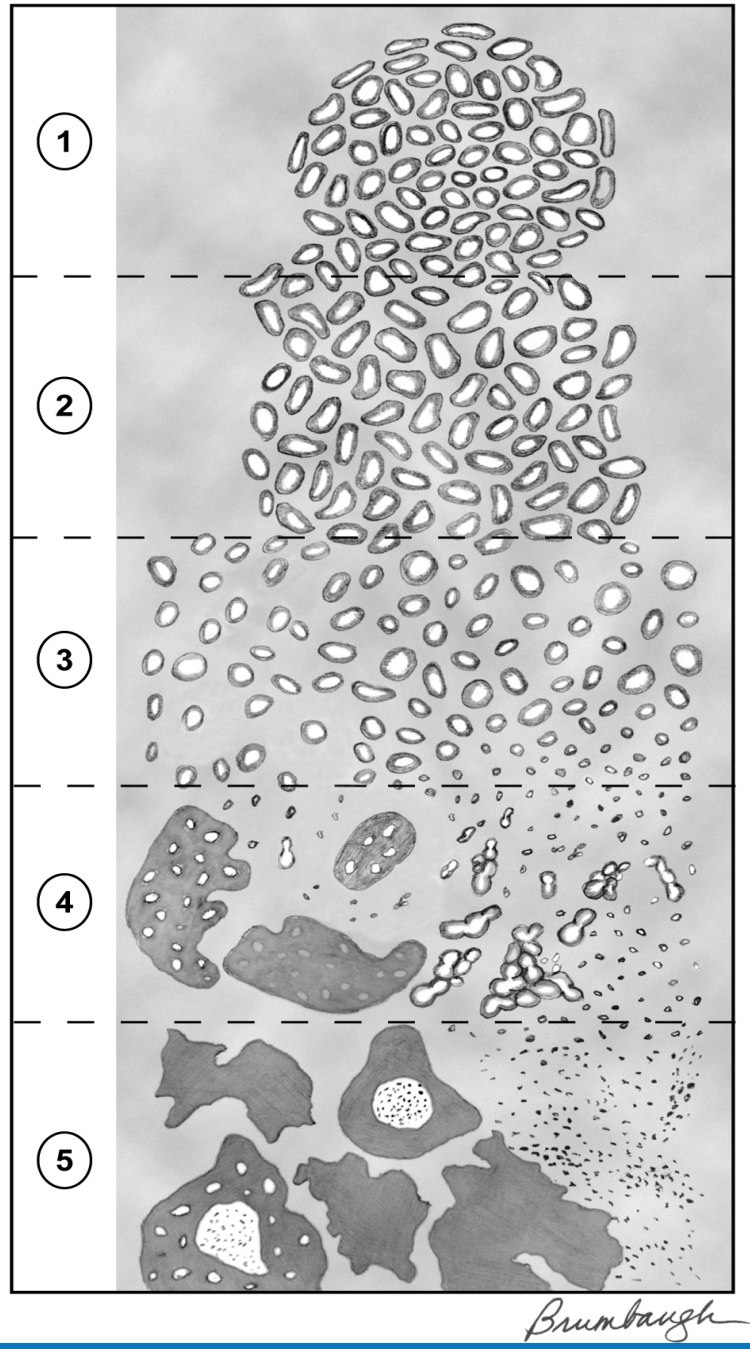
1
2
3
4
5
Brumbaugh

Gleason Pattern 5 is Frequently Underdiagnosed on Prostate Needle-core Biopsy

Turki O. Al-Hussain, Michael S. Nagar, and Jonathan I. Epstein

Urology 2012; 79: 178-81

Identification of Gleason Pattern 5 on Prostatic Needle Core Biopsy: Frequency of Underdiagnosis and Relation to Morphology

Daniel A. Fajardo, MD, Hiroshi Miyamoto, MD, PhD,* Jeremy S. Miller, MD,* Thomas K. Lee, MD,* and Jonathan I. Epstein, MD*†‡*

Am J Surg Pathol 2011;35: 1706-11

Problems with Prostate Cancer Grading

- I regularly review prostate cancer biopsies sent in by patients or clinicians where either change to a high grade (Gleason 6 to 7) or to a lower grade (Gleason 7 to 6), which can affect a patient's candidacy for AC.

