Towards an Optimized Definition of "Adverse Pathology"/"Significant Prostate Cancer" with Improved Utility in Clinical Management and Research

Jesse K. McKenney, MD

Cleveland Clinic
Robert J. Tomsich Pathology & Laboratory Medicine Institute

THE 47TH ANNUAL SCIENTIFIC MEETING
of the Australasian Division of the International Academy of Pathology

Exploring Methodology for Studying Clinical Outcome-Based Histologic Classification

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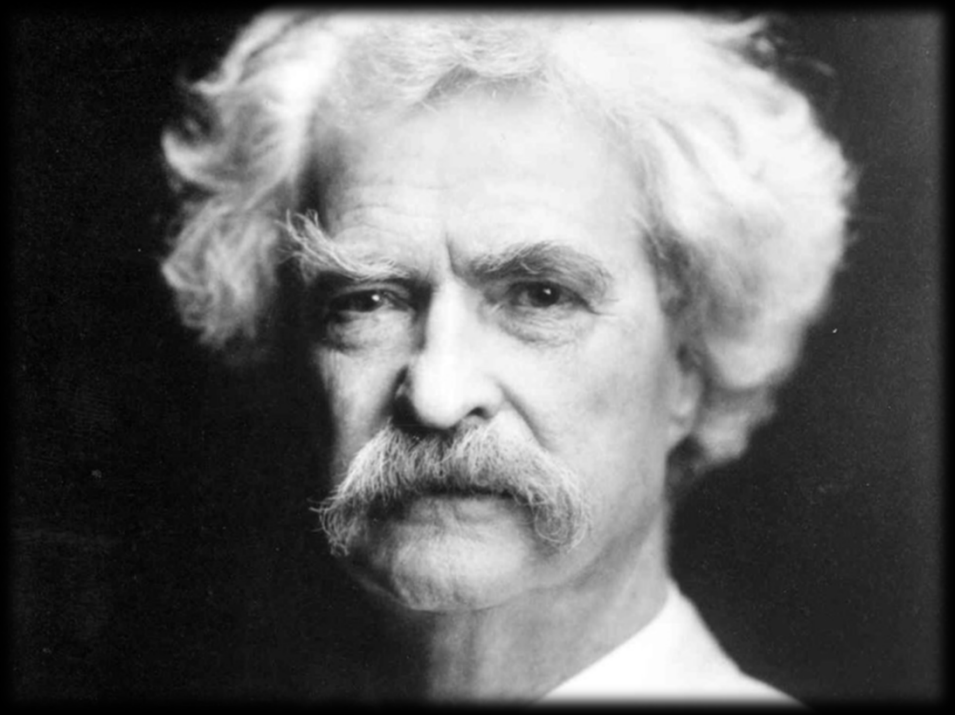
Disclosure of Relevant Financial Relationships

I have no relevant financial relationships.



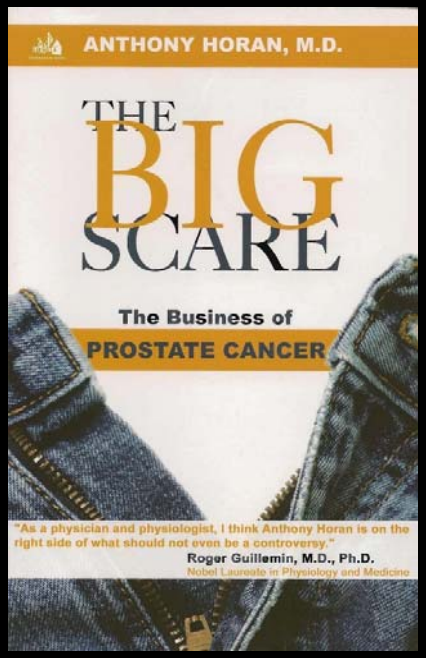
“The death of [histology] has been grossly exaggerated”

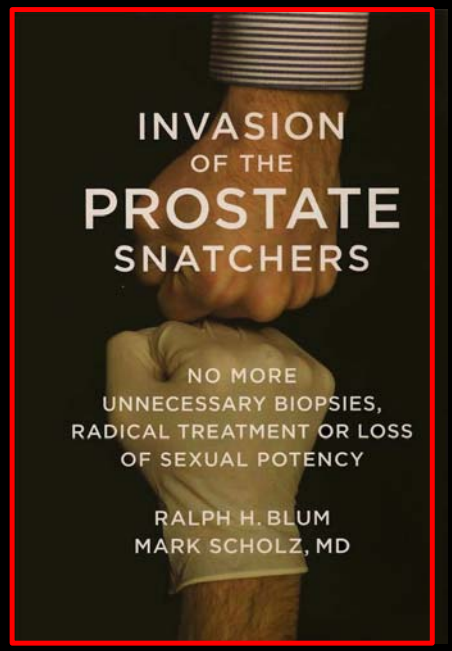
Background

- Many prostate cancers will remain clinically occult for the life of a patient
- Controversy persists regarding screening, need for any treatment, optimal methods of treatment…

Background

- "No treatment" is now acceptable
  - Active surveillance
  - Watchful waiting





- Who needs treatment?
  - Reproducibility of clinical recommendations?
  - Reproducibility of pathologic assessment?

Variables in Risk Stratification

- What can we use to predict the risk for aggressive behavior in prostate cancer?
  - Tissue biomarkers?
    - » Molecular classifiers?
  - Serum biomarkers?
  - Tumor volume estimates in biopsy?
  - Imaging characteristics?
  - Architectural patterns by histologic evaluation?
    - » modified Gleason grading

The Grading/Classification of Prostate Cancer

Histologic Grading: A Definition

1. The identification and grouping of histologic attributes along a *scale* that conveys a range of aggressiveness to a malignant *neoplasm*
2. Outcome prediction model based on histologic attributes of a neoplasm

Origins of Grading

David Paul von Hansemann

Cellular Anaplasia and Malignancy

Hansemann D. Studien uber die Spezi-ficitat, den Altruismus und die Anaplasie der Zellen. Berlin: Verlag von August Hirschwald; 1893.

Origins of Grading

Dr. A.C. Broders, M.D.

- **Since Broders' initial work in 1920's**
  - **40 separate grading systems have been proposed for prostate cancer**

Utility of Grading in Different Tumors

- Pancreatic ductal adenocarcinoma
  - Uniformly lethal
  - Early detection and intervention?
  - Prevention?

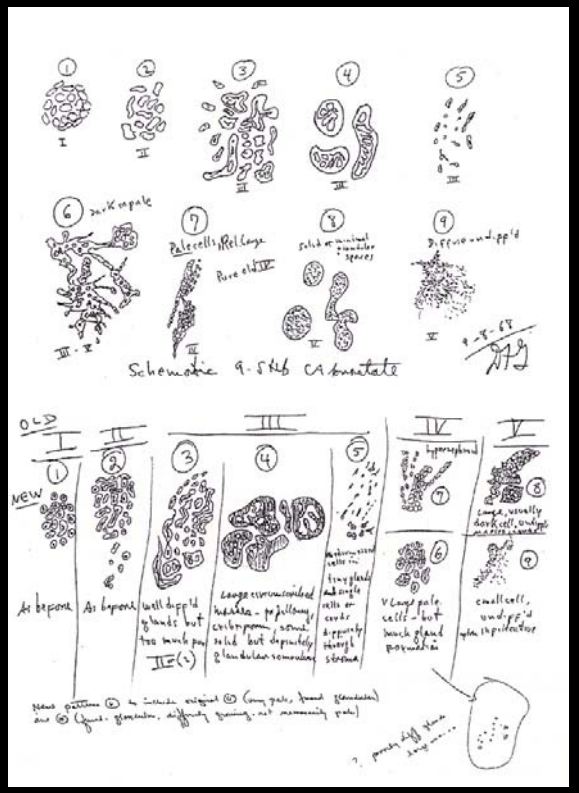
- Prostatic adenocarcinoma
  - Wide range of biologic aggressiveness
  - Morbidity within a patient's lifespan?
  - Risk stratification

Gleason Grading History

- VA Cooperative Urological Research Group 1960-1975
  - 14 hospitals
  - 5000 patients
  - Survival as study end-point
- Problem with the study:
  - Histologic evaluation not standardized between hospitals

Donald F. Gleason, M.D.
1920-2008

- **Veterans Administration Cooperative Urological Research Group 1960-1975**
  - **14 hospitals**
  - **5000 patients**
  - **Survival as study end-point**



Cancer Chemother Rep 1966; 50(3):129-36.

SURVIVAL RATES OF PATIENTS WITH PROSTATIC CANCER, TUMOR STAGE, AND DIFFERENTIATION—PRELIMINARY REPORT[1]

John C. Bailar, III,[2] George T. Mellinger,[3] and Donald F. Gleason[4,5]

One of the most important goals of randomized clinical trials of anticancer agents is to provide clinicians with the information they need in choosing the therapeutic agent, including dose schedule and route of administration, that gives the highest probability of a favorable response at an acceptable level of toxicity. Without discussing the problems of defining

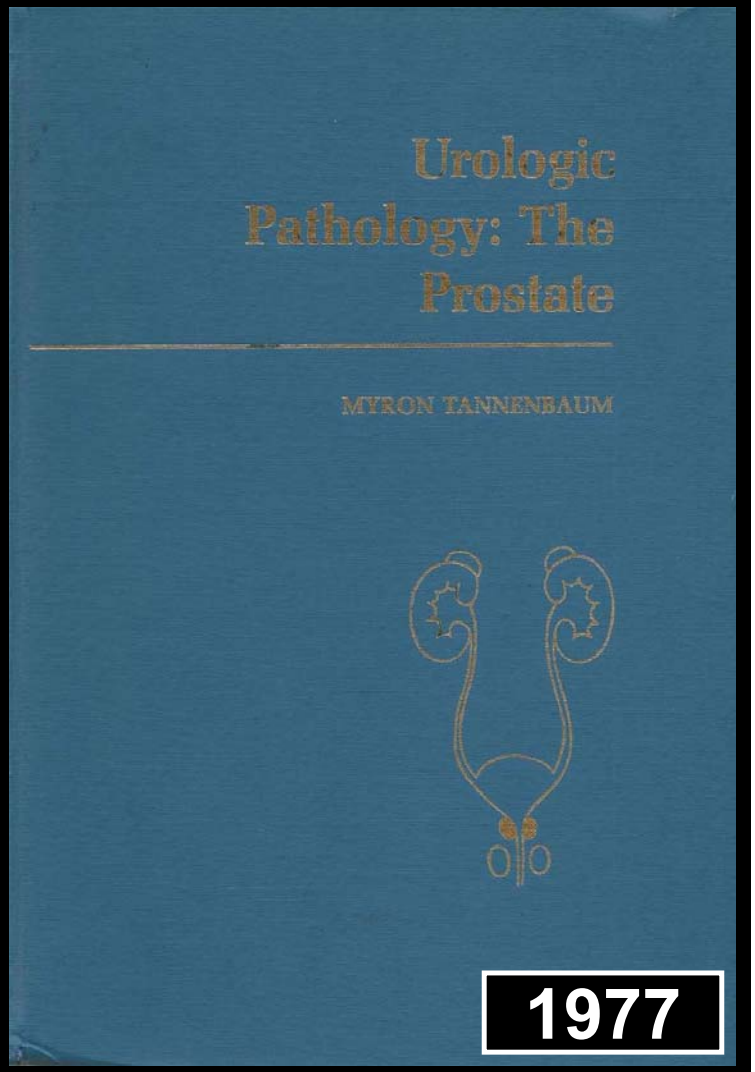
This paper questions the rule that no (or very few) patients should be separated from the main part of the analysis after randomization and suggests new methods for improving the classification of patients admitted to the study. For illustration we use data from a randomized clinical trial of the treatment of prostatic cancer in the Minneapolis Veterans

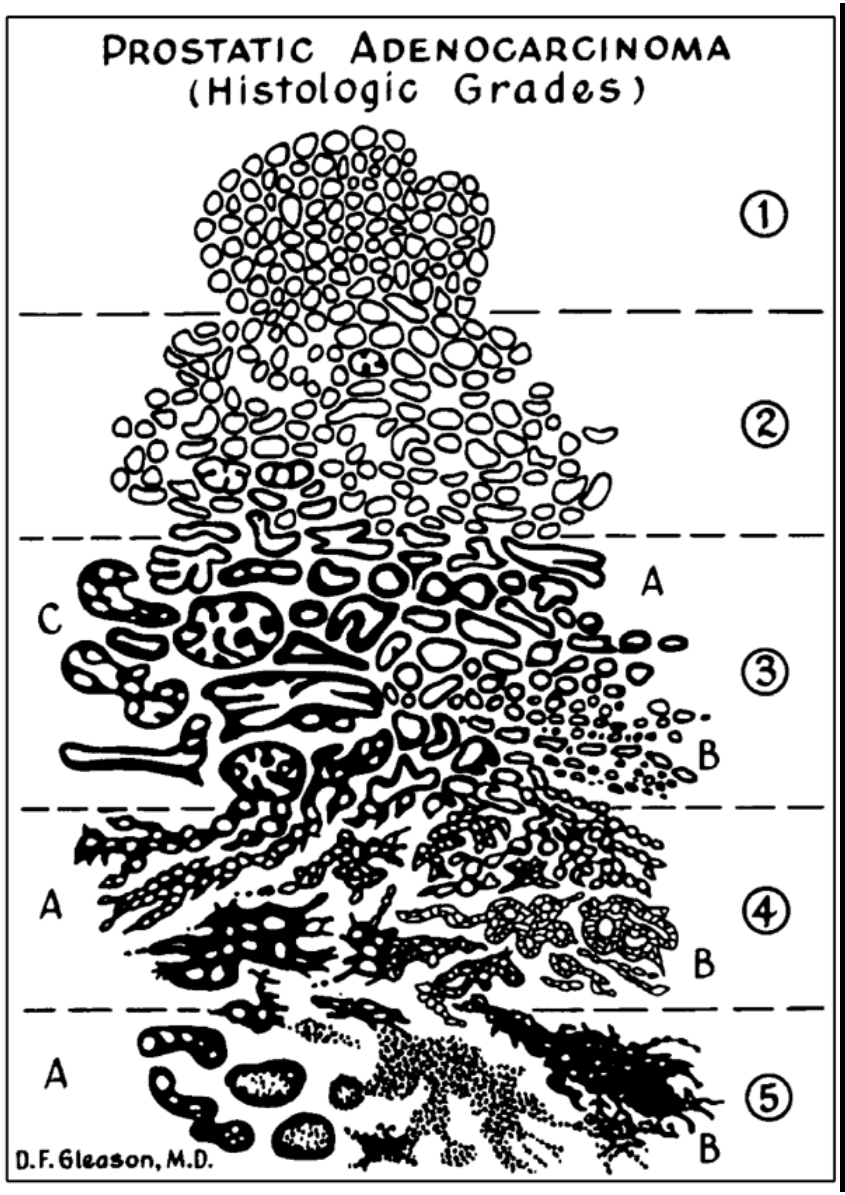
- **9 distinct "patterns"**
- **But only 5 groups with separate prognosis**

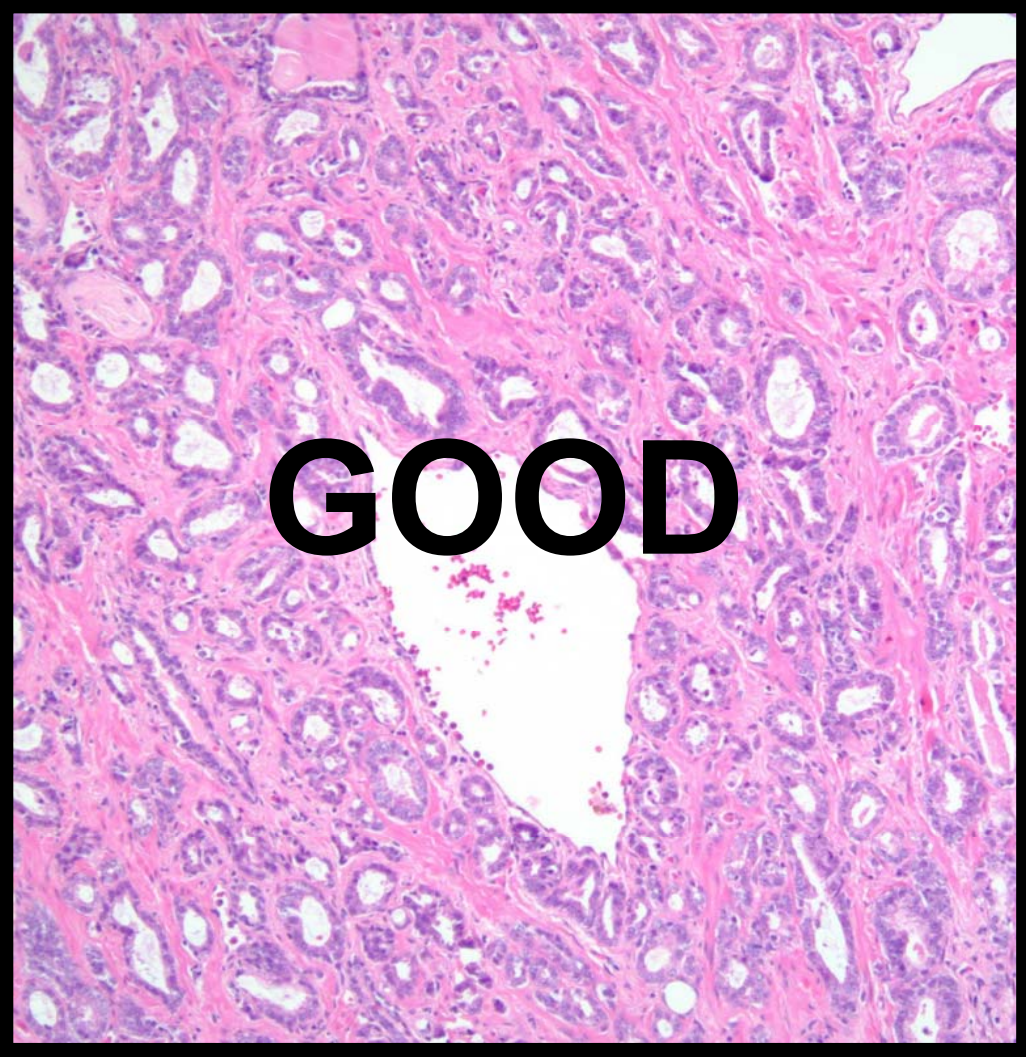
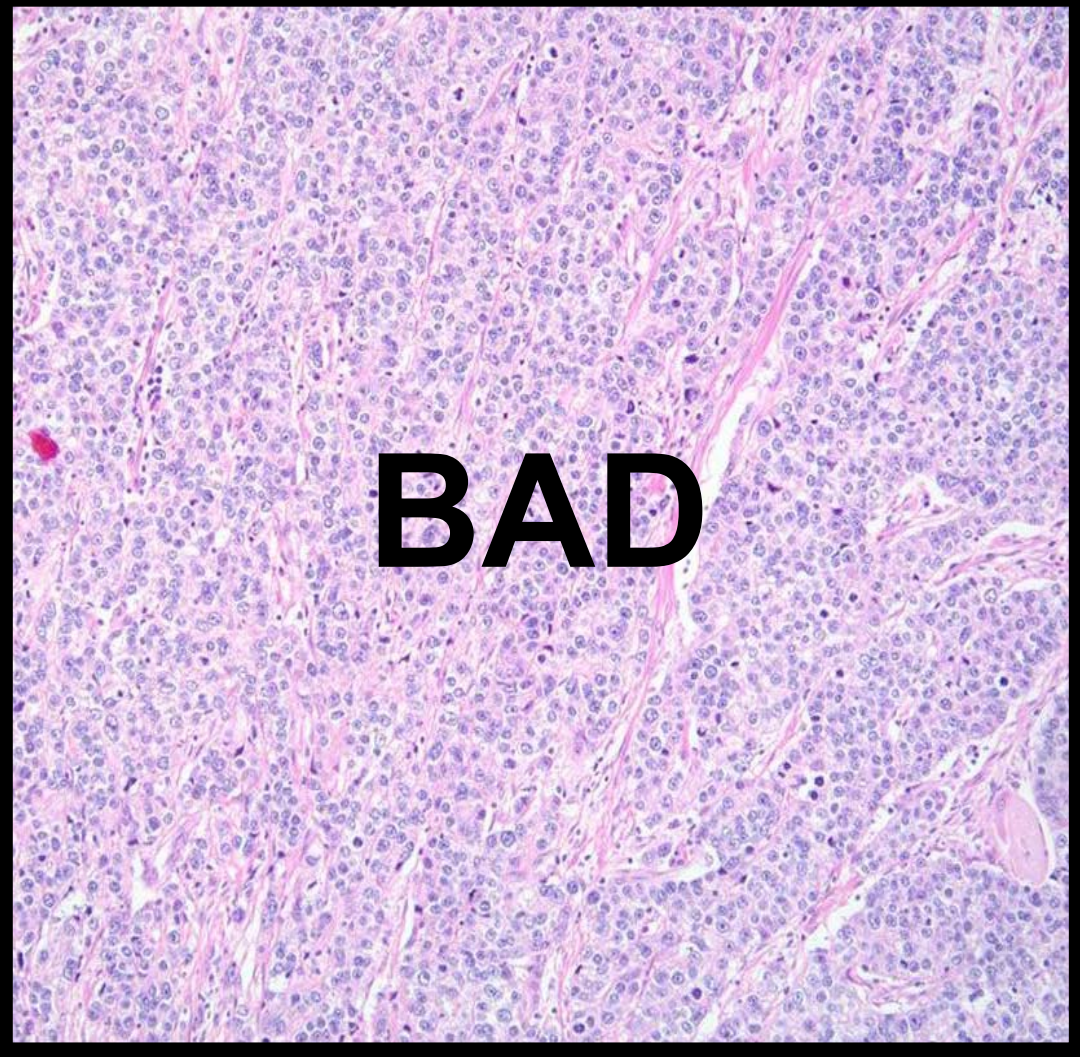
through the exclusion of patients who are so ill that none of the treatments to be studied is likely to produce a favorable response. Less often there are rules for the exclusion of patients who are likely to respond favorably to *all* the study treatments. However, when a patient is admitted to the study and randomly assigned to a treatment, he is usually kept in the study unless it is found that he did not

treatment methods under study, and (*b*) patients who will (with high probability) *not* respond favorably to any of the treatment methods under study.

If it can be predicted accurately from *pretreatment* information for each patient whether he belongs in group (*a*) or in group (*b*), it is obvious that little information will be gained on the efficacy of treatment. How-


Urologic Pathology: The Prostate
MYRON TANNENBAUM
1977


PROSTATIC ADENOCARCINOMA
(Histologic Grades)
①
②
C
A
③
B
A
④
B
A
⑤
B
D.F. Gleason, M.D.

Well-formed Glands	Solid Sheets
	

Gleason Summation Method

- Some cancers have different patterns
- The presence of separate patterns was “prognostic”
- Devised the summation method
  - 4+3=7
  - 3+3=6

Major Problem for Current Clinical Management!