- Unrelated to AS, I also frequently change other grades, which can affect treatment, especially how radiation therapy is given.

- Correct grade is critical and the foundation for the optimal treatment for prostate cancer.

Discrepant Grading Between Needle Biopsy and Radical Prostatectomy

Two large patient cohorts – a recent study

Approximately 8% of biopsy Grade Group 2 (3+4=7) were downgraded to Grade Group 1 (3+3=6) on radical prostatectomy, most likely as a result of overgrading the biopsy potentially leading to over treatment, further emphasizing the paramount importance of accurate biopsy grading.

Why Discrepant Grading?

- Most pathologists are good diagnostically and grade accurately
- Some either due to inexperience or lack of skill can grade blatantly in error
- However, in some cases, the grading can be subjective and should rely on pathologists with extensive experience.

Prognostic Gleason grade grouping: data based on the modified Gleason scoring system

Phillip M. Pierorazio*, Patrick C. Walsh*, Alan W. Partin* and Jonathan I. Epstein*†‡

BJU International 2013; 111:753-60

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New 5 Grade System

- Grade Group 1 (≤6)
- Grade Group 2 (3+4)
- Grade Group 3 (4+3)
- Grade Group 4 (4+4/3+5/5+3)
- Grade Group 5 (4+5/5+4/5+5)

RP Grade
5 Year Biochemical Risk Free Survival

Grade	Gleason	BRFS
1	3+3=6	96%
2	3+4=7	88%
3	4+3=7	63%
4	4+4=8	48%
5	9-10	26%

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More Accurately Reflects Biology of Disease than Current System

Grade Group 1 (as opposed to 6/10): Excellent prognosis – no metastases.

Grade Group 2 (as opposed to 7/10): Very good prognosis – rare metastases

Grade Group 3: Greater distinction from Grade Group 2

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More Accurately Reflects Biology of Disease than Current System

Grade Group 4 (as opposed to combined 8-10): Better prognosis than 9-10.

Grade Group 5: No need to distinguish 9 vs 10.

It is recommended to use the new grading system in parallel to the Gleason grading system

Needle Biopsy: Adenocarcinoma of the prostate
Gleason score 4+3=7 (Grade Group 3)

Can We Even Do Better Than Just Splitting Gleason Score 7 Into 3+4=7 and 4+3=7?

Recommended to Report Percent Pattern 4 in Gleason Score 7 on Biopsy

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Rationale for Reporting Percent Pattern 4 for Grade Group 2 on Needle Biopsy

- With increased utilization of active surveillance (AS) for many patients with very low risk/low risk prostate cancer, some urologists also consider AS for select favorable intermediate risk patients (low-volume Grade Group 2 disease, depending on life expectancy and other clinical/radiologic factors)

- Reporting of percent Gleason pattern 4 in cases with Grade Group 2 may determine AS eligibility

3+4=7 with <10% pattern 4 **May be candidate AS**

3+4=7 with close to 50% pattern 4 **Not a candidate AS**

Rationale for Reporting Percent Pattern 4 for Grade Group 3 on Needle Biopsy

- Reporting percent pattern 4 in cases with highest needle biopsy Grade Group 3 may have impact in patients electing radiation therapy

- Grade Group 2 [favorable intermediate risk] = no ADT
- Grade Group 3 [unfavorable intermediate risk] = +/- ADT)

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4+3=7 with 90% pattern 4 (ie. GG3 bordering GG4)

RT + ADT

4+3=7 with 60% pattern 4 (ie. GG3 bordering GG2)

RT no ADT

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Measuring Cancer

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- Number of positive cores

- Total mm. of cancer
- % of cancer per core

Equal number of studies claiming superiority of one technique over another.

Measuring Discontinuous Foci

- Cancer involving 5% of the area of the core or
- Small foci of cancer discontinuously involving 80% of the length of the core
- Studies have shown that in the vast majority of cases this represent a single larger tumor going in and out of plane of section of needle biopsy so should be considered 80% core involvement.

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Perineural Invasion

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- Independent prediction of EPE at RP
- Predictive of progression following XRT

- Easy to assess, reproducible
- Recommend include on needle biopsy reports

Are There Subgroups of Favorable Gleason Score 3+4=7 (Grade Group 2) Who Would be Candidates for Active Surveillance

- Extent of cancer
- Percent Pattern 4
- Cribriform vs. non-cribriform

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The NCCN definition of Favorable Intermediate Risk (FIR)

Gleason score 3+4=7 (GG2)

&

<50% positive cores

&

Possibly either very abnormal DRE

or

PSA 10-20

But not both very abnormal DRE and high PSA

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Outcomes of Active Surveillance for Men With Intermediate Risk Prostate Cancer: A Population-Based Analysis

166,244 patients SEER database

Urology 2021; 155: 101-109

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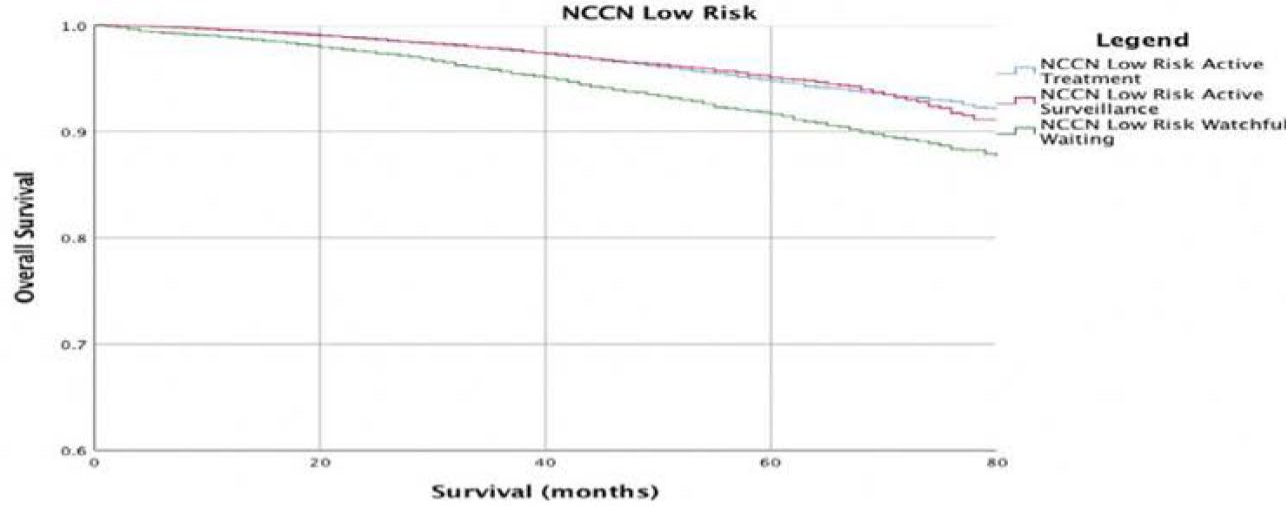
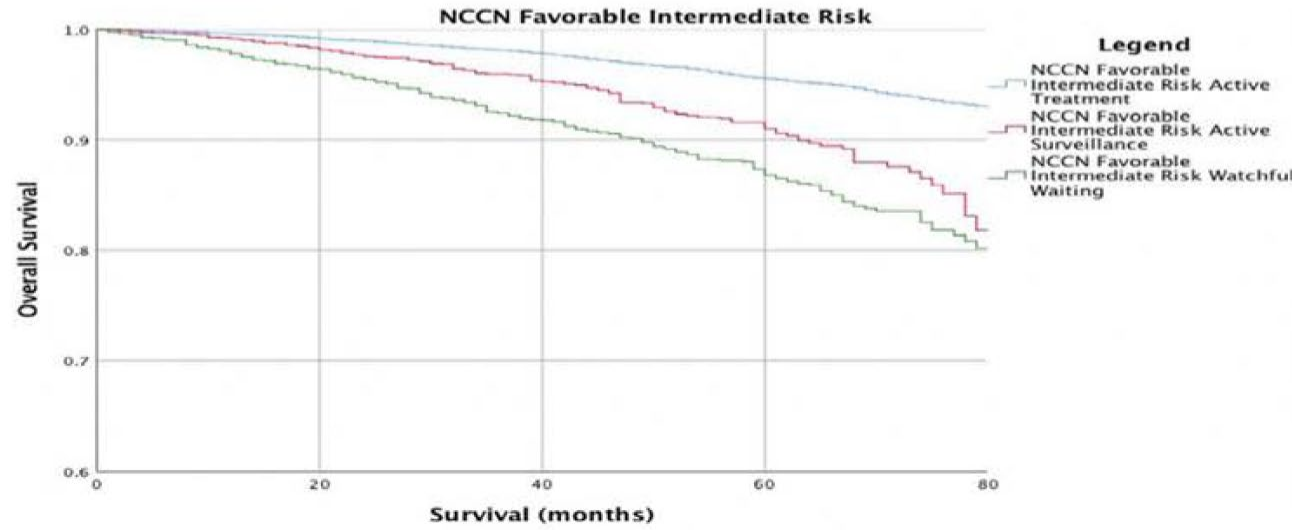
A