Gleason Grading History

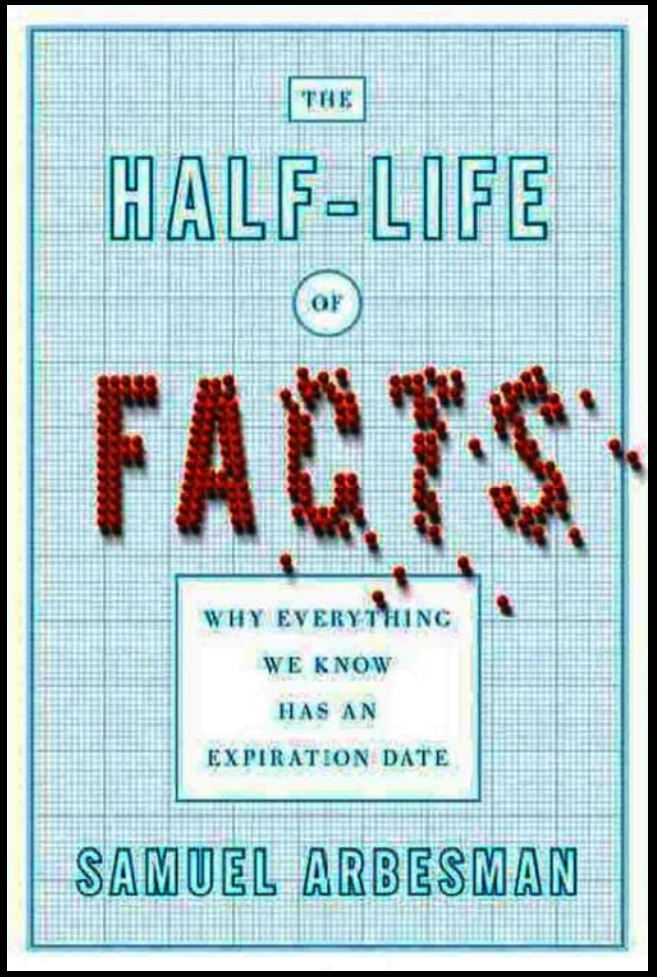
- Changes over time
  - Smaller and smaller prostate needle cores
  - More radical prostatectomies
- Cancer no longer commonly diagnosed by symptoms
  - PSA screening era (FDA approval in 1994 as diagnostic tool)
  - Not as uniformly aggressive
  - Patient cohort changed!!

PSA Screening for Prostate Cancer

Most cancers aggressive → Most cancers indolent

Good news… Bad news → RP/XRT vs Waiting/AS

Objective Reality Bias in Medicine



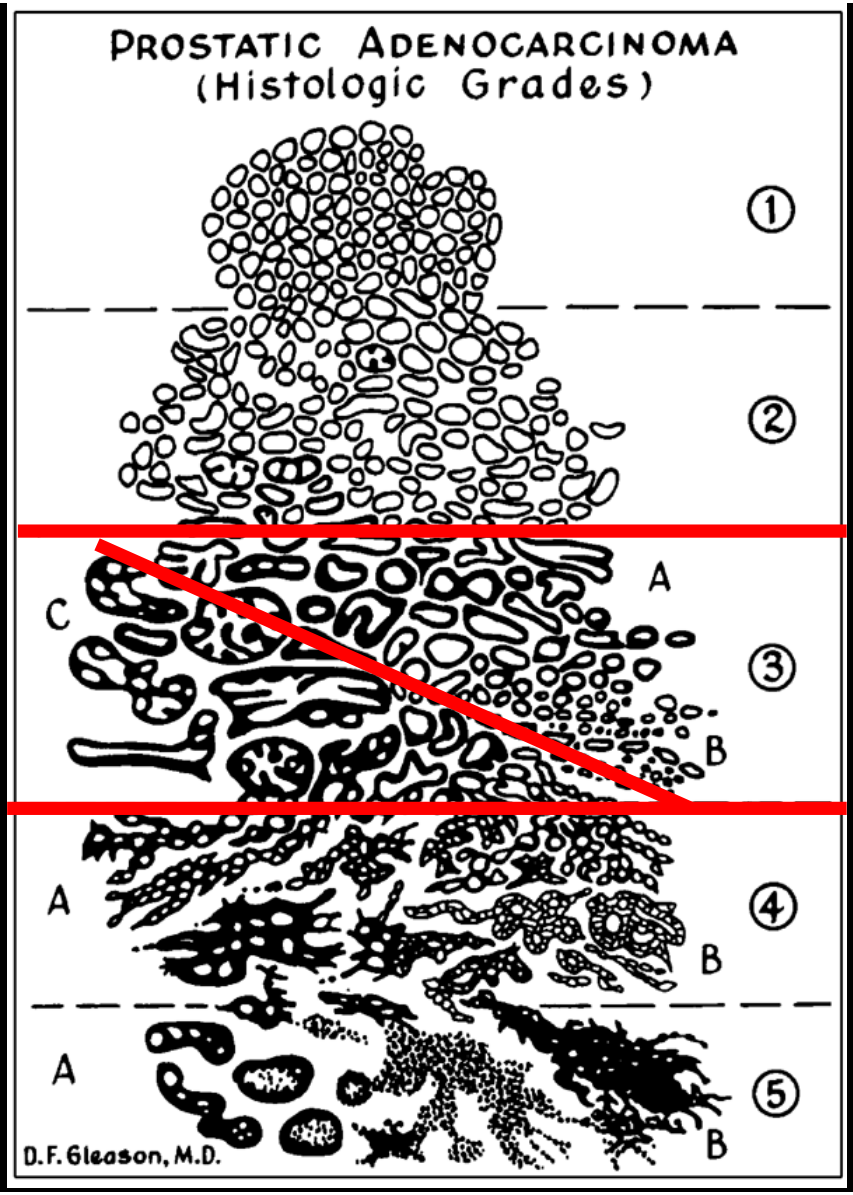
If there is a major change in how a specific “neoplasm” is screened and diagnosed and/or clinically managed, the prior classification may not be optimized for the new clinical scenario

Model?

Current Hypothesis?

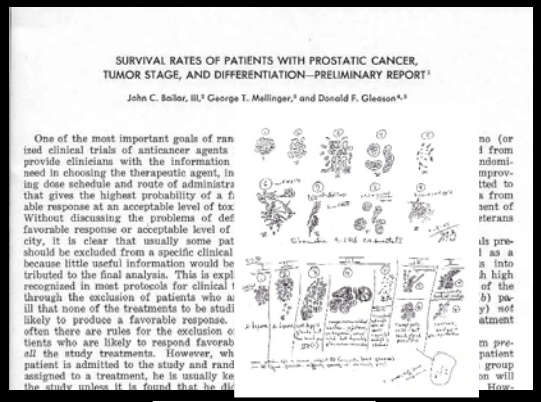
Objective Reality: Grade NOT an Entity

- Thresholds for grades are “fluid” and depend on:
  - Population studied
    - PSA screen detected?
  - Outcome measure used
    - BCR?
    - Metastasis free survival?
    - Death from disease?
  - Which stratification is most clinically relevant… decision to be made?
  - Analogy to clinical lab test: sensitivity and specificity?



Do we need 5 groups?

Gradual Grading Changes Over Time



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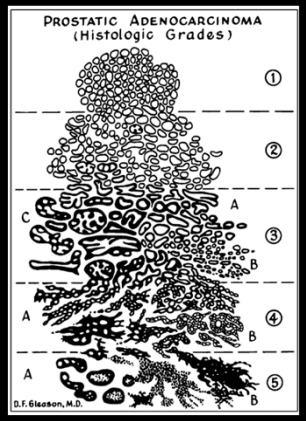
recognized in most protocols for clinical t
through the exclusion of patients who a
ill that none of the treatments to be studi
likely to produce a favorable response.
often there are rules for the exclusion o
tients who are likely to respond favorab
all the study treatments. However, wh
patient is admitted to the study and rand
assigned to a treatment, he is usually ke
the study unless it is found that he di

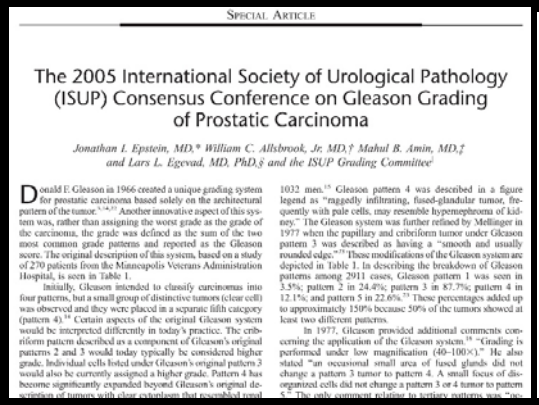
1966

Chapter 9

Histologic Grading and Clinical Staging of Prostatic Carcinoma

1977





SPECIAL ARTICLE

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

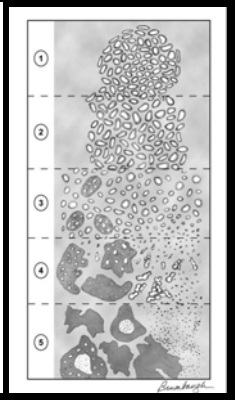
Jonathan I. Epstein, MD, William C. Allsbrook, Jr, MD,† Mahul B. Amin, MD,‡ and Lars L. Egevad, MD, PhD,§ and the ISUP Grading Committee‖*

Donald F. Gleason in 1966 created a unique grading system for prostatic carcinoma based solely on the architectural pattern of the tumor.[1–4,7] Another innovative aspect of this system was, rather than assigning the worst grade as the grade of the carcinoma, the grade was defined as the sum of the two most common grade patterns and reported as the Gleason score. The original description of this system, based on a study of 270 patients from the Minneapolis Veterans Administration Hospital, is seen in Table 1.

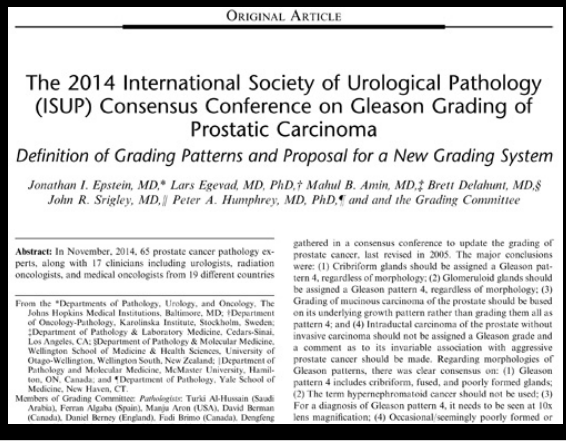
Initially, Gleason intended to classify carcinomas into four patterns, but a small group of distinctive tumors (clear cell) was observed and they were placed in a separate fifth category (pattern 4).[1] Certain aspects of the original Gleason system would be interpreted differently in today's practice. The cribriform pattern described as a component of Gleason's original patterns 2 and 3 would today typically be considered higher grade. Individual cells forked under Gleason's original pattern 3 would also be currently assigned a higher grade. Pattern 4 has become significantly expanded beyond Gleason's original description of tumors with clear cytoplasm that resembled renal

1032 men.[15] Gleason pattern 4 was described in a figure legend as "raggedly infiltrating, fused-glandular tumor, frequently with pale cells, may resemble hypernephroma of kidney." The Gleason system was further refined by Mellinger in 1977 when the papillary and cribriform tumor under Gleason pattern 3 was described as having a "smooth and usually rounded edge."[16] These modifications of the Gleason system are depicted in Table 1. In describing the breakdown of Gleason patterns among 2911 cases, Gleason pattern 1 was seen in 3.5%; pattern 2 in 24.4%; pattern 3 in 87.7%; pattern 4 in 12.1%; and pattern 5 in 22.6%.[15] These percentages added up to approximately 150% because 50% of the tumors showed at least two different patterns.

In 1977, Gleason provided additional comments concerning the application of the Gleason system.[16] "Grading is performed under low magnification (40–100×)." He also stated "an occasional small area of fused glands did not change a pattern 3 tumor to pattern 4. A small focus of disorganized cells did not change a pattern 3 or 4 tumor to pattern 5." The only comment relative to tertiary patterns was "no-



Am J Surg Pathol 2005 29:1228-42



ORIGINAL ARTICLE

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 and the Grading Committee*

Abstract: In November, 2014, 65 prostate cancer pathology experts, along with 17 clinicians including urologists, radiation oncologists, and medical oncologists from 19 different countries

From the *Departments of Pathology, Urology, and Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD; †Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden; ‡Department of Pathology & Laboratory Medicine, Cedars-Sinai, Los Angeles, CA; §Department of Pathology & Molecular Medicine, Wellington School of Medicine & Health Sciences, University of Otago-Wellington, Wellington South, New Zealand; ‖Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; and ¶Department of Pathology, Yale School of Medicine, New Haven, CT.

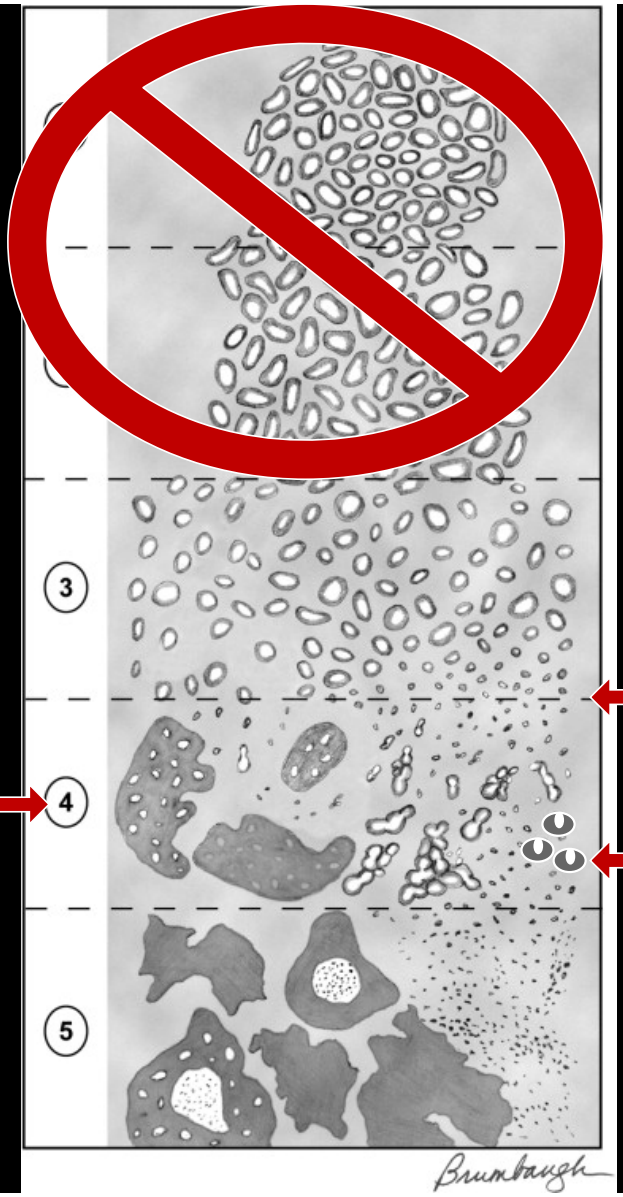
Members of Grading Committee: *Pathologists:* Turki Al-Hussain (Saudi Arabia), Ferran Algaba (Spain), Manju Aron (USA), David Berman (Canada), Daniel Berney (England), Fedi Brimo (Canada), Dengfeng

gathered in a consensus conference to update the grading of prostate cancer, last revised in 2005. The major conclusions were: (1) Cribriform glands should be assigned a Gleason pattern 4, regardless of morphology; (2) Glomeruloid glands should be assigned a Gleason pattern 4, regardless of morphology; (3) Grading of mucinous carcinoma of the prostate should be based on its underlying growth pattern rather than grading them all as pattern 4; and (4) Intraductal carcinoma of the prostate without invasive carcinoma should not be assigned a Gleason grade and a comment as to its invariable association with aggressive prostate cancer should be made. Regarding morphologies of Gleason patterns, there was clear consensus on: (1) Gleason pattern 4 includes cribriform, fused, and poorly formed glands; (2) The term hypernephromatoid cancer should not be used; (3) For a diagnosis of Gleason pattern 4, it needs to be seen at 10x lens magnification; (4) Occasional/seemingly poorly formed or

Am J Surg Pathol 2016 40:244-52

2014/2016

3+3
3+4
4+3
4+4
4+5
5+4
5+5

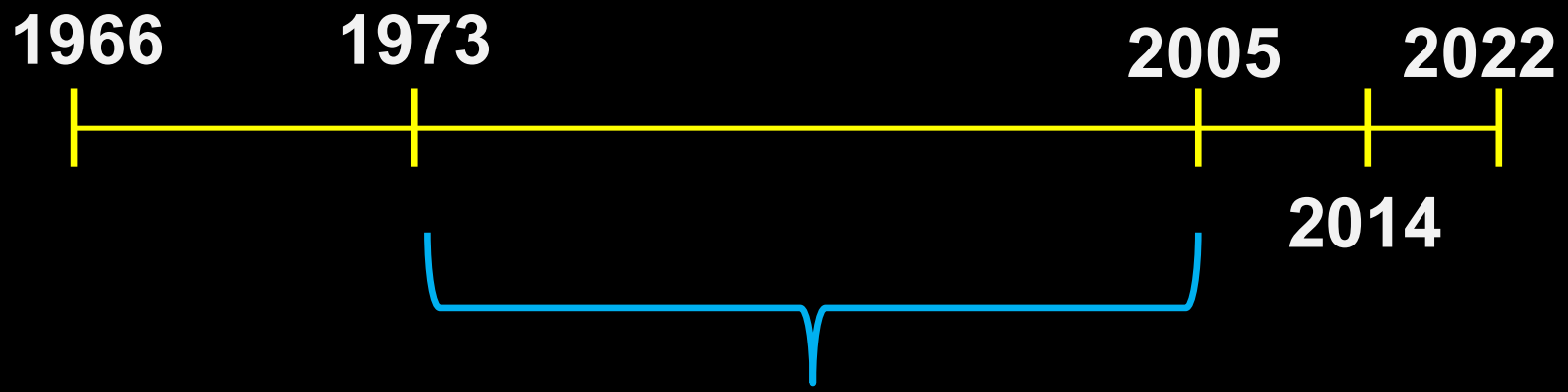


Cribriform

Conservative!

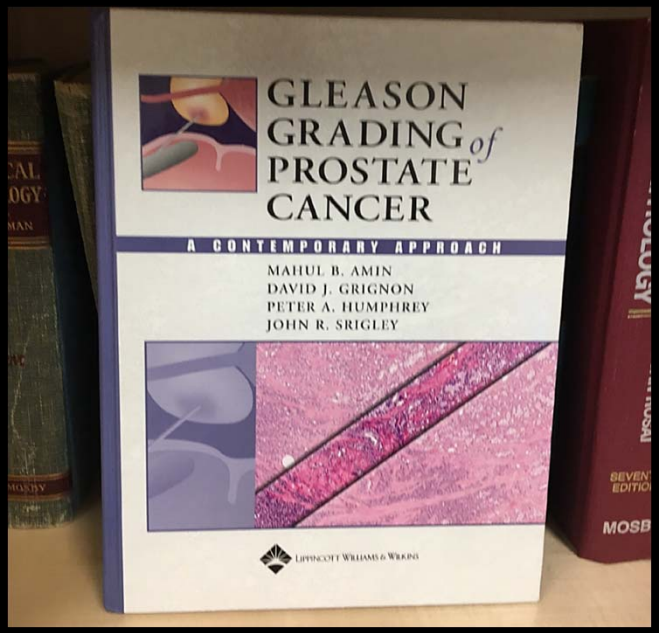
Glomerulations

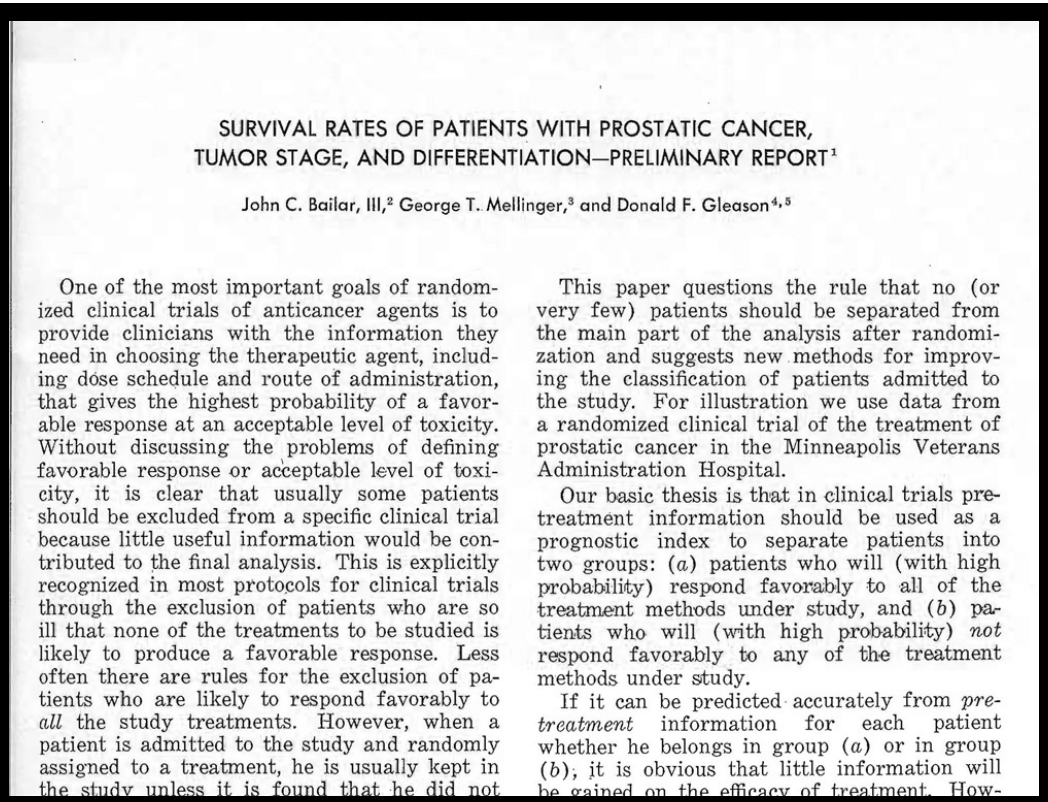
Ask yourself…
where is your grading threshold?



Over-grading of pattern 4 by current standards
Under-grading of cribriform

My Story with Grading and Prostate Cancer





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This paper questions the rule that no (or very few) patients should be separated from the main part of the analysis after randomization and suggests new methods for improving the classification of patients admitted to the study. For illustration we use data from a randomized clinical trial of the treatment of prostatic cancer in the Minneapolis Veterans Administration Hospital.

Our basic thesis is that in clinical trials pretreatment information should be used as a prognostic index to separate patients into two groups: (*a*) patients who will (with high probability) respond favorably to all of the treatment methods under study, and (*b*) patients who will (with high probability) *not* respond favorably to any of the treatment methods under study.

If it can be predicted accurately from *pretreatment* information for each patient whether he belongs in group (*a*) or in group (*b*), it is obvious that little information will be gained on the efficacy of treatment. How-

Cancer Chemother Rep 1966;50(3):129

Mellinger GT, Gleason D, Bailar J 3rd. The histology and prognosis of prostatic cancer. *J Urol* 1967;97(2):331-7

Original data on individual patterns

?