No. At Risk

NCCN LR AT	20494	18546	14783	9214	1403
NCCN LR AS	14363	12024	7773	3509	456
NCCN LR WW	10426	8727	6091	3283	502

B



Percent Pattern 4 in AS Selection Criteria for Gleason Score 3+4=7

- Is there a cut-off for percent pattern 4 that is helpful to identify which men with 3+4=7 can undergo AS?
- Many urologists would allow ≤10% Gleason pattern 4 in 3+4=7 for consideration for AS.
- Need long term follow-up studies of men on AS.

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Cribriform Glands in AS Selection Criteria for Gleason Score 3+4=7

Vast majority of studies on prostate cancer with cribriform architecture demonstrate associations with both adverse clinical outcomes and molecular features typically seen in advanced disease.

Cribriform Glands

- Size of the cribriform gland affect prognosis
- Most studies suggest larger cribriform glands are associated with worse prognosis
- Should report whether large cribriform glands are present or absent in Grade Groups 2 and 3
- Need long term follow-up studies of men on AS, yet large cribriform glands with Grade Group 2 should rule out AS.

ATYPICAL NEEDLE BIOPSIES

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Atypical Sign-out

What are atypical biopsies?

- Some are cancers that are minimal and difficult to diagnose
- Some are benign mimickers of cancer
- The majority of atypical biopsies can be diagnosed more definitively by an expert prostate pathologist as either benign or malignant.

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Atypical on Biopsy: Subsequent Risk of Cancer

On average 40%

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Atypical Sign-out

Follow up is warranted with serum or urine tests, imaging; in some cases, repeat biopsy with relative increased sampling of the atypical site may be recommended.

Some urologists not rebiopsy after an atypical initial biopsy, as most cancers found after an atypical diagnosis are Grade Group 1 and would likely not even be treated.

However, a minority are higher grade and would want to diagnose.

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PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

Low Grade PIN

- Do not comment on in diagnosis
- Lack of prognostic significance
- Lack of reproducibility in diagnosis
- Patients subjected to unnecessary procedures and concern

Single Core with HGPIN

- Men do not need a routine repeat needle biopsy.

Multifocal HGPIN

- In men with multifocal HGPIN (2 or more cores) there is an increased risk of cancer of 40% on repeat biopsy.

- Same recommendation for atypical findings on biopsy.

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INTRADUCTAL CARCINOMA

- Distinctive morphology vs. HGPIN
- Typically associated with high grade cancer and poor pathology at RP & relatively poor prognosis with other therapies
- Most cases of intraductal carcinoma are an advanced stage of tumor progression with intraductal spread of tumor
- However, in some cases, can be a precursor lesion to high grade cancer

- One option: Definitive therapy (RT/RP) for men with IDC-P on needle biopsy even in the absence of pathologically documented invasive prostate cancer.

- Another option: Repeat biopsy to identify high grade invasive prostate cancer prior to initiating therapy.

- Intraductal carcinoma typically associated with invasive carcinoma

- Worsens prognosis and may mean more resistance to radiation or hormonal therapy.