- Practice habits
- Anecdotal experience
- Consensus recommendations
- Reproducibility

Canary Modeling Approach

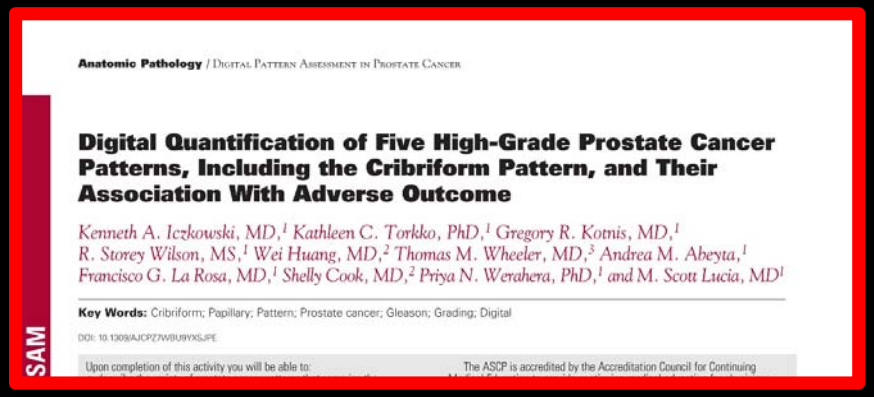
Canary Prostate Cancer Group

1. Retrospective TMA RP cohort
2. Prospective Active Surveillance Study

CANARY FOUNDATION

Stopping Cancer Early – The Best Possible Investment

Prior Studies Suggest All Pattern 4 is *NOT* Equal



Anatomic Pathology / Digital Pattern Assessment in Prostate Cancer

Digital Quantification of Five High-Grade Prostate Cancer Patterns, Including the Cribriform Pattern, and Their Association With Adverse Outcome

Kenneth A. Iczkowski, MD,[1] Kathleen C. Torkko, PhD,[1] Gregory R. Kotnis, MD,[1] R. Storey Wilson, MS,[1] Wei Huang, MD,[2] Thomas M. Wheeler, MD,[3] Andrea M. Abeyta,[1] Francisco G. La Rosa, MD,[1] Shelly Cook, MD,[2] Priya N. Werahera, PhD,[1] and M. Scott Lucia, MD[1]

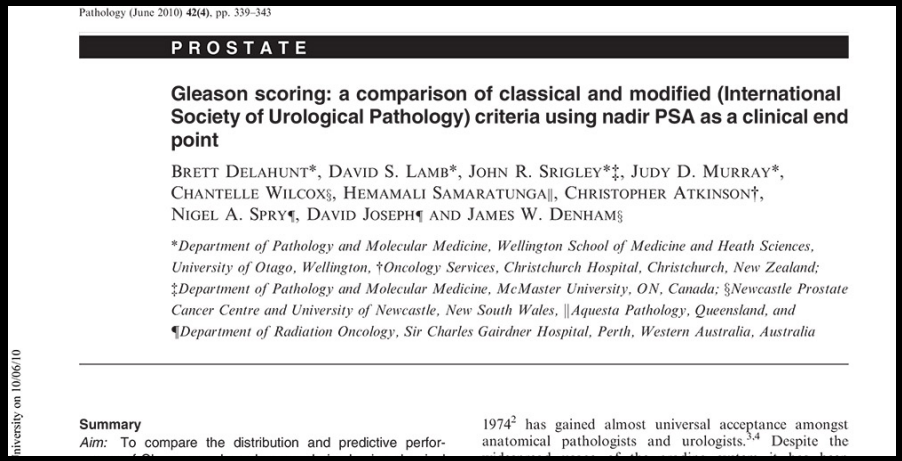
Key Words: Cribriform; Papillary; Pattern; Prostate cancer; Gleason; Grading; Digital

DOI: 10.1309/AJCPZ7WBU9YXSJPE

SAM

Upon completion of this activity you will be able to:

The ASCP is accredited by the Accreditation Council for Continuing



Pathology (June 2010) **42(4)**, pp. 339–343

PROSTATE

Gleason scoring: a comparison of classical and modified (International Society of Urological Pathology) criteria using nadir PSA as a clinical end point

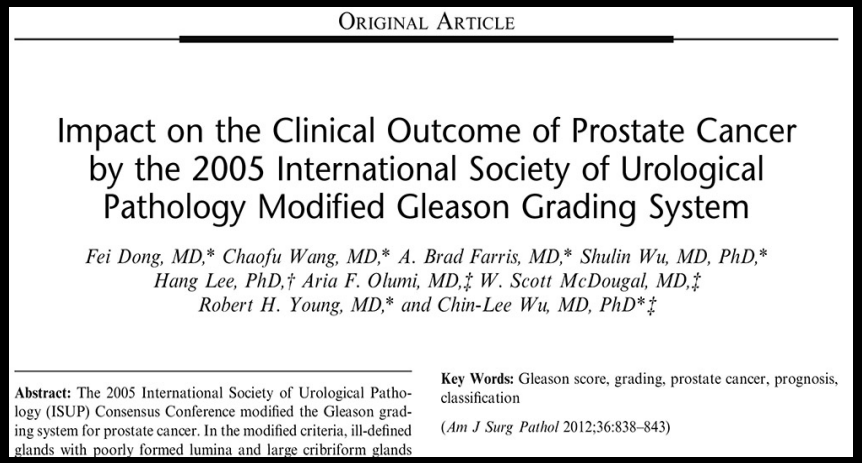
Brett Delahunt*, David S. Lamb*, John R. Srigley*‡, Judy D. Murray*, Chantelle Wilcox§, Hemamali Samaratunga‖, Christopher Atkinson†, Nigel A. Spry¶, David Joseph¶ and James W. Denham§

*Department of Pathology and Molecular Medicine, Wellington School of Medicine and Heath Sciences, University of Otago, Wellington, †Oncology Services, Christchurch Hospital, Christchurch, New Zealand; ‡Department of Pathology and Molecular Medicine, McMaster University, ON, Canada; §Newcastle Prostate Cancer Centre and University of Newcastle, New South Wales, ‖Aquesta Pathology, Queensland, and ¶Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

Summary

Aim: To compare the distribution and predictive perfor-

1974[2] has gained almost universal acceptance amongst anatomical pathologists and urologists.[3,4] Despite the



Original Article

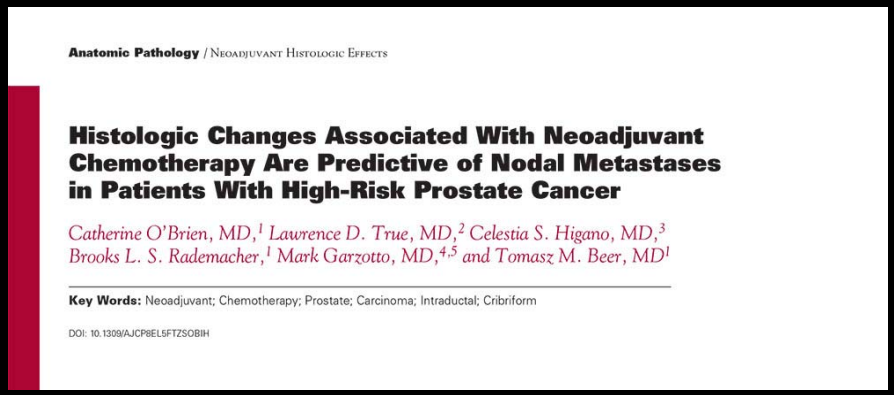
Impact on the Clinical Outcome of Prostate Cancer by the 2005 International Society of Urological Pathology Modified Gleason Grading System

Fei Dong, MD, Chaofu Wang, MD,* A. Brad Farris, MD,* Shulin Wu, MD, PhD,* Hang Lee, PhD,† Aria F. Olumi, MD,‡ W. Scott McDougal, MD,‡ Robert H. Young, MD,* and Chin-Lee Wu, MD, PhD*‡*

Abstract: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference modified the Gleason grading system for prostate cancer. In the modified criteria, ill-defined glands with poorly formed lumina and large cribriform glands

Key Words: Gleason score, grading, prostate cancer, prognosis, classification

(*Am J Surg Pathol* 2012;36:838–843)



Anatomic Pathology / Neoadjuvant Histologic Effects

Histologic Changes Associated With Neoadjuvant Chemotherapy Are Predictive of Nodal Metastases in Patients With High-Risk Prostate Cancer

Catherine O'Brien, MD,[1] Lawrence D. True, MD,[2] Celestia S. Higano, MD,[3] Brooks L. S. Rademacher,[1] Mark Garzotto, MD,[4,5] and Tomasz M. Beer, MD[1]

Key Words: Neoadjuvant; Chemotherapy; Prostate; Carcinoma; Intraductal; Cribriform

DOI: 10.1309/AJCP8EL5FTZSOBIH

Cribriform Gleason pattern 4 had clinical outcome similar to Gleason pattern 5

Prior Studies Suggest All Pattern 4 is *NOT* Equal

Cribriform pattern 4 is aggressive cancer!

Most other pattern 4 is indolent

Over 50 confirmatory peer-reviewed studies

T Van der Kwast, MD
GJLH van Leenders, MD

Prostate Cancer Classification/Grading: The Premise

1. We are miscalculating risk of prostate cancer in a significant subset of patients, particularly for 3+4=7/GG2
   - The summation method is severely flawed
   - Subset of pattern 4 is very aggressive
     - Most cribriform
     - Other patterns?

2. This could easily be resolved without extra costs to the health care system

Histology Study 1: Highlighting the Problem

Reproducibility

The Potential Impact of Reproducibility of Gleason Grading in Men With Early Stage Prostate Cancer Managed by Active Surveillance: A Multi-Institutional Study

Jesse K. McKenney,* Jeff Simko,† Michael Bonham, Lawrence D. True, Dean Troyer, Sarah Hawley, Lisa F. Newcomb, Ladan Fazli,‡ Lakshmi P. Kunju, Marlo M. Nicolas, Funda Vakar-Lopez, Xiaotun Zhang, Peter R. Carroll,§ James D. Brooks and the Canary/Early Detection Research Network Prostate Active Surveillance Study Investigators

J Urol 2011;186:465-469

- Reproducibility of classic Gleason patterns is high
- 3+3 vs 3+4 due to "poorly formed glands" is POOR
- Should this be a decision-management threshold in AS?
  - Reproducibility in diagnosis and treatment
  - Clinical outcome? Does it even matter?

Virchows Arch (2011) 459:175–182
DOI 10.1007/s00428-011-1106-x

ORIGINAL ARTICLE

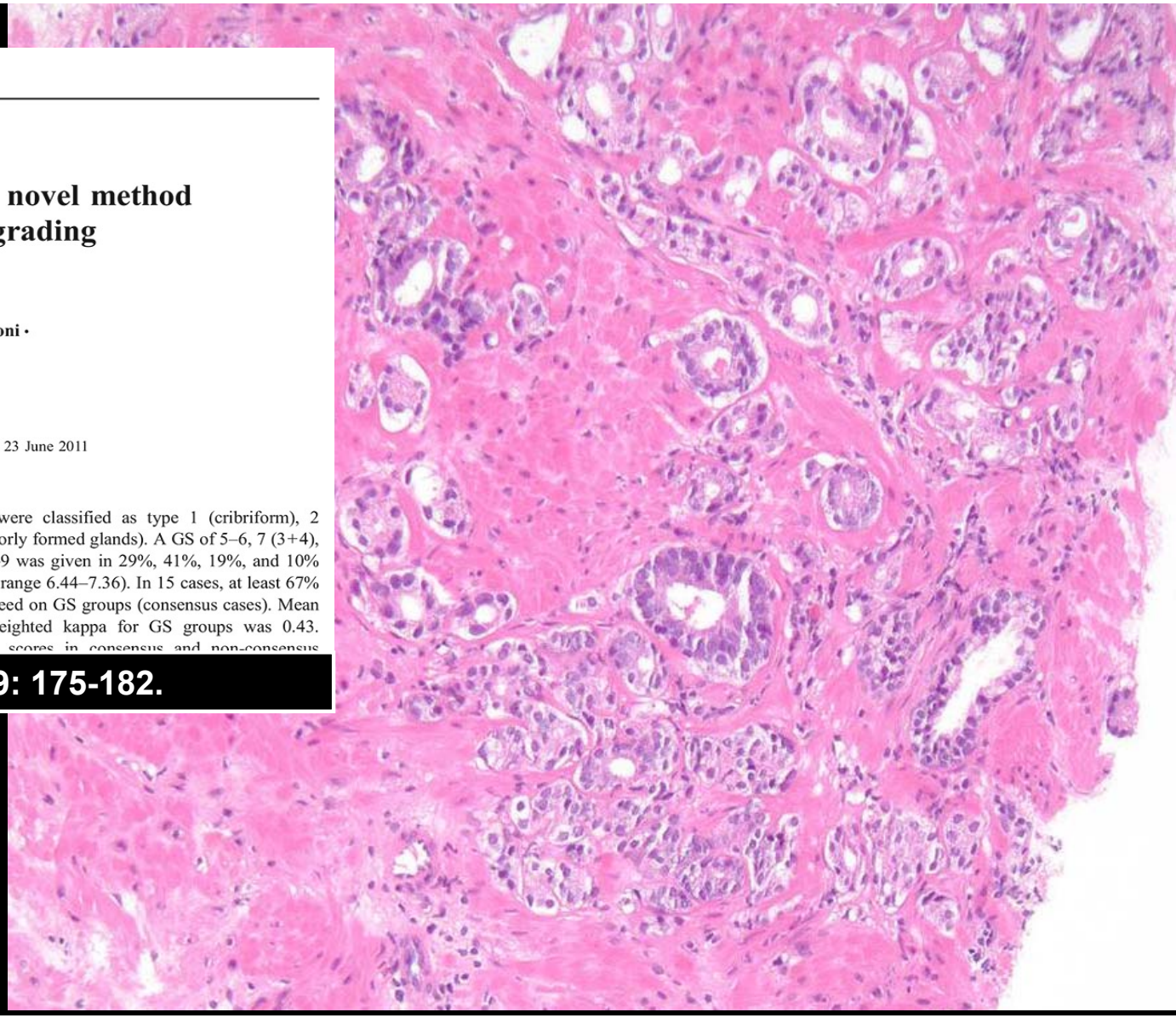
Interactive digital slides with heat maps: a novel method to improve the reproducibility of Gleason grading

Lars Egevad · Ferran Algaba · Daniel M. Berney · Liliane Boccon-Gibod · Eva Compérat · Andrew J. Evans · Rainer Grobholz · Glen Kristiansen · Cord Langner · Gina Lockwood · Antonio Lopez-Beltran · Rodolfo Montironi · Pedro Oliveira · Matthias Schwenkglenks · Ben Vainer · Murali Varma · Vincent Verger · Philippe Camparo

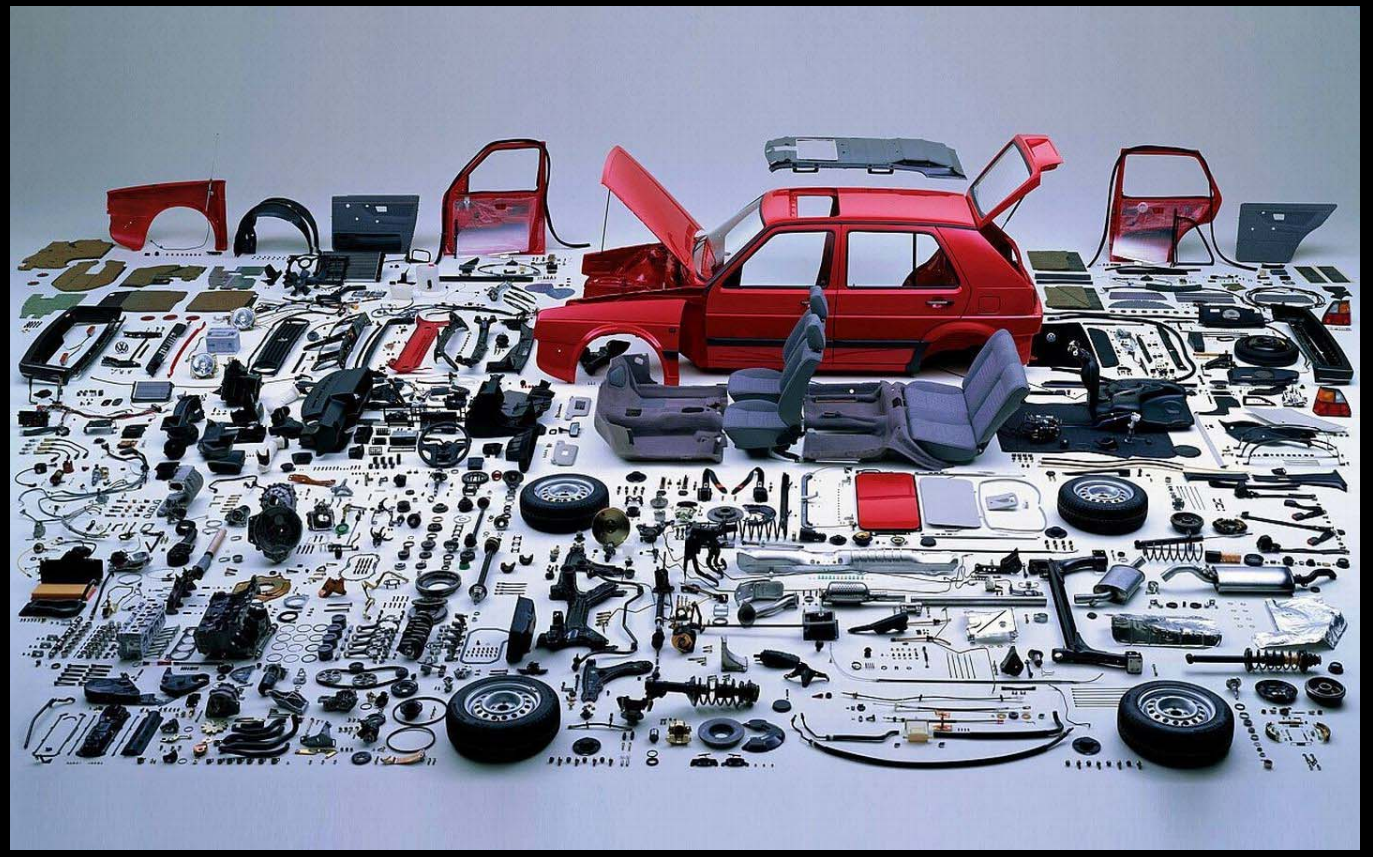
Received: 23 March 2011 / Revised: 12 May 2011 / Accepted: 9 June 2011 / Published online: 23 June 2011

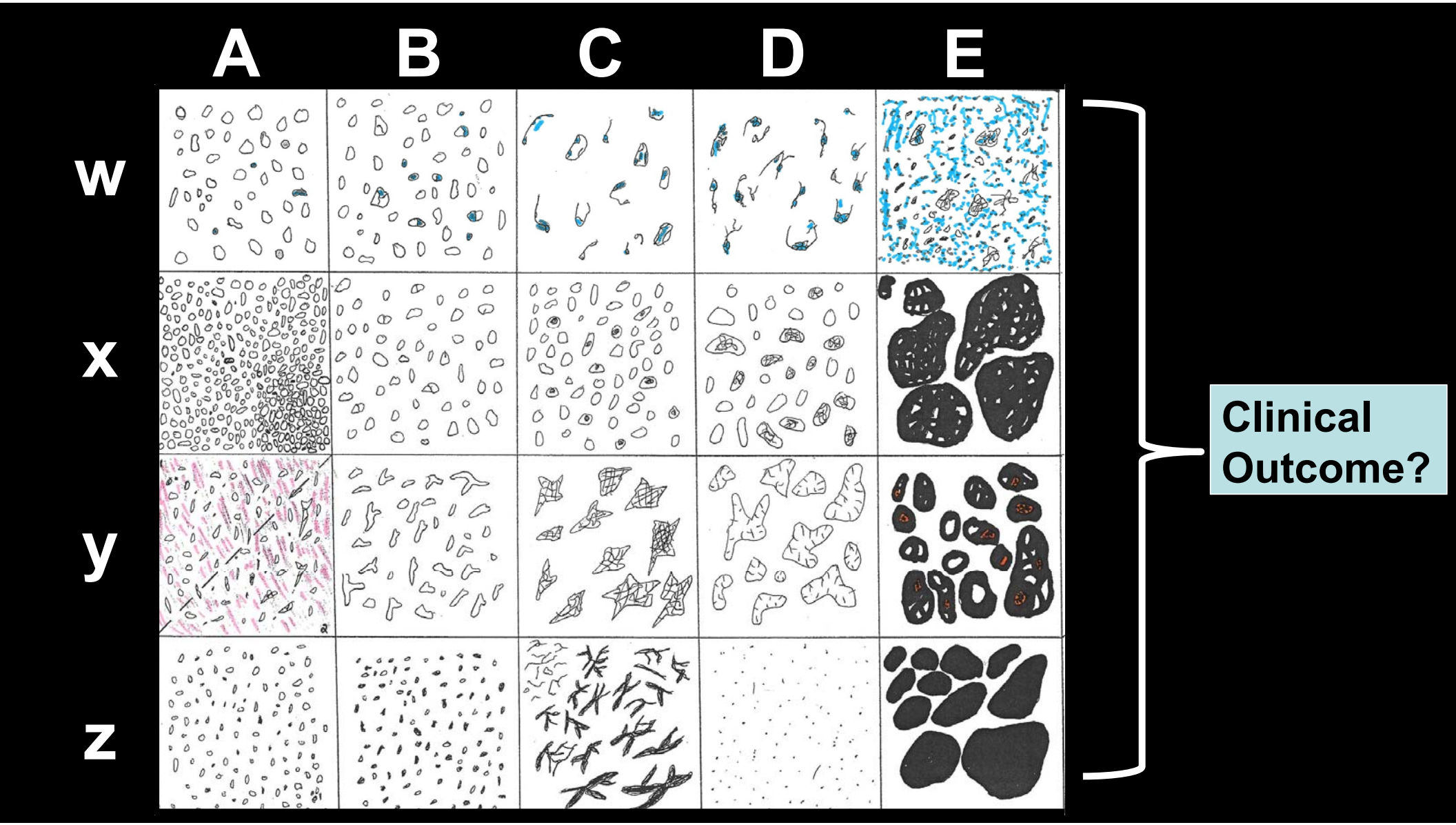
Abstract Our aims were to analyze reporting of Gleason pattern (GP) 3 and 4 prostate cancer with the ISUP 2005 Gleason grading and to collect consensus cases for standardization. We scanned 25 prostate biopsy cores diagnosed as Gleason score (GS) 6–7. Fifteen genitourinary pathologists graded the digital slides and circled GP 4 and 5 in a slide viewer. Grading difficulty was scored as 1–3. GP 4 components were classified as type 1 (cribriform), 2 (fused), or 3 (poorly formed glands). A GS of 5–6, 7 (3+4), 7 (4+3), and 8–9 was given in 29%, 41%, 19%, and 10% (mean GS 6.84, range 6.44–7.36). In 15 cases, at least 67% of observers agreed on GS groups (consensus cases). Mean interobserver weighted kappa for GS groups was 0.43. Mean difficulty scores in consensus and non-consensus

***Virchows Archive* 2011; 459: 175-182.**



Canary Phase 2: Deconstruction




A
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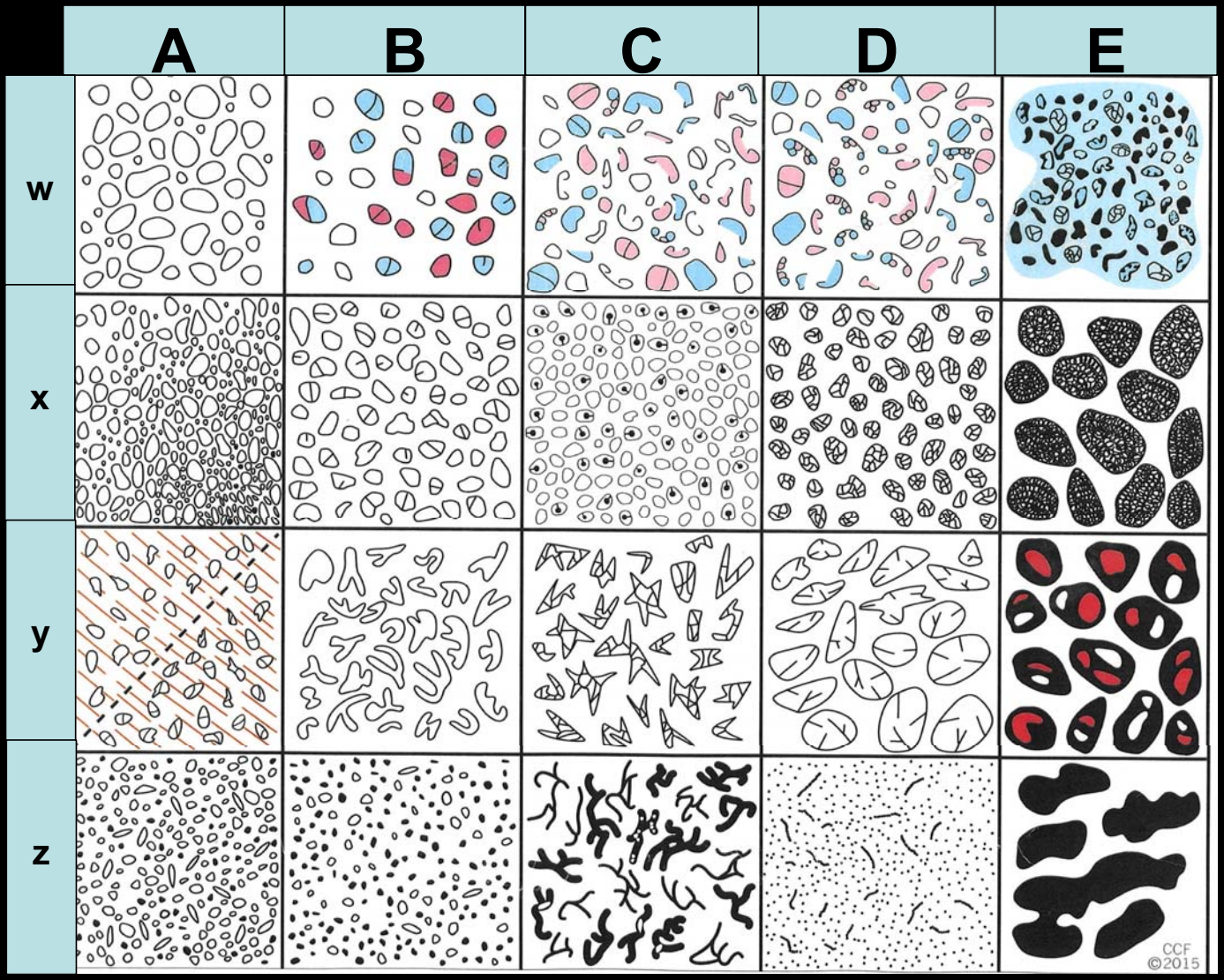
Clinical Outcome?



Canary Architectural Method

Histologic Grading of Prostatic Adenocarcinoma Can Be Further Optimized

Analysis of the Relative Prognostic Strength of Individual Architectural Patterns in 1275 Patients From the Canary Retrospective Cohort

Jesse K. McKenney, MD, Wei Wei, MS,† Sarah Hawley, MS,‡ Heidi Auman, PhD,‡ Lisa F. Newcomb, PhD,§‖ Hilary D. Boyer, BSc,§ Ladan Fazli, MD,¶ Jeff Simko, MD, PhD,# Antonio Hurtado-Coll, MD,¶ Dean A. Troyer, MD, PhD,** Maria S. Tretiakova, MD, PhD,‖ Funda Vakar-Lopez, MD,‖ Peter R. Carroll, MD, MPH,# Matthew R. Cooperberg, MD, MPH,# Martin E. Gleave, MD,¶ Raymond S. Lance, MD,** Dan W. Lin, MD,§‖ Peter S. Nelson, MD,§‖ Ian M. Thompson, MD,†† Lawrence D. True, MD,‖ Ziding Feng, PhD,† and James D. Brooks, MD‡‡*

Proof-of-Principle

Abstract: Histologic
prognosis in prostat
plays a critical role
sought to optimize the prognostic stratification of grading and
developed a method of recording and studying individual architectural patterns by light microscopic evaluation that is independent of standard Gleason grade. Some of the evaluated
Gleason grading (eg, re-
histologic patterns were
l in a retrospective post-
atients represented by the
sue microarrays. In uni-
re with varied epithelial
lative risk of recurrence-
= 7. Cases having focal
be designated as pattern
ibriform patterns with
nsile cribriform growth.
zard analyses of
inomas, reactive
recurrence-free
ntial regrouping
of architectural patterns into categories with similar risk. In summary, we argue that Gleason score assignment by current consensus guidelines are not entirely optimized for clinical use, including active surveillance. Our data suggest that focal poorly formed gland and cribriform patterns, currently classified as Gleason pattern 4, should be in separate prognostic groups, as the latter is associated with worse outcome. Patterns with extravasated mucin are likely overgraded in a subset of cases with more complex epithelial bridges, whereas stromogenic cancers have a worse outcome than conveyed by Gleason grade alone. These findings serve as a foundation to facilitate optimization of histologic grading and strongly support incorporating reactive stroma into routine assessment.

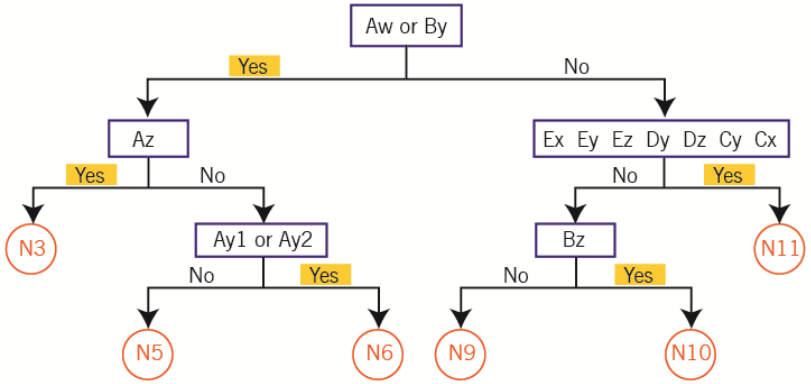
Key Words: prostate, adenocarcinoma, Gleason, grade, cribri-

CANARY FOUNDATION
Stopping Cancer Early – The Best Possible Investment

***Am J Surg Pathol* 2016; 40: 1439-56**

Results: Correlation with Outcome

A.



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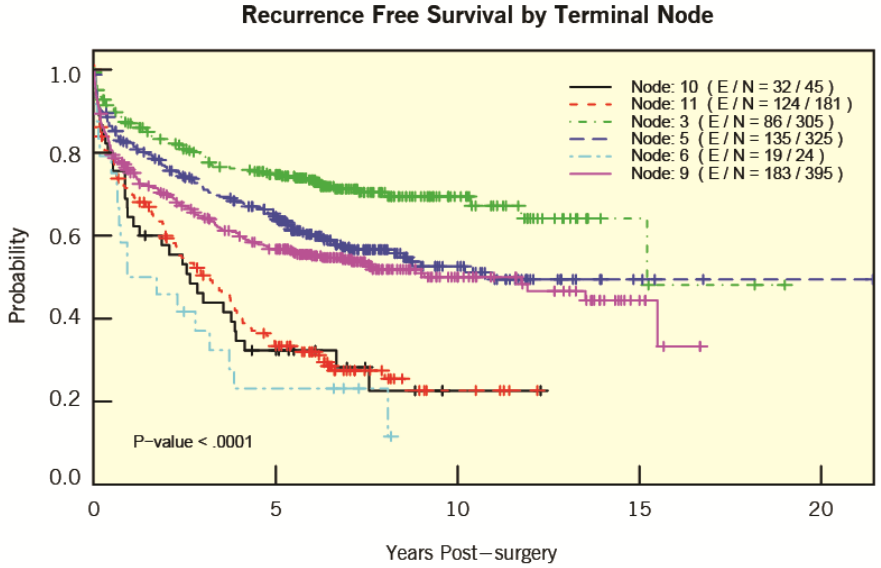
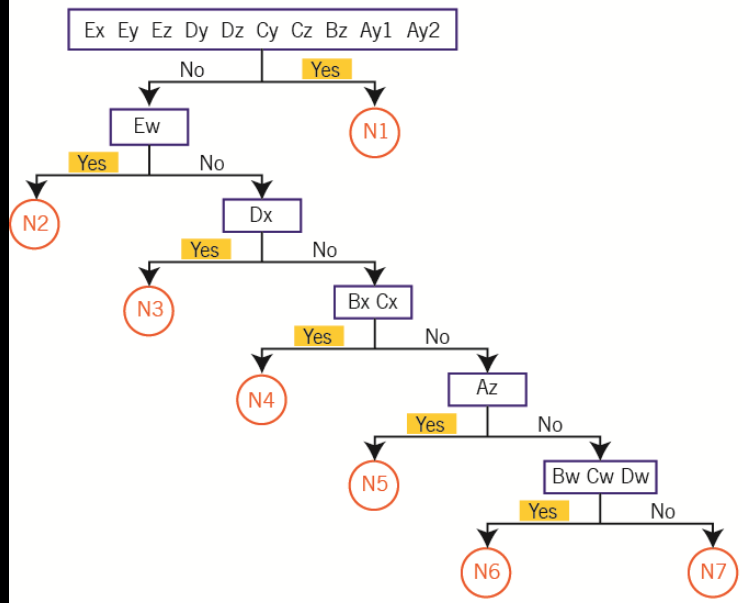


Am J Surg Pathol 2016; 40: 1439-56

Results: Correlation with Outcome

Manually generated decision tree analysis

A.



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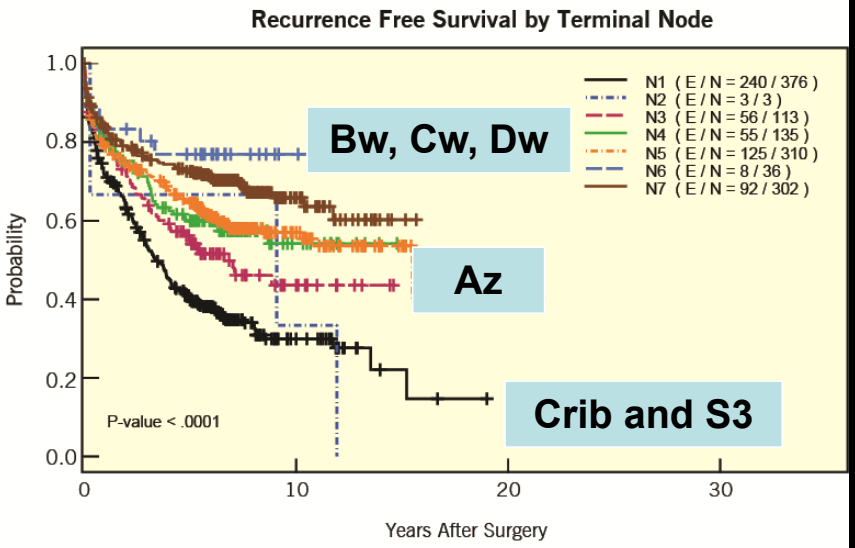
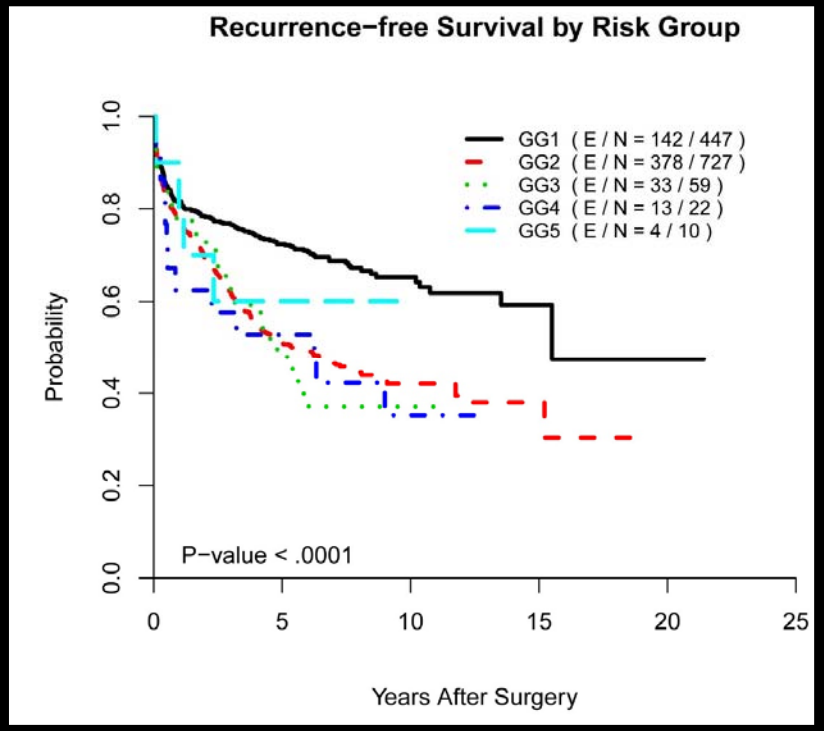
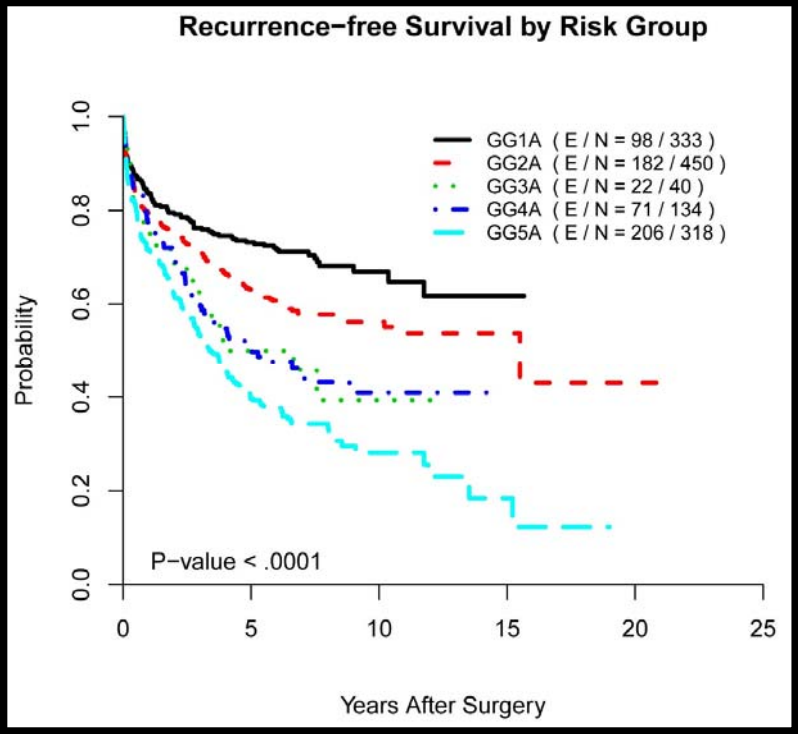


Am J Surg Pathol 2016; 40: 1439-56

Current Grade Groups
From ISUP 2016



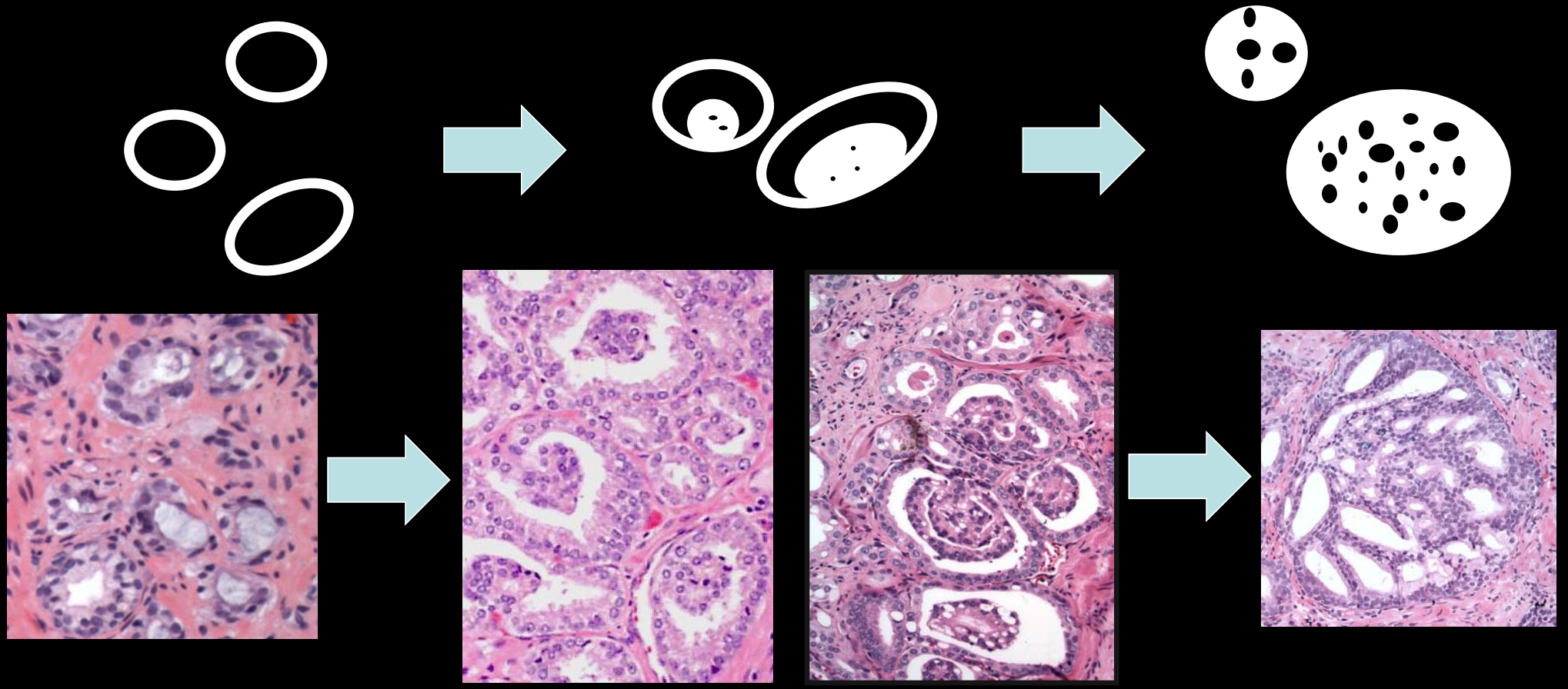
Modified Grade Groups
From Canary 2018



Unpublished

Canary Phase 3: Cribriform Definition

Cribriform?



Mod Pathol 2019;32:139-146

ARTICLE

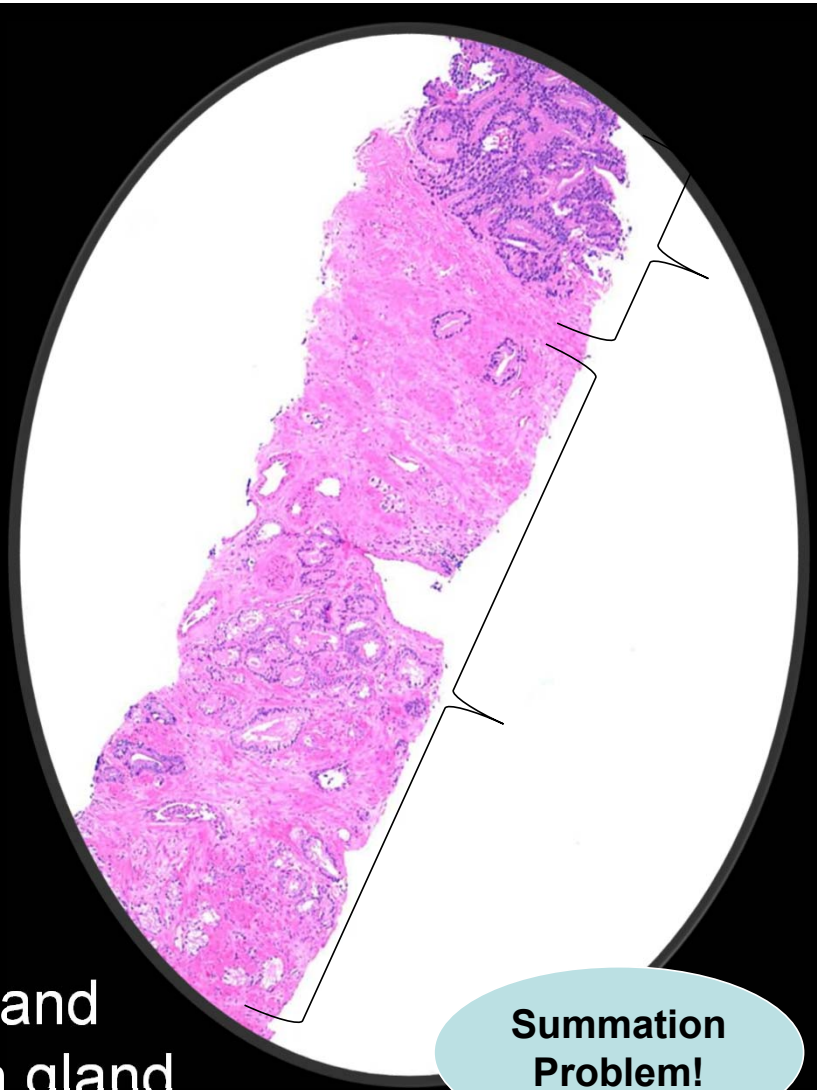
Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis

Eva Hollemans[1] · Esther I. Verhoef[1] · Chris H. Bangma[2] · John Rietbergen[3] · Jozien Helleman[2] · Monique J. Roobol[2] · Geert J.L.H. van Leenders[1]

Received: 29 June 2018 / Revised: 22 August 2018 / Accepted: 23 August 2018

Abstract

Invasive cribriform and intraductal carcinoma are associated with adverse clinical outcome in patients with Gleason score 7 prostate cancer. It is yet unclear whether invasive cribriform and intraductal carcinoma of the prostate both have independent prognostic value, or whether field size of invasive cribriform carcinoma has impact on disease outcome. Our objective was to determine the prognostic impact of intraductal and invasive cribriform prostate cancer histological subtypes in radical prostatectomies. We reviewed 420 prostatectomy specimens with ISUP grade 2 prostate cancer, assessed the percentages of Gleason grade 4 and tertiary 5, and performed immunohistochemistry for basal cells to discriminate intraductal from invasive cribriform growth. Small and large invasive cribriform fields were distinguished based on a diameter of at least twice the size of adjacent pre-existent normal glands. Clinicopathological parameters and biochemical recurrence-free survival were used as endpoints. Cribriform architecture was observed in 228 (54.3%) men, 103 (24.5%) of



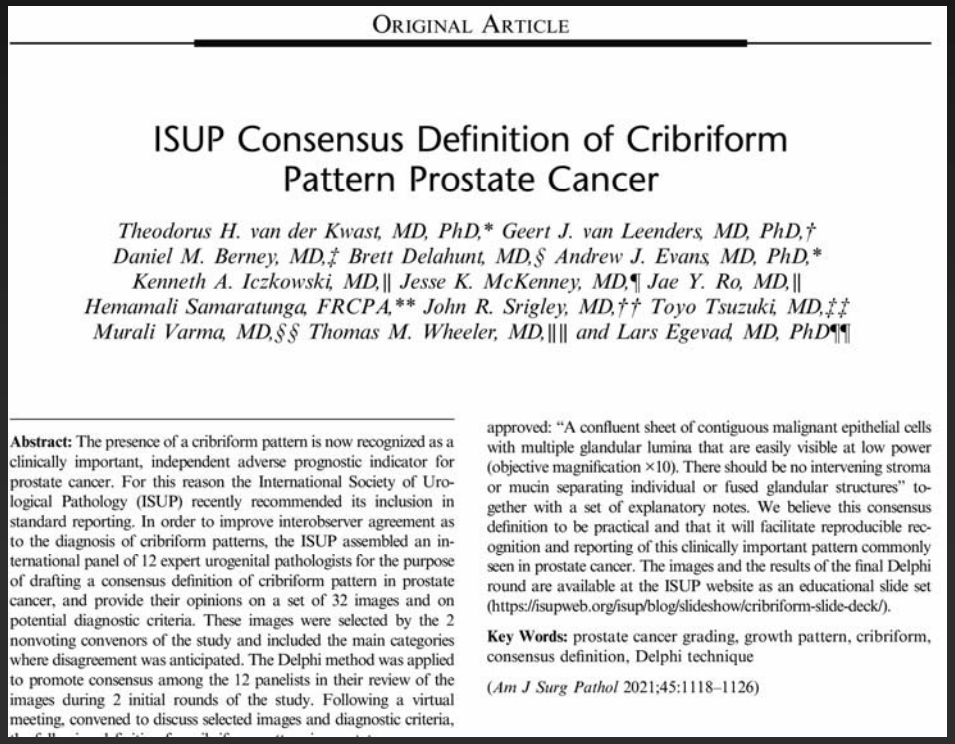
Definition of “large cribriform”?