ATYPICAL NTRADUCTAL PROLIFERATION (AIP)

- Atypical glands have some but not all the features of IDC-P.

- There is a spectrum – AIP not suspicious for IDC vs. AIP suspicious for IDC

- If AIP suspicious for IDC on biopsy that otherwise would be good for AS, or if AIP the only finding on biopsy, would recommend repeat biopsy to rule out intraductal carcinoma.

PROSTATIC DUCT ADENOCARCINOMA

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“Ductal” Terminology Confusing

- Usual or >95% of prostate cancers are formally called “Acinar adenocarcinoma of the prostate”.

- “Prostatic duct adenocarcinoma” - different morphology under the microscope than usual prostate cancer.

- Occurs as a pure tumor in 1% of prostate cancers and about 5-10% mixed with usual (acinar) prostate cancer.

“Ductal” Terminology Confusing

- “Intraductal carcinoma” (ductal refers to location)

  Usual (acinar) prostate cancer growing within pre-existing benign prostate glands.

Prostatic Duct Adenocarcinoma

- May arise in large periurethral ducts and project into the urethra clinically mimicking bladder cancer.
- Presents with LUTS and hematuria. Rectal often normal.
- Diagnosis made on TURP

Grading Prostatic Duct Adenocarcinoma

- Most common types: Gleason pattern 4 (ie. pure Gleason score 4+4=8)
- Minority Gleason pattern 5 (ie. Gleason scores 9-10)
- Newer variant: PIN-like ductal adenocarcinoma (PIN-like carcinoma): 3+3=6

Prognosis Prostatic Duct Adenocarcinoma

- Stage for stage similar prognosis compared to usual (acinar) prostate cancer of the same grade.

SMALL CELL CARCINOMA

Etiology

- Most have de novo clinical presentation of small cell carcinoma of the prostate.

- Subset of patients previously diagnosed with prostate adenocarcinoma may develop small cell carcinoma in later stages of castration-resistant prostate cancer (CRPC) progression as a result of treatment resistance.

Treatment of Small Cell Carcinoma

- Treated with chemotherapy used in small cell carcinoma of the lung.

- Not radical prostatectomy, radiation therapy, or hormone therapy.

Prognosis of Small Cell Carcinoma

- Median survival following diagnosis of small cell cancer of the prostate
  - Overall 10 months
  - Initially organ-confined 21 months

Misdiagnosis of Small Cell Carcinoma

- Not uncommon for Gleason score 5+5=10 to be misdiagnosed as small cell carcinoma.

ARTIFICIAL INTELLIGENCE (AI) AND PROSTATE BIOPSIES

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- Slides are scanned – expensive equipment most labs do not have

- Scanned slides analyzed by computer programs

- Computer programs for diagnosing and grading prostate cancer based on analyzing many biopsies of benign and cancer - depends on who diagnosed and graded the cancer and the nature of the cases examined which will determine the accuracy of the program.

- Avoiding pathologists underdiagnosis of small carcinomas.

- AI is set for maximum sensitivity to make sure identifies anything abnormal.

- Can reassure a pathologist that a case is totally benign.

- Greater degree of standardization of grading.
- Studies have shown equivalent to general pathologists.
- Has not been shown to be more accurate grading than prostate cancer pathology experts.

- A problem with the use of AI in prostate pathology is the multiple benign mimics of prostate cancer and morphological variants of cancer that are too unusual to allow sufficient training of AI.

- AI systems need to be able to account for variations between labs in staining and account for artifacts.

- AI trained to have maximum sensitivity in detecting any cancer, therefore will have less specificity (ie. will overcall some cancers in order not to miss any cancer).

- Can’t sue AI is there is a diagnostic error. Will be an aid but not a substitute for the pathologist.

- The reporting pathologist must ultimately be responsible for accepting or rejecting the diagnosis proposed by AI.

- Pathologists will rely too much on the output of an AI system, leading to diagnostic errors.

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Summary

- A wealth of information can be obtained from the biopsy pathology report.
- Dependent on the accuracy of the pathologist.
- Critical importance to have high quality pathologists for obtaining the best diagnostic and prognostic information for your patients.

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