- 12 luminal spaces
- Exceeding size of average benign gland
- At least twice size of average benign gland

Summation Problem!

If cribriform size is so important…

What is the optimal method to define “large” cribriform?



ORIGINAL ARTICLE

ISUP Consensus Definition of Cribriform Pattern Prostate Cancer

Theodorus H. van der Kwast, MD, PhD, Geert J. van Leenders, MD, PhD,† Daniel M. Berney, MD,‡ Brett Delahunt, MD,§ Andrew J. Evans, MD, PhD,* Kenneth A. Iczkowski, MD,‖ Jesse K. McKenney, MD,¶ Jae Y. Ro, MD,‖ Hemamali Samaratunga, FRCPA,** John R. Srigley, MD,†† Toyo Tsuzuki, MD,‡‡ Murali Varma, MD,§§ Thomas M. Wheeler, MD,‖‖ and Lars Egevad, MD, PhD¶¶*

Abstract: The presence of a cribriform pattern is now recognized as a clinically important, independent adverse prognostic indicator for prostate cancer. For this reason the International Society of Urological Pathology (ISUP) recently recommended its inclusion in standard reporting. In order to improve interobserver agreement as to the diagnosis of cribriform patterns, the ISUP assembled an international panel of 12 expert urogenital pathologists for the purpose of drafting a consensus definition of cribriform pattern in prostate cancer, and provide their opinions on a set of 32 images and on potential diagnostic criteria. These images were selected by the 2 nonvoting convenors of the study and included the main categories where disagreement was anticipated. The Delphi method was applied to promote consensus among the 12 panelists in their review of the images during 2 initial rounds of the study. Following a virtual meeting, convened to discuss selected images and diagnostic criteria, approved: “A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification ×10). There should be no intervening stroma or mucin separating individual or fused glandular structures” together with a set of explanatory notes. We believe this consensus definition to be practical and that it will facilitate reproducible recognition and reporting of this clinically important pattern commonly seen in prostate cancer. The images and the results of the final Delphi round are available at the ISUP website as an educational slide set (https://isupweb.org/isup/blog/slideshow/cribriform-slide-deck/).

Key Words: prostate cancer grading, growth pattern, cribriform, consensus definition, Delphi technique

(*Am J Surg Pathol* 2021;45:1118–1126)

Am J Cancer Res 2021;11(8):3990-4001
www.ajcr.us /ISSN:2156-6976/ajcr0137228

Original Article

Diagnosis of “cribriform” prostatic adenocarcinoma: an interobserver reproducibility study among urologic pathologists with recommendations

Rajal B Shah[1], Qi Cai[1], Manju Aron[2], Daniel M Berney[3], John C Cheville[4], Fang-Ming Deng[5], Jonathan Epstein[6], Samson W Fine[7], Elizabeth M Genega[8], Michelle S Hirsch[9], Peter A Humphrey[10], Jennifer Gordetsky[11], Glen Kristiansen[12], Lakshmi P Kunju[13], Cristina Magi-Galluzzi[14], Nilesh Gupta[15], George J Netto[14], Adeboye O Osunkoya[16], Brian D Robinson[17], Kiril Trpkov[18], Lawrence D True[19], Patricia Troncoso[20], Murali Varma[21], Thomas Wheeler[22], Sean R Williamson[23], Angela Wu[13], Ming Zhou[8]

[1]Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, TX, USA; [2]Department of Pathology, University of Southern California, Los Angeles, CA, USA; [3]Department of Cellular Pathology, Bartshealth NHS Trust and Barts Cancer Institute, Queen Mary University of London, United Kingdom; [4]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; [5]Department of Pathology, New York University Medical Center, New York, NY, USA; [6]Department of Pathology, Urology, Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA; [7]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]Department of Pathology, Tufts Medical Center, Boston, MA, USA; [9]Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; [10]Department of Pathology, Yale School of Medicine, New Haven, CT, USA; [11]Department of Pathology, Microbiology and Immunology, Urology, Vanderbilt University Medical Center, Nashville, TN, USA; [12]Institute of Pathology of The University Hospital Bonn, Bonn, Germany; [13]Department of Pathology at Michigan Medicine, University of Michigan Medical School, Ann Arbor, MI, USA; [14]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA; [15]Department of Pathology, Henry Ford Health System, Detroit, MI, USA; [16]Department of Pathology and Urology,

Training Cohort for Cribriform Size

Histologic Grading of Prostatic Adenocarcinoma Can Be Further Optimized

Analysis of the Relative Prognostic Strength of Individual Architectural Patterns in 1275 Patients From the Canary Retrospective Cohort

Jesse K. McKenney, MD, Wei Wei, MS,† Sarah Hawley, MS,‡ Heidi Auman, PhD,‡ Lisa F. Newcomb, PhD,§‖ Hilary D. Boyer, BSc,§ Ladan Fazli, MD,¶ Jeff Simko, MD, PhD,# Antonio Hurtado-Coll, MD,¶ Dean A. Troyer, MD, PhD,** Maria S. Tretiakova, MD, PhD,‖ Funda Vakar-Lopez, MD,‖ Peter R. Carroll, MD, MPH,# Matthew R. Cooperberg, MD, MPH,# Martin E. Gleave, MD,¶ Raymond S. Lance, MD,** Dan W. Lin, MD,§‖ Peter S. Nelson, MD,§‖ Ian M. Thompson, MD,†† Lawrence D. True, MD,‖ Ziding Feng, PhD,† and James D. Brooks, MD‡‡*

Abstract: Histologic grading remains the gold standard for prognosis in prostate cancer, and assessment of Gleason score plays a critical role in active surveillance management. We sought to optimize the prognostic stratification of grading and developed a method of recording and studying individual architectural patterns by light microscopic evaluation that is independent of standard Gleason grade. Some of the evaluated patterns are not assessed by current Gleason grading (eg, reactive stromal response). Individual histologic patterns were correlated with recurrence-free survival in a retrospective post-radical prostatectomy cohort of 1275 patients represented by the highest-grade foci of carcinoma in tissue microarrays. In univariable analysis, fibromucinous rupture with varied epithelial complexity had a significantly lower relative risk of recurrence-free survival in cases graded as 3+4 = 7. Cases having focal "poorly formed glands," which could be designated as pattern 3+4 = 7, had lower risk than cribriform patterns with either small cribriform glands or expansile cribriform growth. In separate multivariable Cox proportional hazard analyses of both Gleason score 3+3 = 6 and 3+4 = 7 carcinomas, reactive stromal patterns were associated with worse recurrence-free survival. Decision tree models demonstrate potential regrouping of architectural patterns into categories with similar risk. In summary, we argue that Gleason score assignment by current consensus guidelines are not entirely optimized for clinical use, including active surveillance. Our data suggest that focal poorly formed gland and cribriform patterns, currently classified as Gleason pattern 4, should be in separate prognostic groups, as the latter is associated with worse outcome. Patterns with extravasated mucin are likely overgraded in a subset of cases with more complex epithelial bridges, whereas stromogenic cancers have a worse outcome than conveyed by Gleason grade alone. These findings serve as a foundation to facilitate optimization of histologic grading and strongly support incorporating reactive stroma into routine assessment.

Key Words: prostate, adenocarcinoma, Gleason, grade, cribriform, stromal reaction, mucin, stromogenic

(*Am J Surg Pathol* 2016;40:1439–1456)

From the *Cleveland Clinic, Cleveland, OH; †University of Texas MD Anderson Cancer Center, Houston; ‡‡University of Texas Health

REVIEW ARTICLE

A Model for the Design and Construction of a Resource for the Validation of Prognostic Prostate Cancer Biomarkers: The Canary Prostate Cancer Tissue Microarray

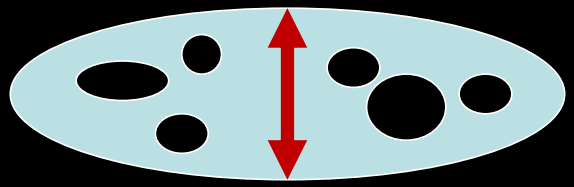
Sarah Hawley, MS, Ladan Fazli, MD,† Jesse K. McKenney, MD,‡ Jeff Simko, MD, PhD,§‖¶ Dean Troyer, MD,#**†† Marlo Nicolas, MD,†† Lisa F. Newcomb, PhD,‡‡ Janet E. Cowan, MA,§ Luis Crouch, MS,§§ Michelle Ferrari, RN,‖‖ Javier Hernandez, MD,¶¶ Antonio Hurtado-Coll, MD,† Kyle Kuchinsky, BS,§ Janet Liew, BS,† Rosario Mendez-Meza, HT (ASCP),†† Elizabeth Smith, MS,#** Imelda Tenggara, MD,§ Xiaotun Zhang, MD,‡‡ Peter R. Carroll, MD, MPH,‖¶ June M. Chan, ScD,‖¶## Martin Gleave, MD,† Raymond Lance, MD,*** Daniel W. Lin, MD,‡‡ Peter S. Nelson, MD,††† Ian M. Thompson, MD,¶¶ Ziding Feng, PhD,‡‡‡ Lawrence D. True, MD,§§§ and James D. Brooks, MD‖‖*

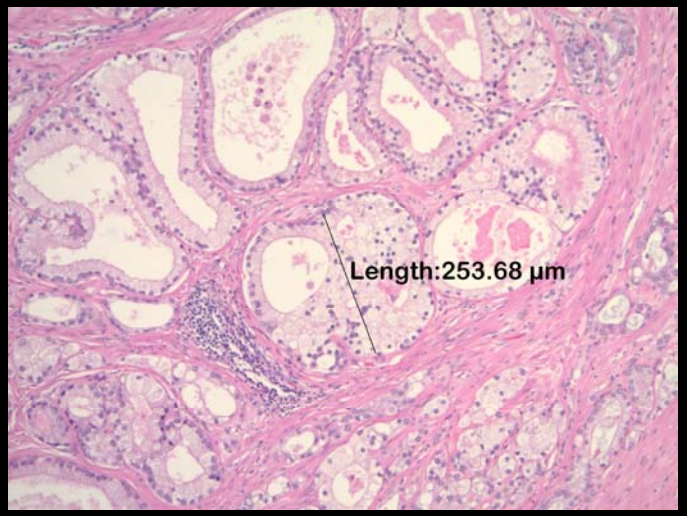
Abstract: Tissue microarrays (TMAs) provide unique resources for rapid evaluation and validation of tissue biomarkers. The Canary Foundation Retrospective Prostate Tissue Microarray Resource used a rigorous statistical design, quota sampling, a variation of the case-

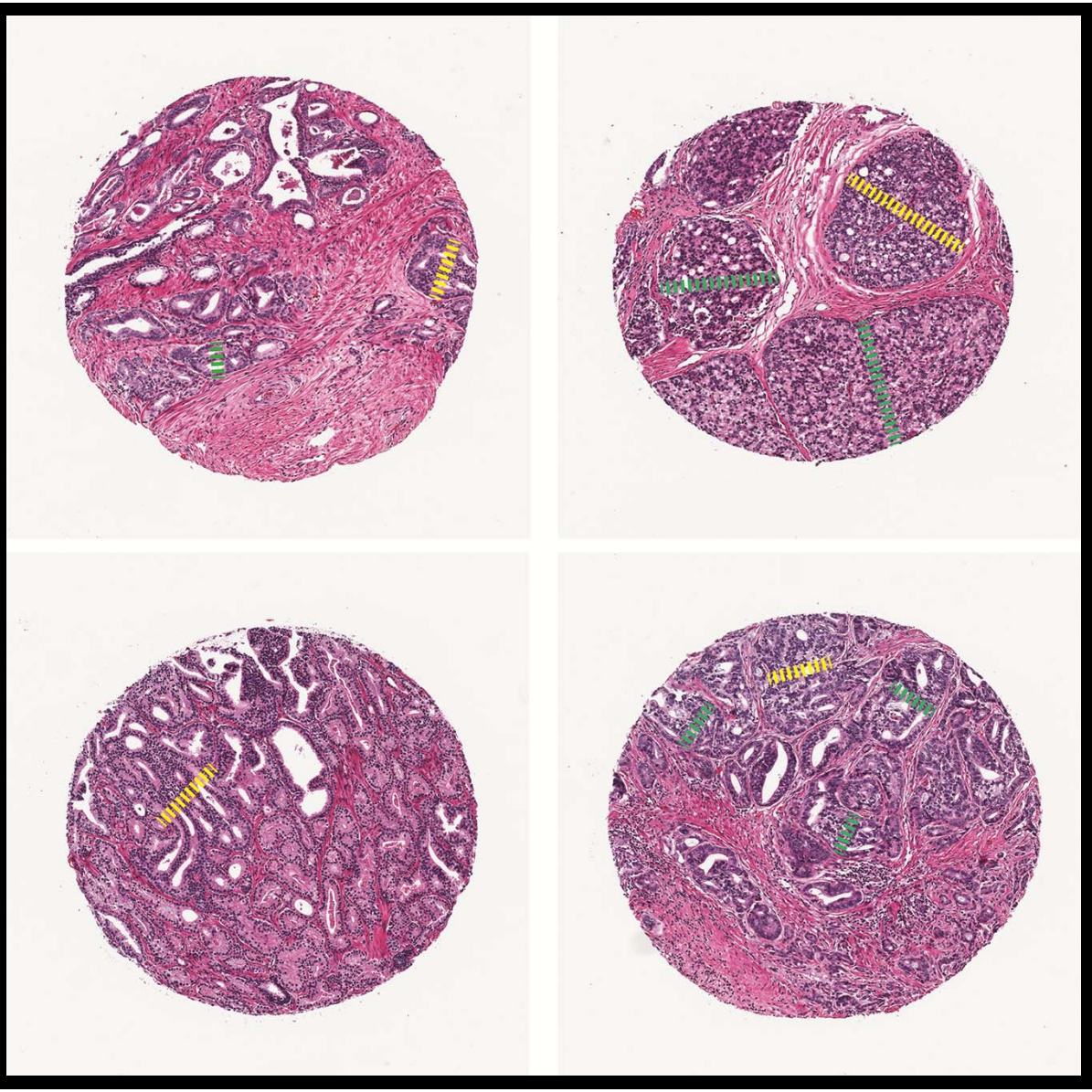
Key Words: prostate cancer, prognosis, tissue microarray, quota sampling

(*Adv Anat Pathol* 2013;20:39–44)

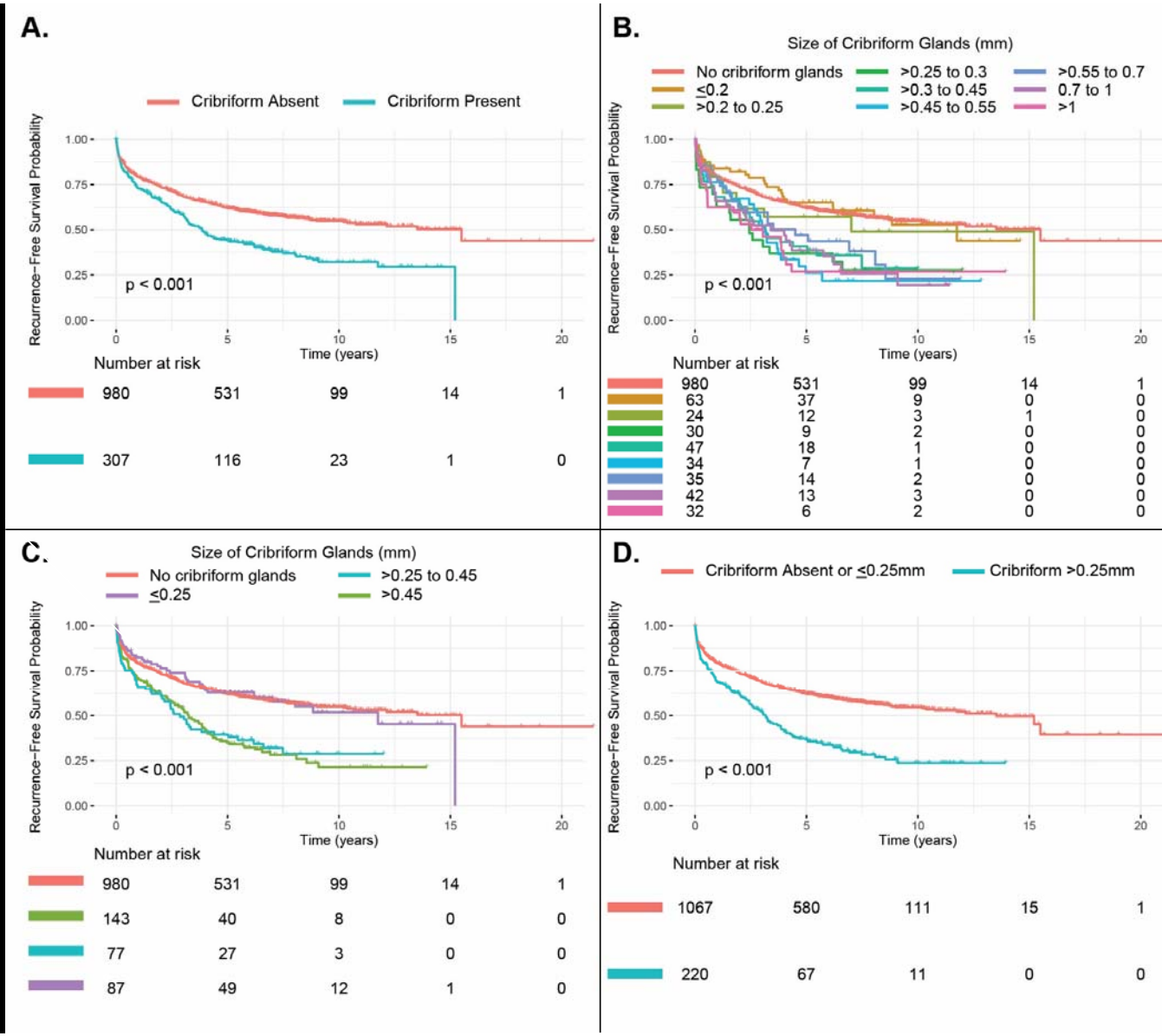
Measuring Cribriform Size







Training Cohort



Human Pathology (2014) xx, xxx–xxx

ELSEVIER

Human PATHOLOGY

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Original contribution

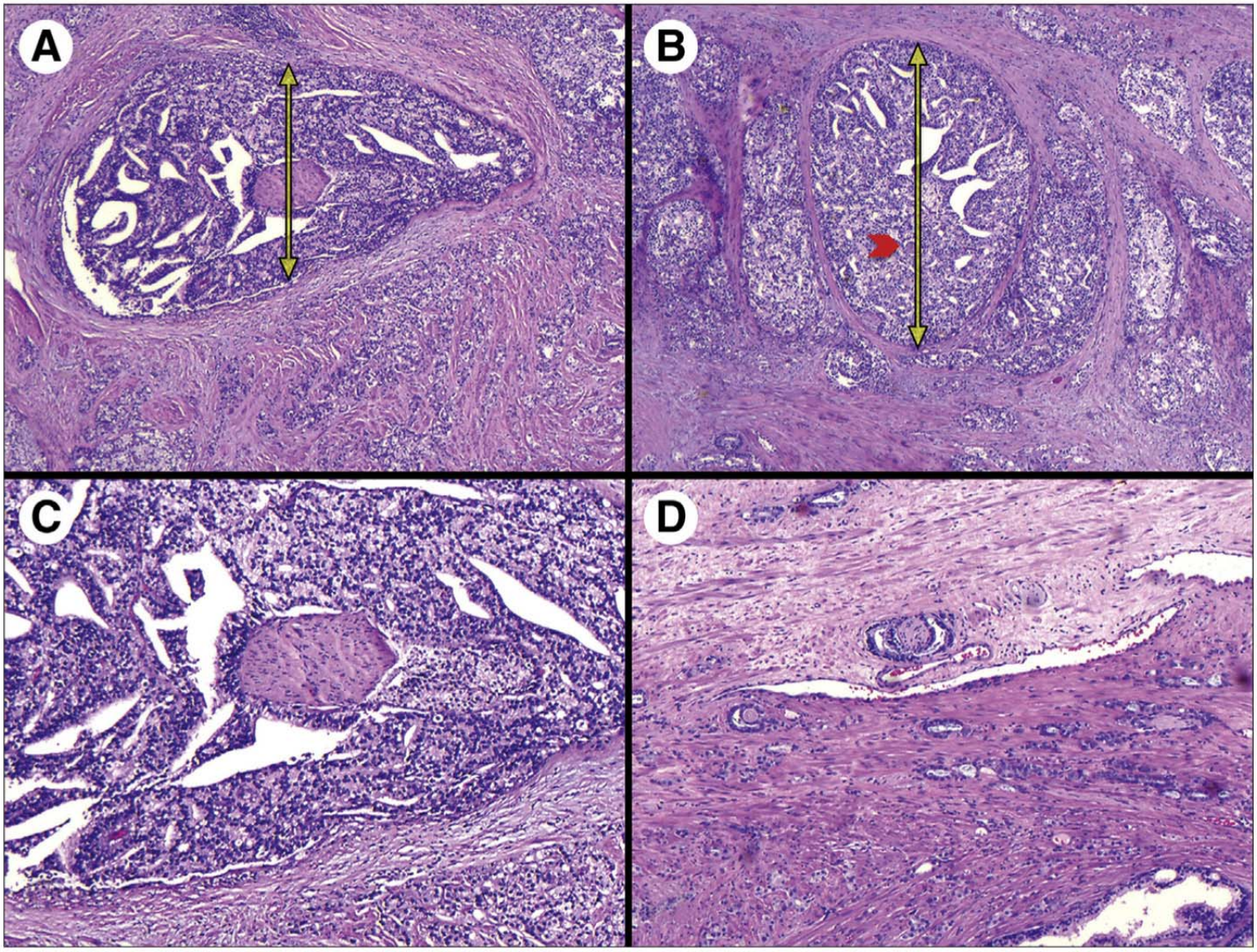
Biological correlates of prostate cancer perineural invasion diameter☆,☆☆,★

Adriana Olar MD[a,1], Dandan He MD[a], Diego Florentin MD[b], Yi Ding PhD[c], Thomas Wheeler MD[a], Gustavo Ayala MD[c,*]

[a]*Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX 77030*
[b]*Department of Internal Medicine, Sinai-Grace Hospital and Wayne State University, Detroit, MI 48235*
[c]*Department of Pathology and Laboratory Medicine, The University of Texas Health Sciences Center at Houston, Medical School, Houston, TX 77030*

Received 23 October 2013; revised 6 February 2014; accepted 14 February 2014

Strongest predictor of outcome after RP
Correlates with biologic markers of aggressiveness



>0.25 mm

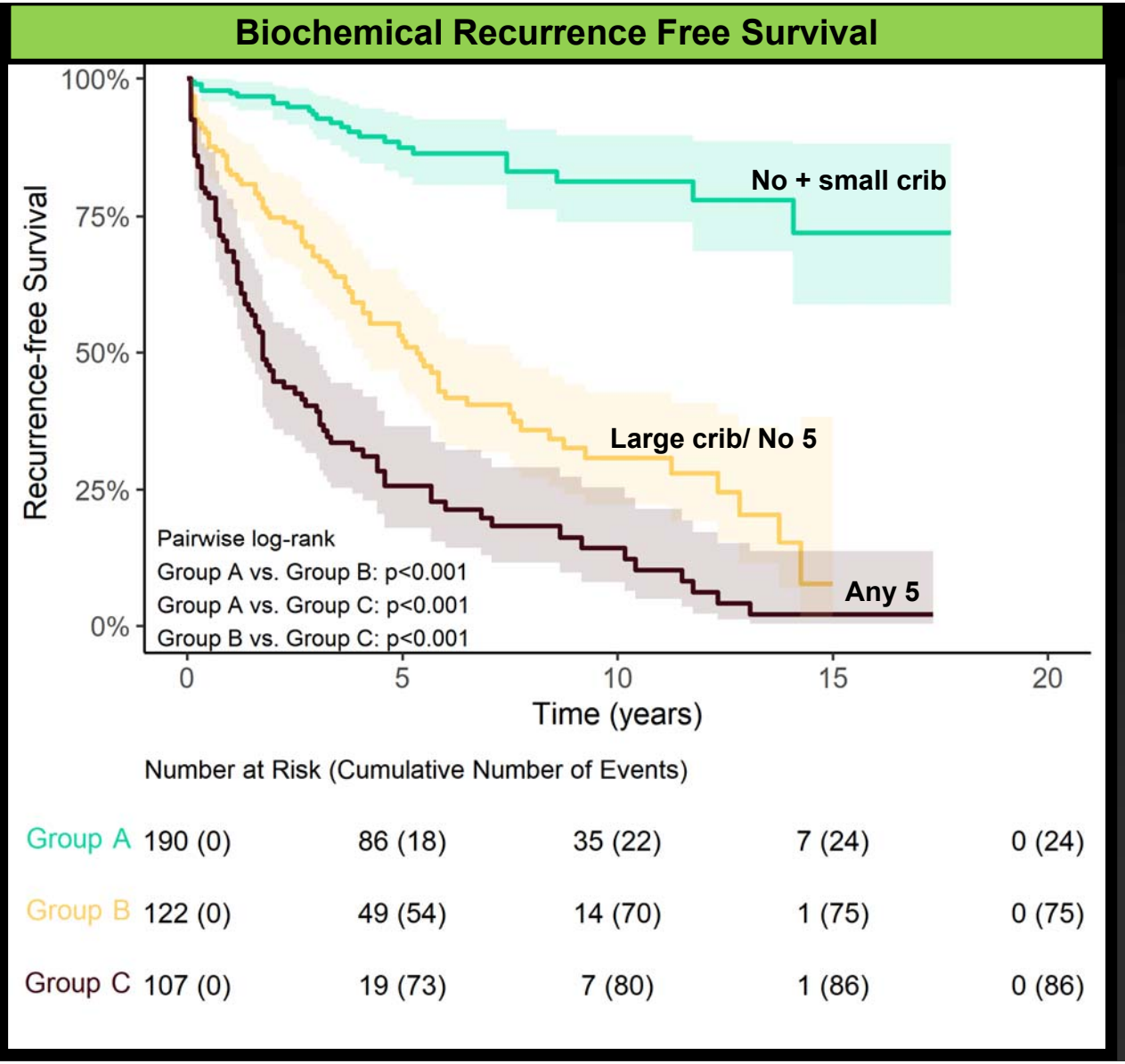
Validation Cohort for Cribriform Size

- Cleveland Clinic RP cohort with long term follow-up
  - BCR: mean F/U 6.4 years (n=419)
  - Metastatic Disease: mean F/U 12.3 years
  - Prostate Cancer Death: mean F/U 14.6 years

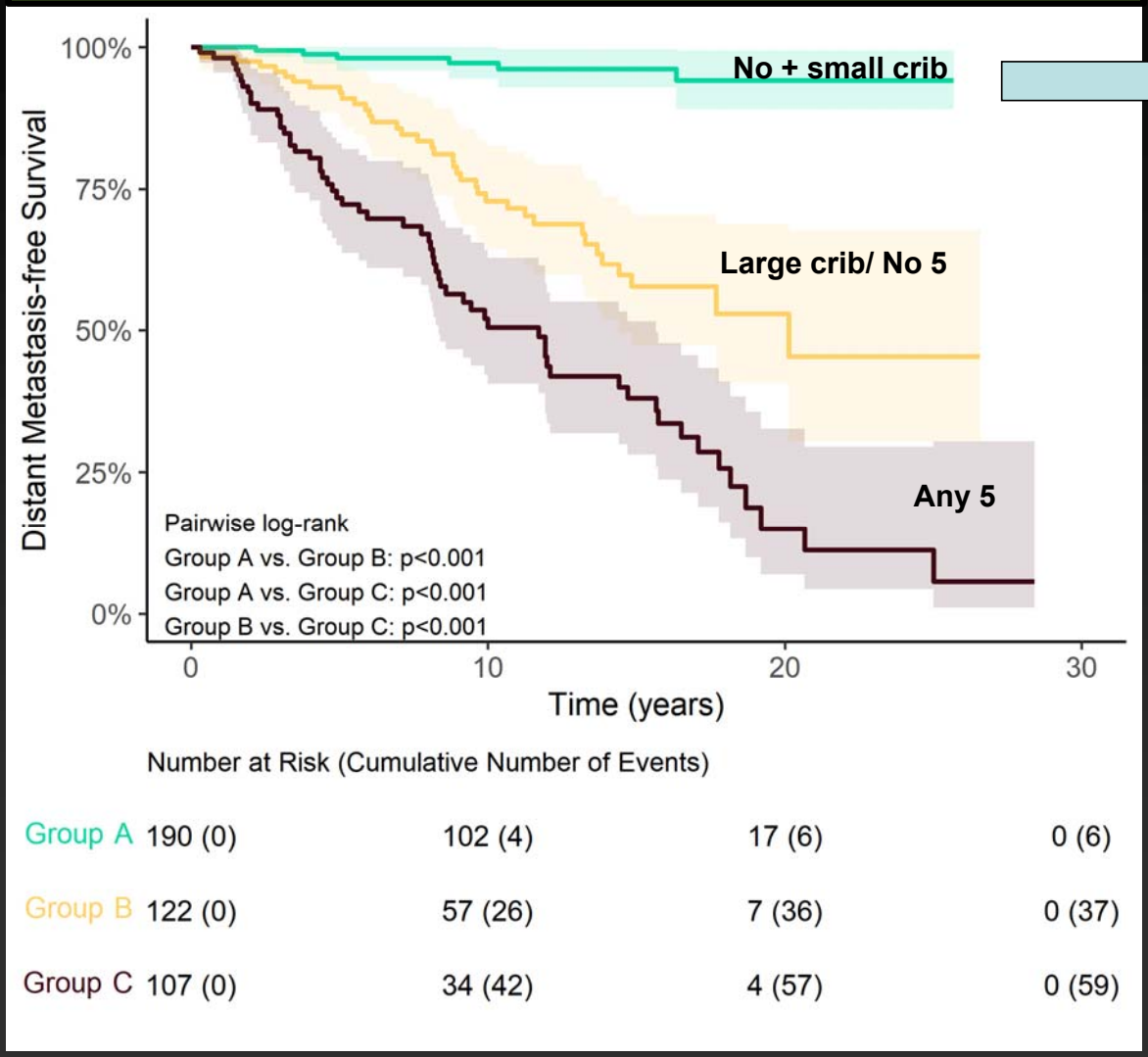
- Group A:
  - YES
    - No cribriform
    - Small cribriform (<0.25 mm)
  - NO
    - Large cribriform
    - Conventional pattern 5

- Group B:
  - YES
    - Any large cribriform
  - NO
    - Conventional pattern 5

- Group C:
  - YES
    - Any conventional pattern 5

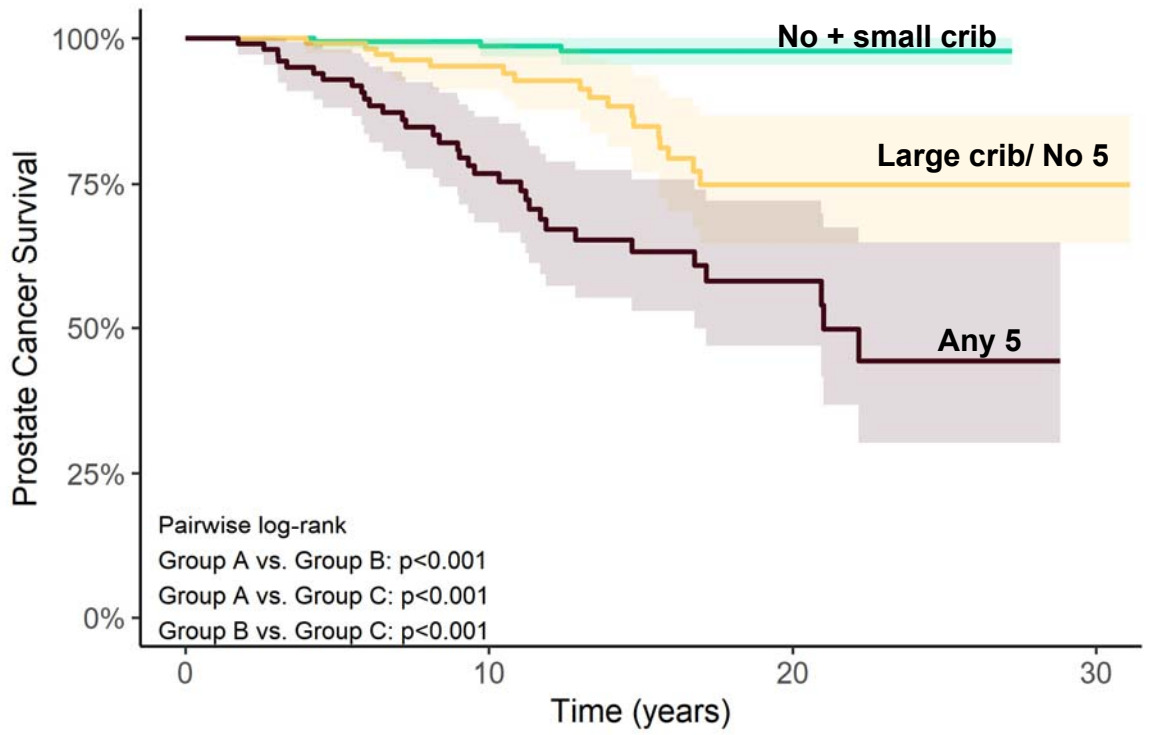


Metastasis Free Survival



Small group with mets?

Prostate Cancer Survival



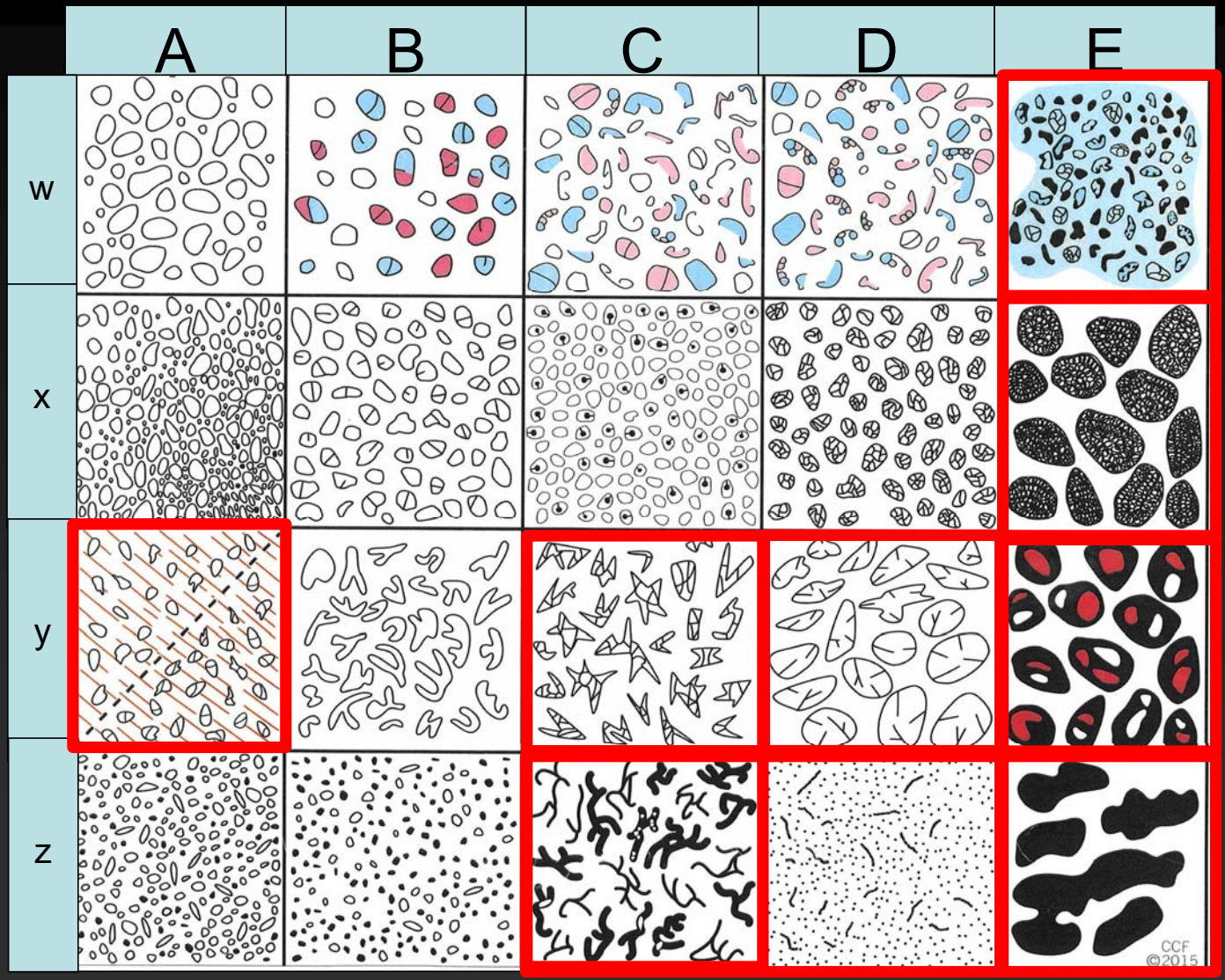
Number at Risk (Cumulative Number of Events)

Group A	190 (0)	135 (2)	29 (3)	0 (3)
Group B	122 (0)	80 (5)	16 (17)	1 (17)
Group C	107 (0)	54 (20)	14 (30)	0 (33)

Canary Phase 4: Final Model (New Unpublished Data)

Final Histologic Model After 15 Yrs of Canary?

- The aggregate data suggest a dichotomous classification for predicting metastatic potential
- Practical utility with current grading?
  - Could get complicated
  - Controversial
- Follow the original simplified Wilms tumor classification nomenclature proposed by Bruce Beckwith?
  - Favorable Histology vs. Unfavorable Histology?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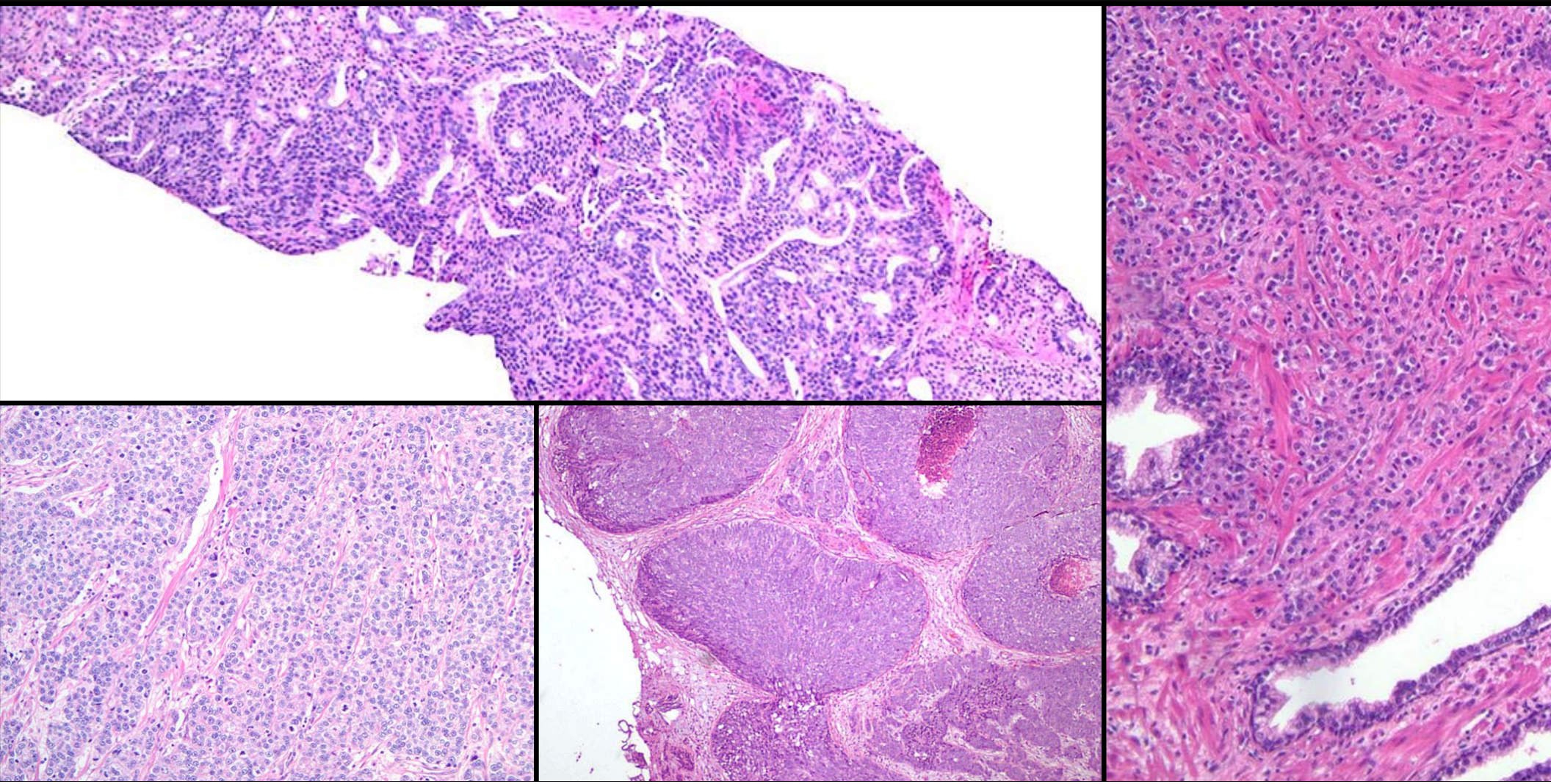
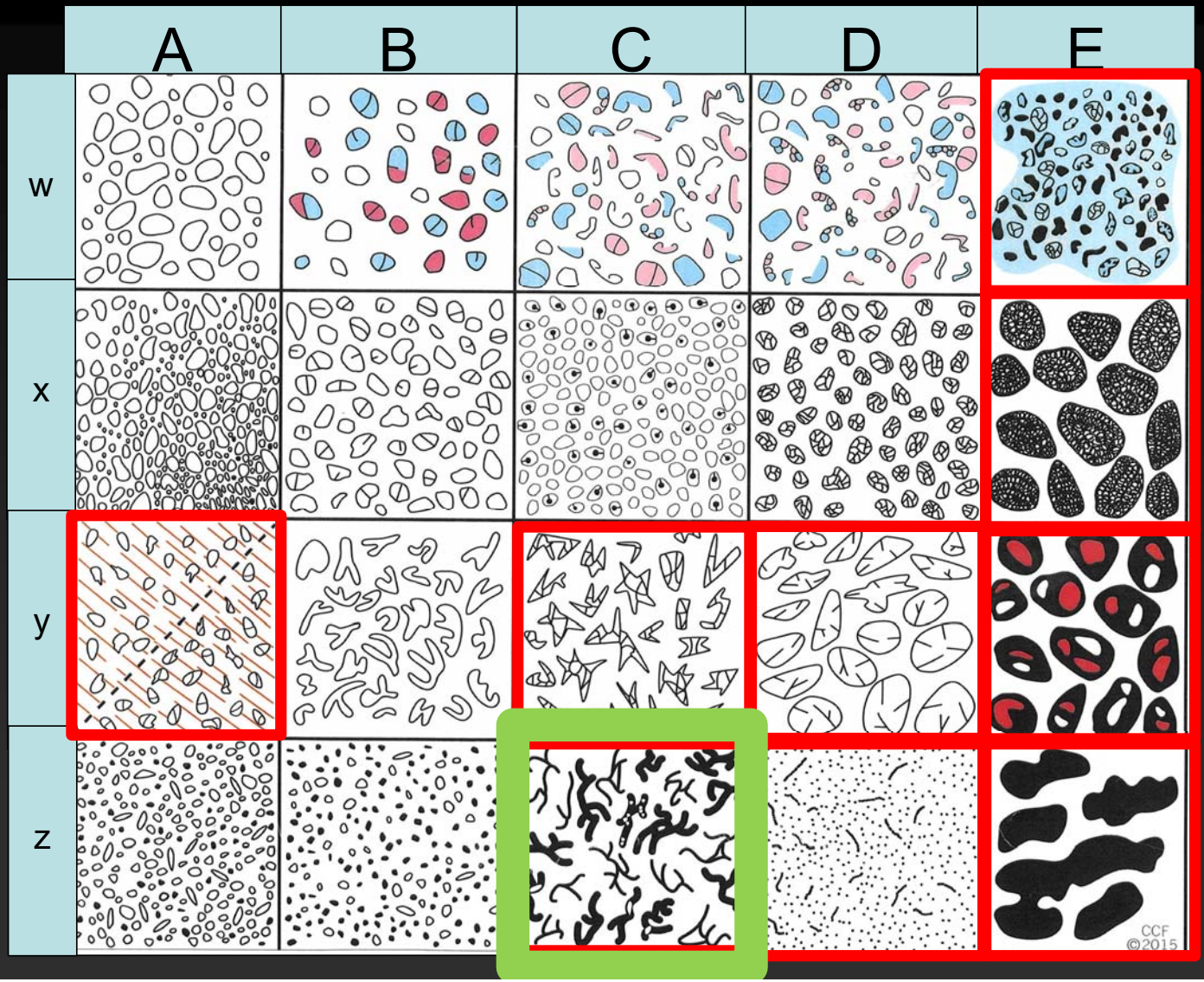
Unfavorable Histology

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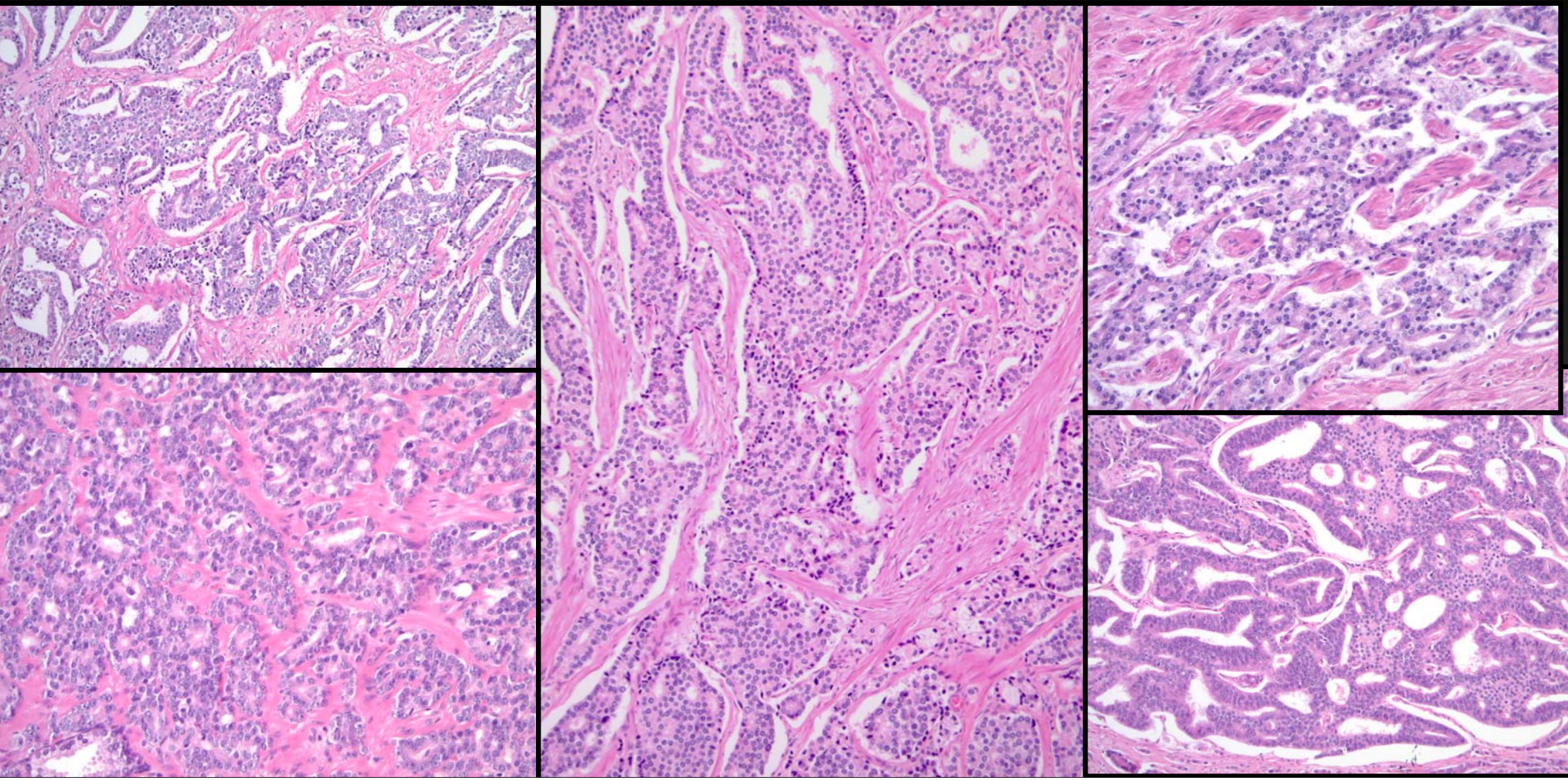
Unfavorable Histology



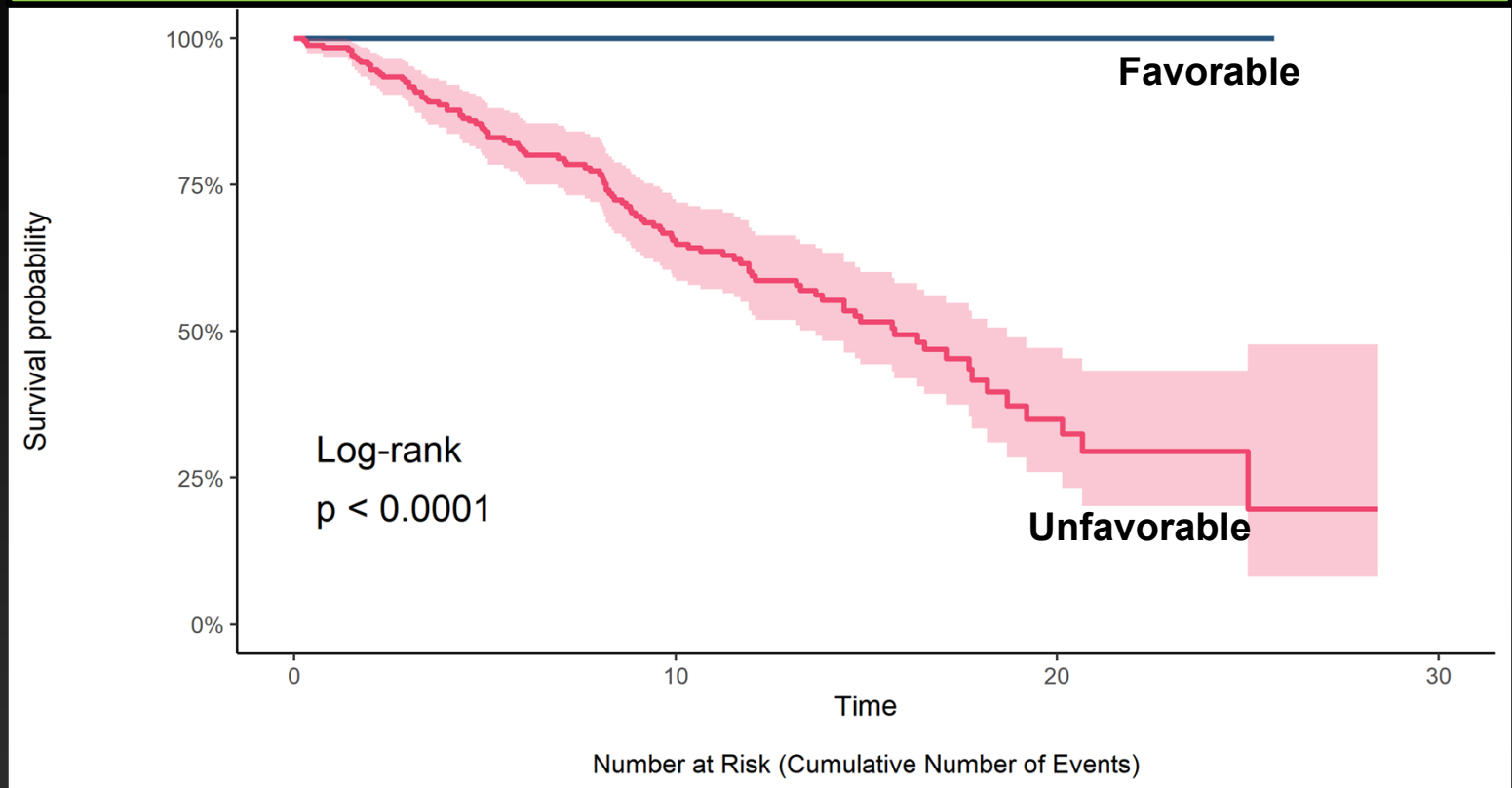
Total	Favorable	Unfavorable
n	161	258

419

Grade Group	Favorable	Unfavorable
1	13 (100%)	0 (0%)
2	142 (67%)	69 (33%)
3	6 (6%)	98 (94%)
4	0 (0%)	18 (100%)
5	0 (0%)	73 (100%)

Pathologic T-stage	Favorable	Unfavorable
T2	114 (71%)	72 (28%)
T3a	46 (29%)	117 (45%)
T3b	1 (0.6%)	69 (27%)

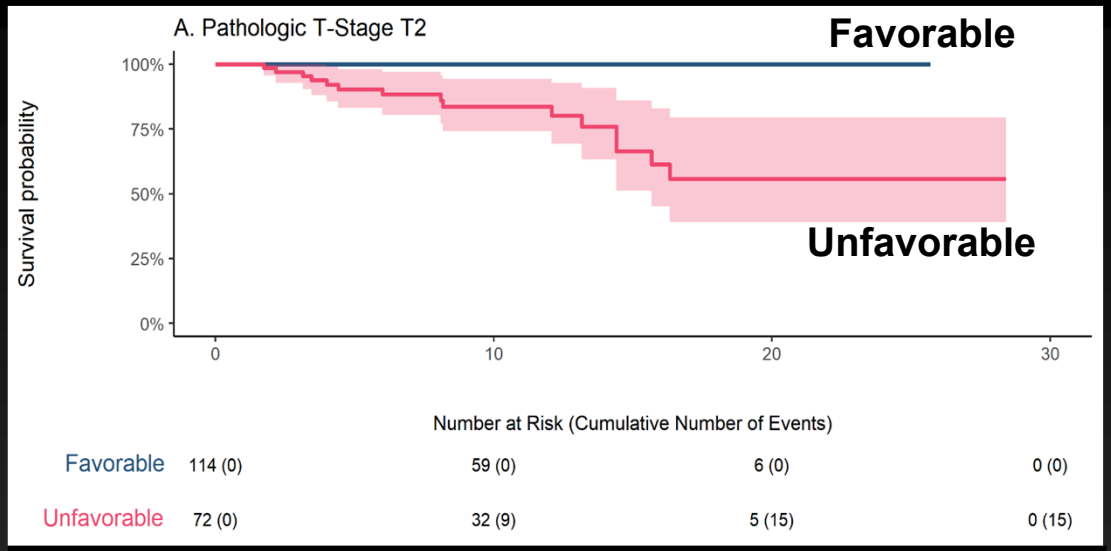
Metastasis Free Survival



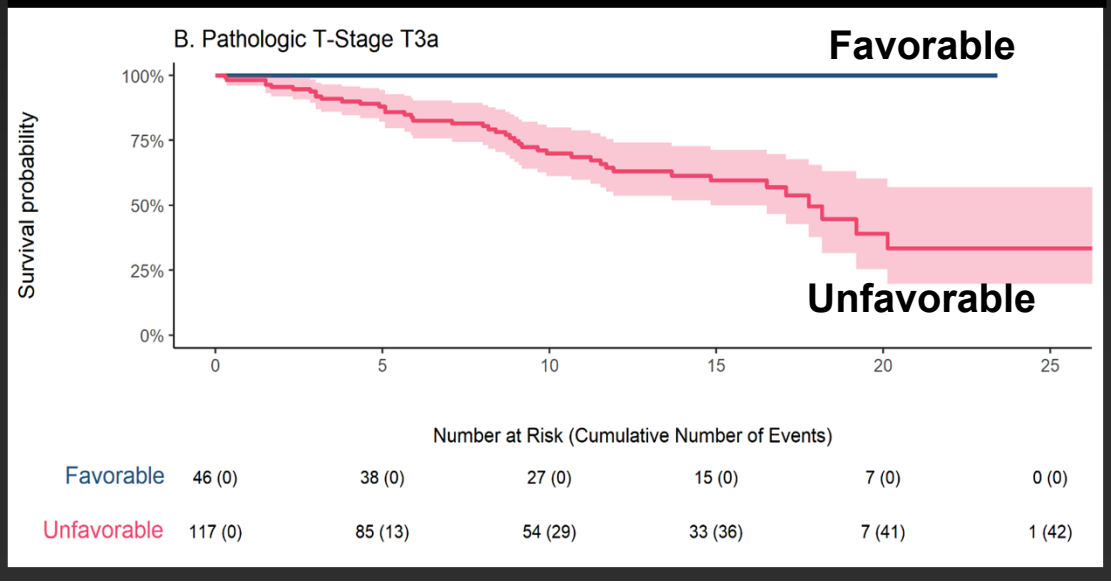
Number at Risk (Cumulative Number of Events)

Favorable	161 (0)	87 (0)	14 (0)	0 (0)
Unfavorable	258 (0)	106 (72)	14 (99)	0 (102)

Metastasis Free Survival

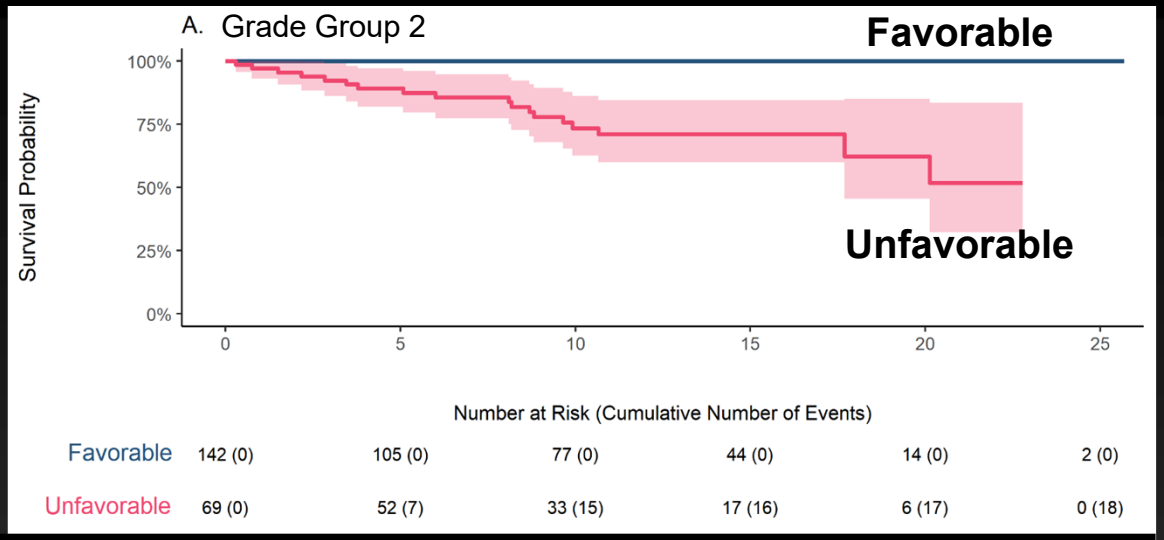


Organ confined

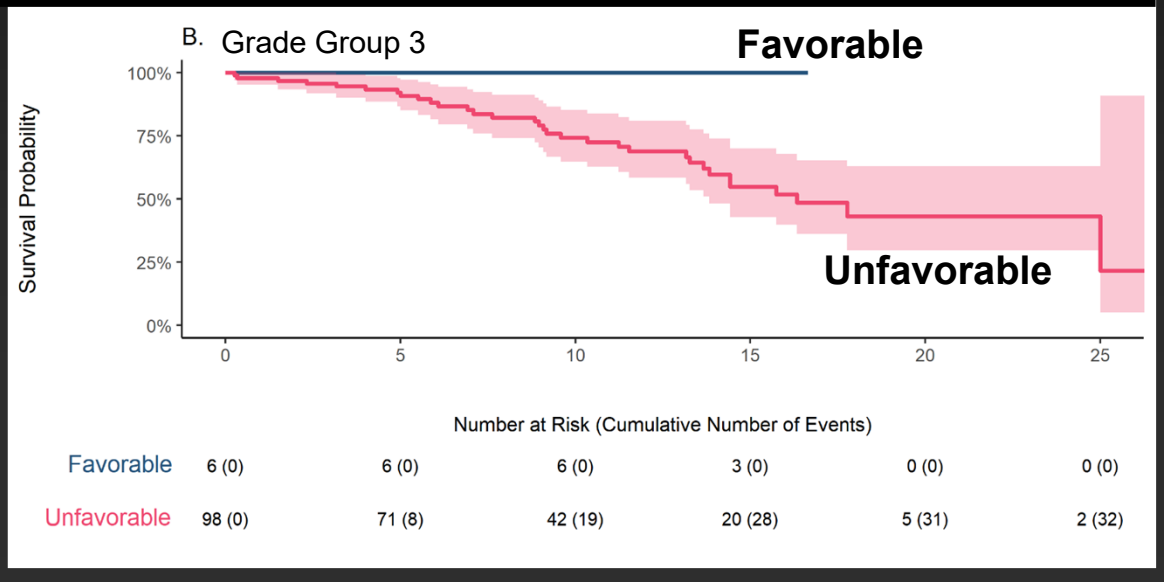


Extraprostatic extension

Metastasis Free Survival



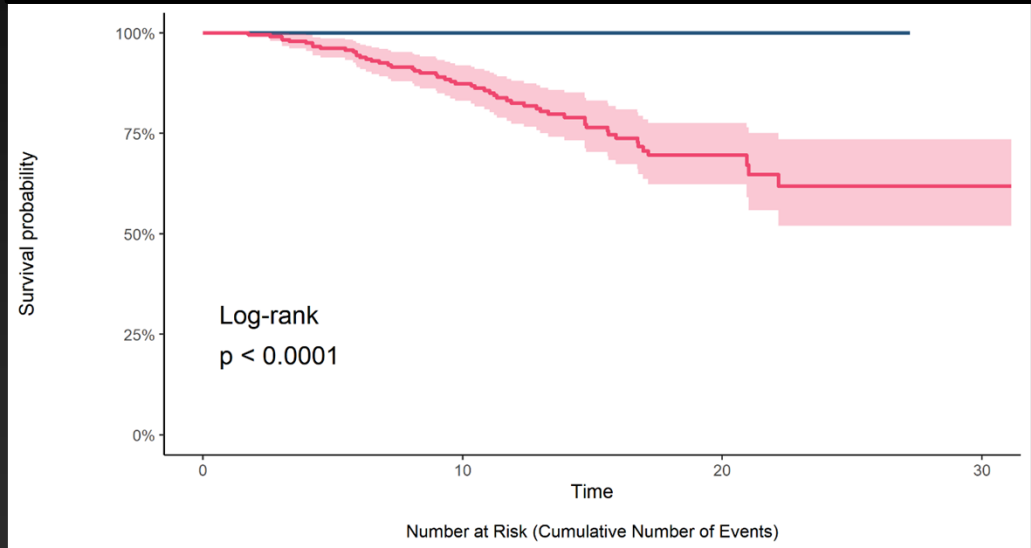
Gleason score 3+4=7



Gleason score 4+3=7

Other Outcome Endpoints

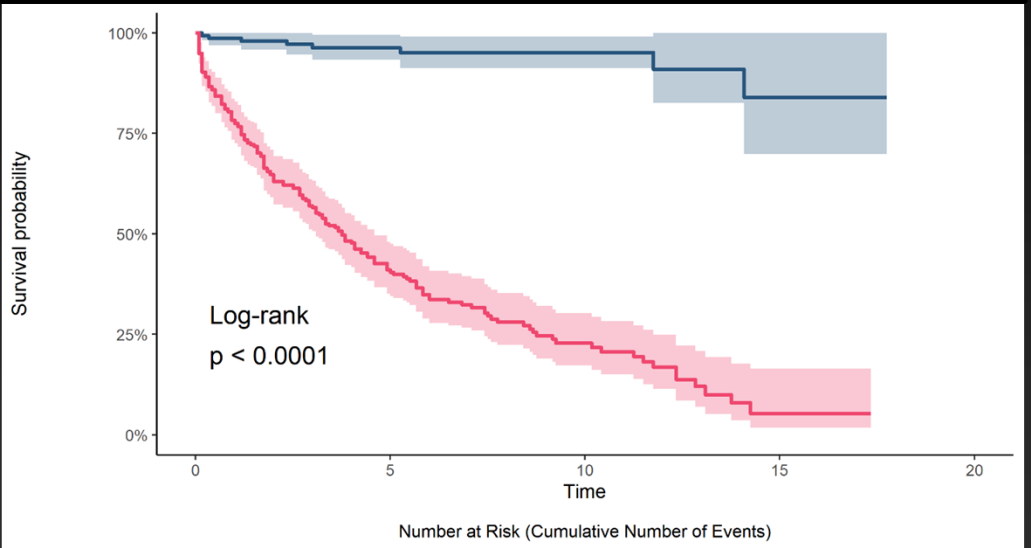
Prostate Cancer Survival



Number at Risk (Cumulative Number of Events)

Favorable	161 (0)	114 (0)	26 (0)	0 (0)
Unfavorable	258 (0)	155 (27)	33 (50)	1 (53)

Biochemical Recurrence Free Survival

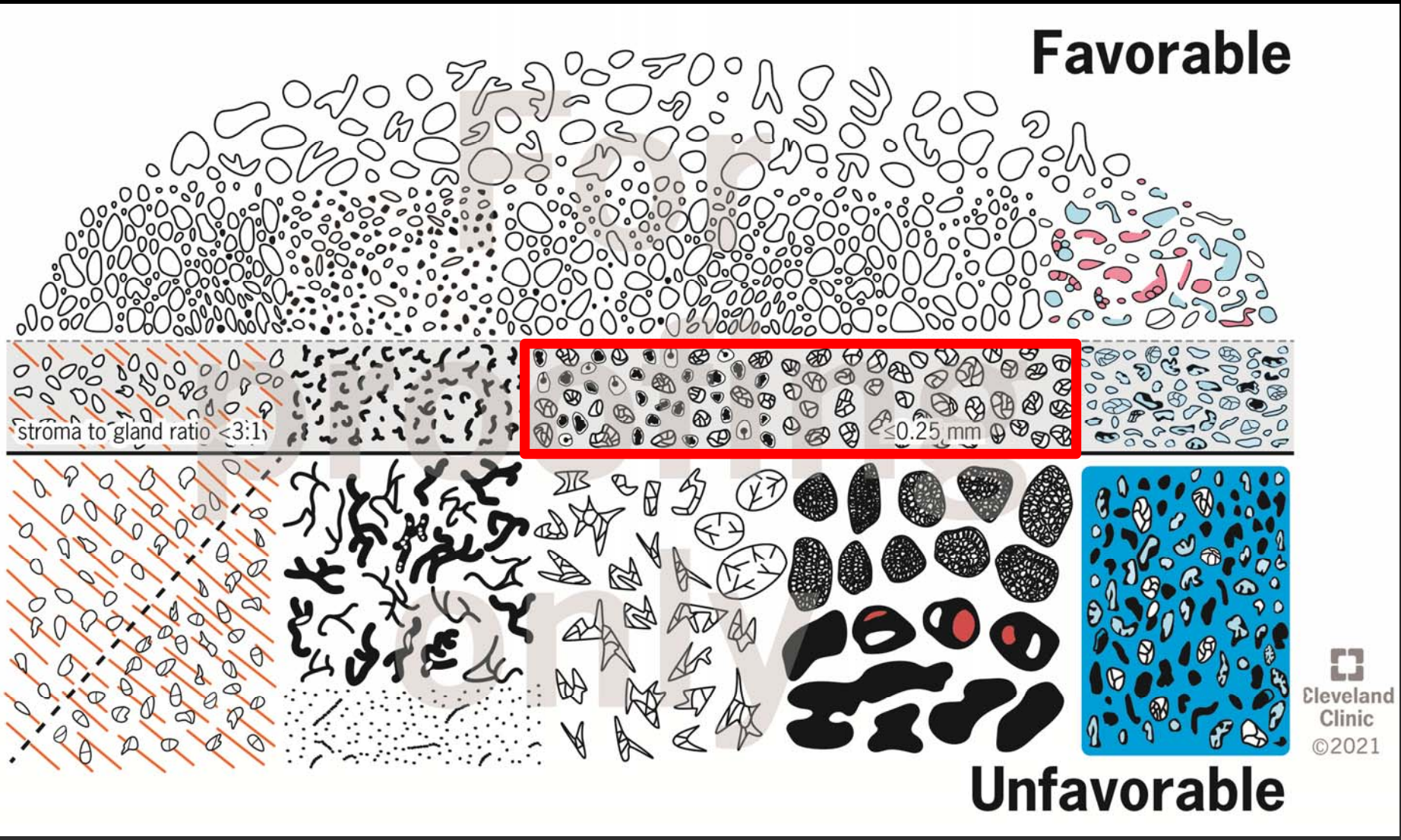


Number at Risk (Cumulative Number of Events)

Favorable	161 (0)	78 (5)	34 (6)	7 (8)	0 (8)
Unfavorable	258 (0)	76 (140)	22 (166)	2 (177)	0 (177)

Percent Unfavorable Histology by Metastasis

Percent Unfavorable	No Mets	Mets
≤10 %	45 (80%)	11 (20%)
10-24 %	27 (61%)	17 (39%)
25-49 %	48 (60%)	31 (39%)
≥50 %	36 (46%)	43 (54%)


Favorable
stroma to gland ratio <3:1
≤0.25 mm
Unfavorable
Cleveland Clinic
©2021

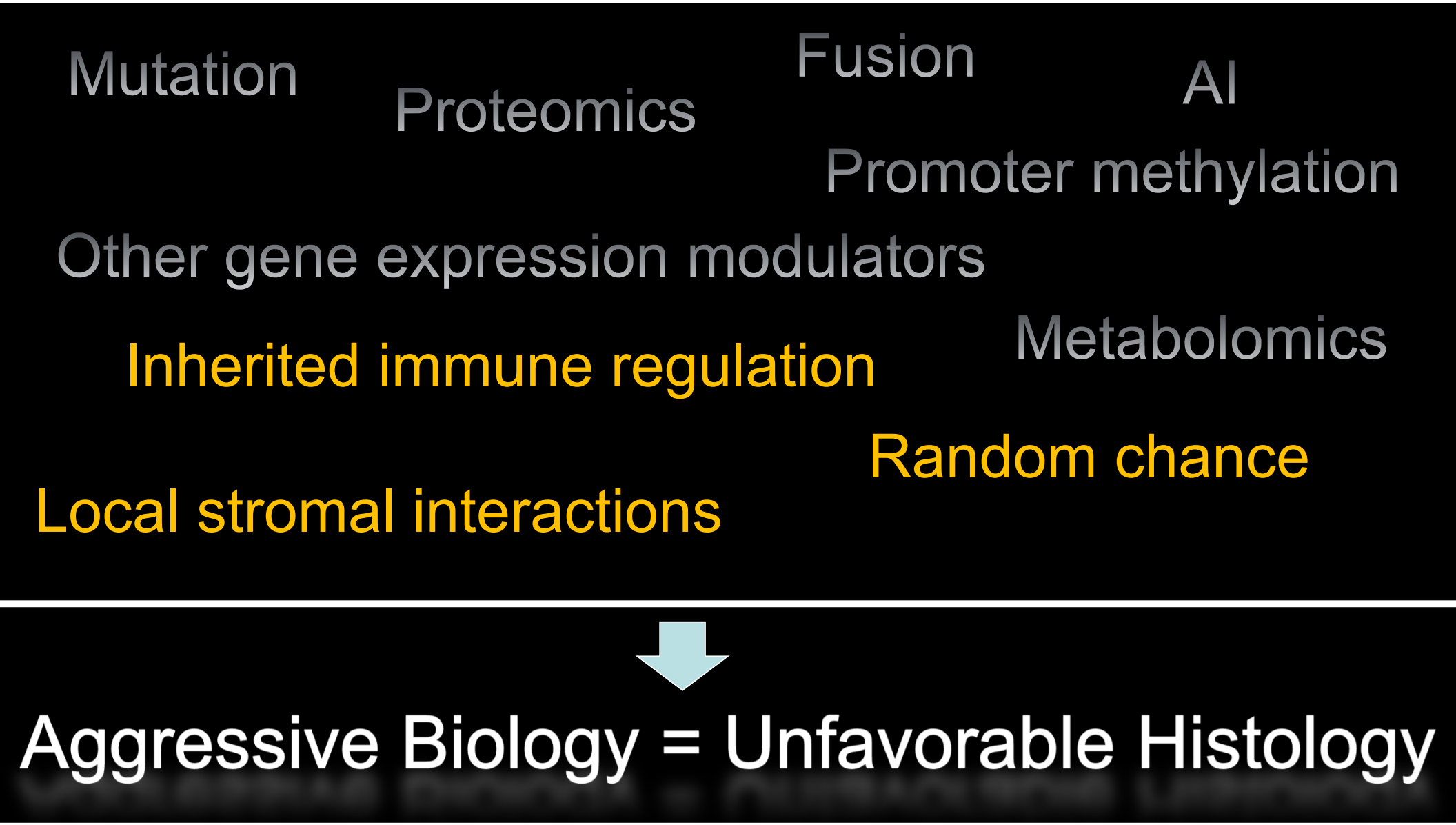
Separate Metastasis Study

- We have collected >250 patients post radical prostatectomy with pathologically proven metastatic disease
  - All have unequivocable “unfavorable histology”

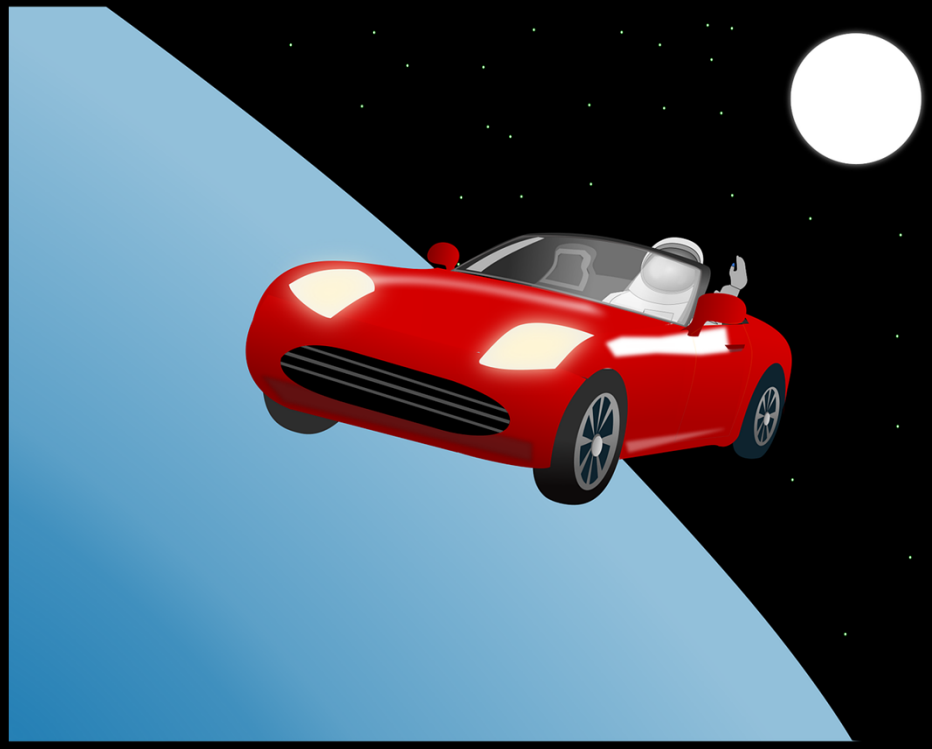
- Anecdotal experience:
  - To date… our group has never seen a metastatic prostate cancer with only “favorable histology” in the prostate
  - n > 20,000 RPs

Conclusions From Modeling Studies

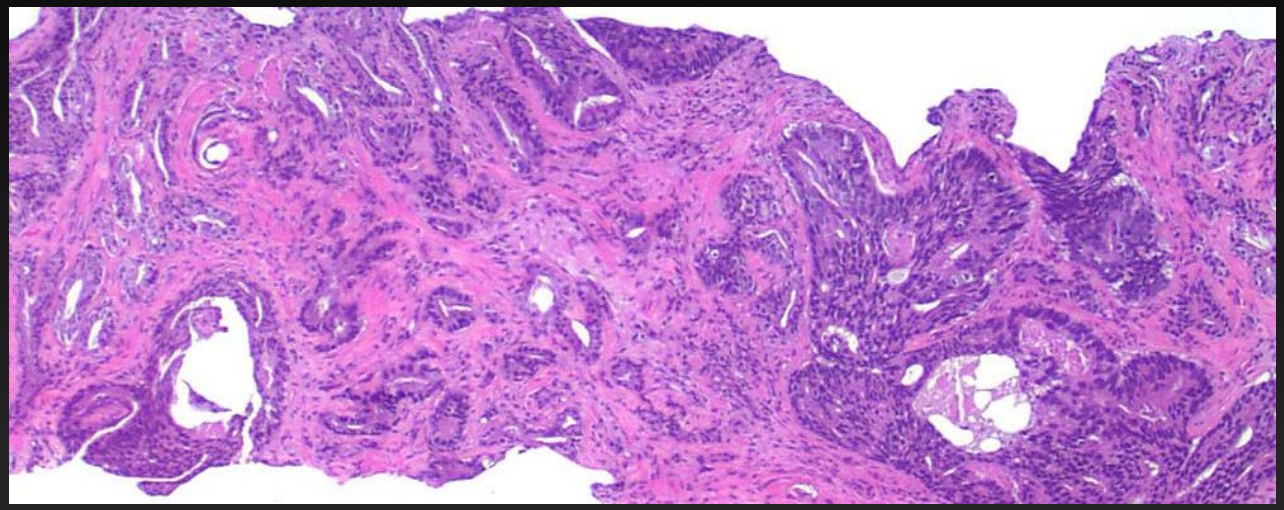
- “Unfavorable histology” at RP is associated with potential for metastatic disease
  - Majority are large cribriform (>0.25 mm) and/or conventional pattern 5
  - Sensitivity (100%) and Specificity (51%)
  - Outperforms Grade Group and AJCC stage
    - Largest impact in GG2
  - Any amount of unfavorable denotes risk
  - Gleason summation method misclassifies some cases
    - “Favorable” does not dilute the effect of “unfavorable”


Mutation
Proteomics
Fusion
AI
Promoter methylation
Other gene expression modulators
Metabolomics
Inherited immune regulation
Random chance
Local stromal interactions
Aggressive Biology = Unfavorable Histology

Phase 5: Future?



The Biopsy Problem



- Our data is based on RP specimens
  - We have assessed the entire tumor
  - Most decision making is done on biopsy specimens
    - Sampling “error”?
    - Progression over time if untreated?

The Biopsy Problem

- Needle core biopsy has poor sensitivity for detecting cribriform cancer (unfavorable histology) in RP

  – Ericson KJ, Wu SS, Lundy SD, Thomas LJ, Klein EA, McKenney JK. Diagnostic Accuracy of Prostate Biopsy for Detecting Cribriform Gleason Pattern 4 Carcinoma and Intraductal Carcinoma in Paired Radical Prostatectomy Specimens: Implications for Active Surveillance. *J Urol* 2020 ;203:311

  Cleveland Clinic, USA
  Sensitivity: 56.5%

  – Masoomian M, Downes MR, Sweet J, Cheung C, Evans AJ, Fleshner N, Maganti M, Van der Kwast T. Concordance of biopsy and prostatectomy diagnosis of intraductal and cribriform carcinoma in a prospectively collected data set. *Histopathology* 2019;74:474

  UHN, Toronto, Canada
  Sensitivity: 47.2%

  – Hollemans E, Verhoef EI, Bangma CH, Schoots I, Rietbergen J, Helleman J, Roobol MJ, van Leenders GJLH. Concordance of cribriform architecture in matched prostate cancer biopsy and radical prostatectomy specimens. *Histopathology* 2019;75:338

  Erasmus MC, Netherlands
  Sensitivity: 60%

What other adjuncts might improve the detection of unsampled unfavorable histology in the prostate at the time of biopsy?

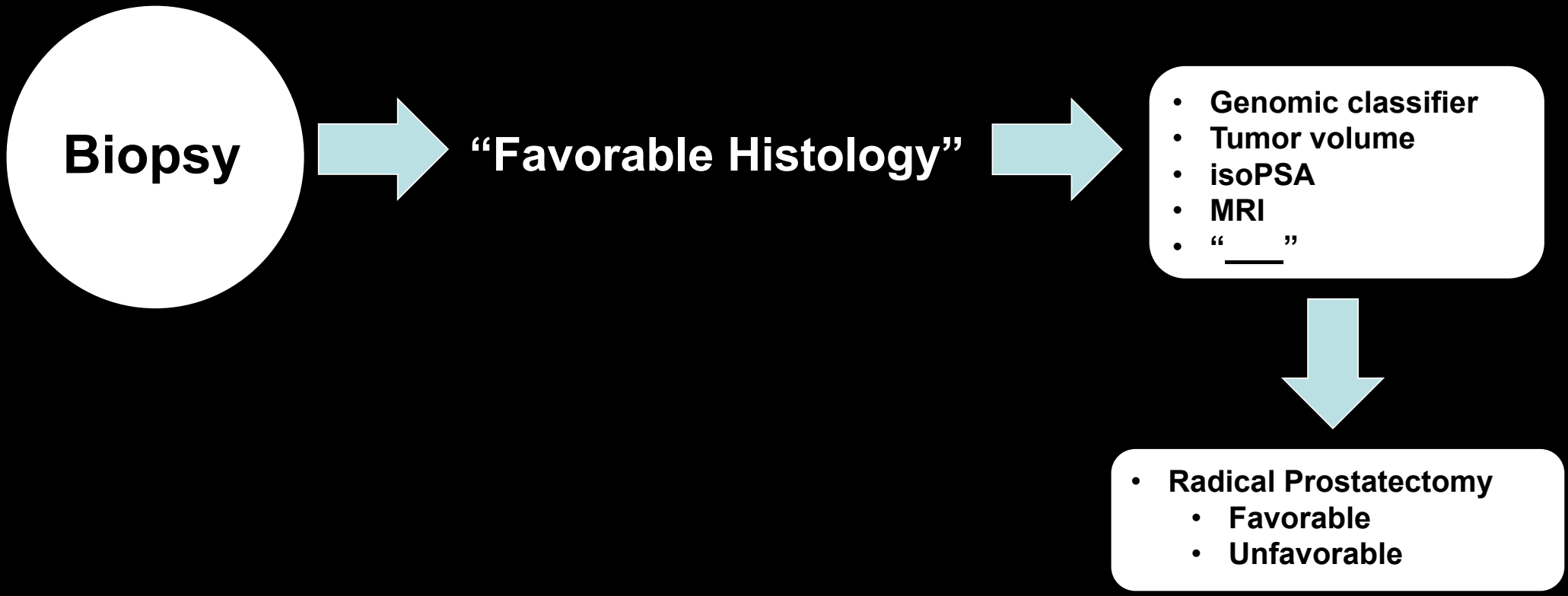
- MRI
- Alternative biopsy strategies
- Genomic classifiers
- Borderline histologic patterns
- PSA
- isoPSA

- Other serum biomarkers
- Other tissue biomarkers

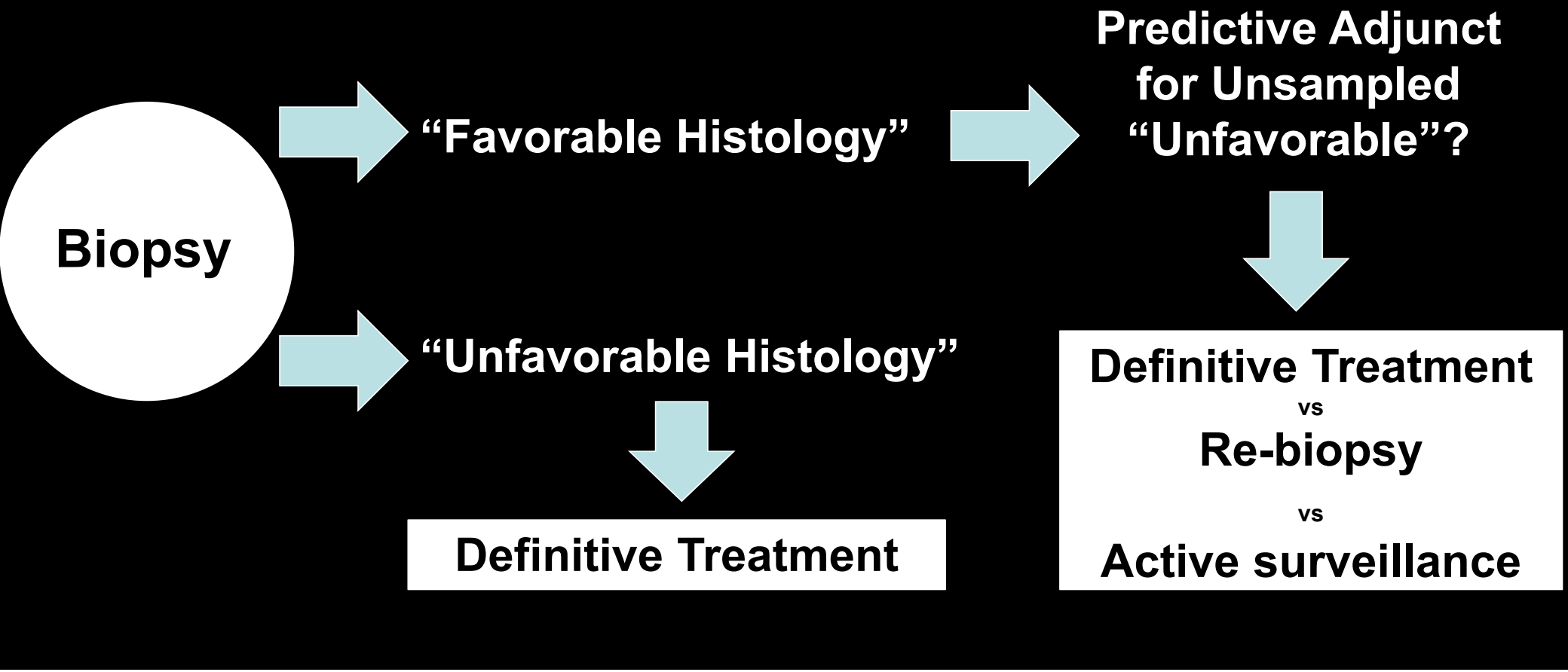
Can we improve reproducibility and increase throughput for additional studies?

- Machine learning

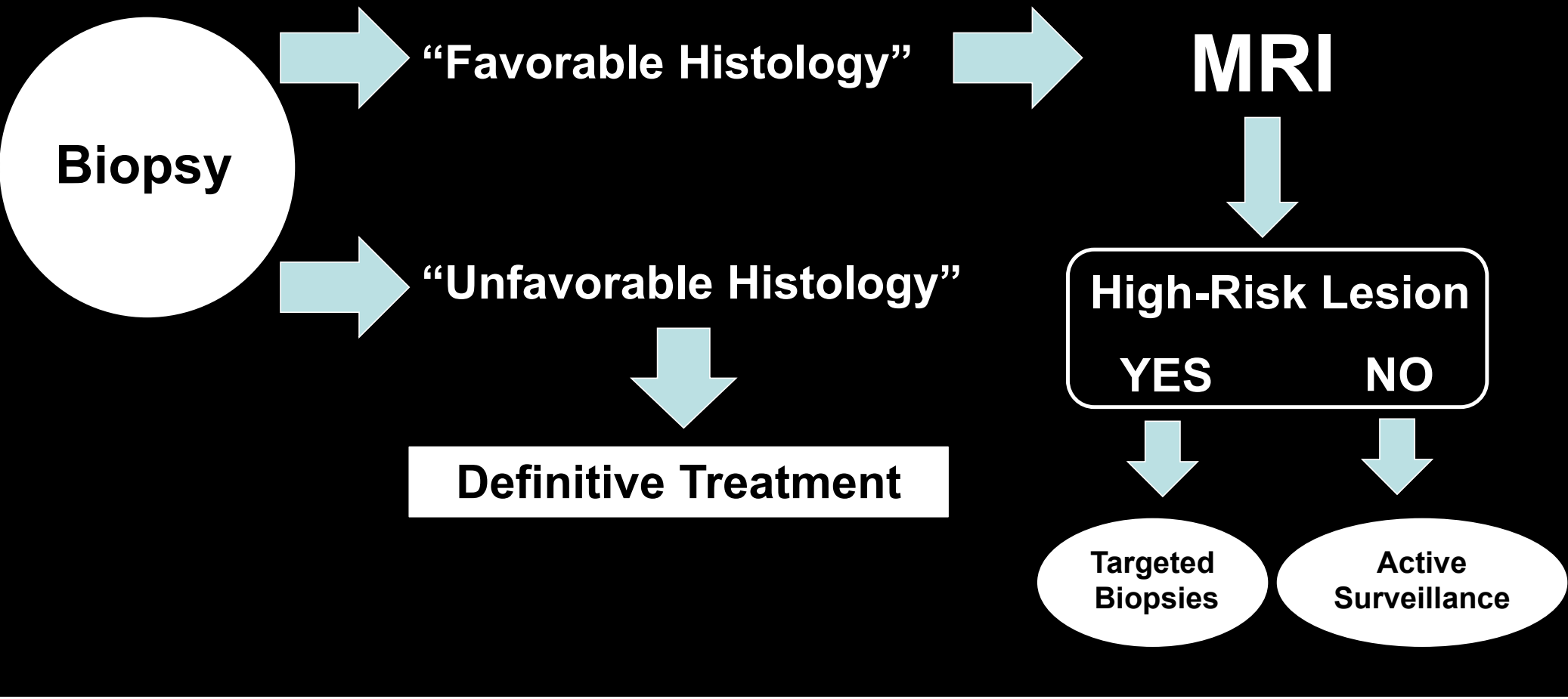
Biopsy Studies in Process



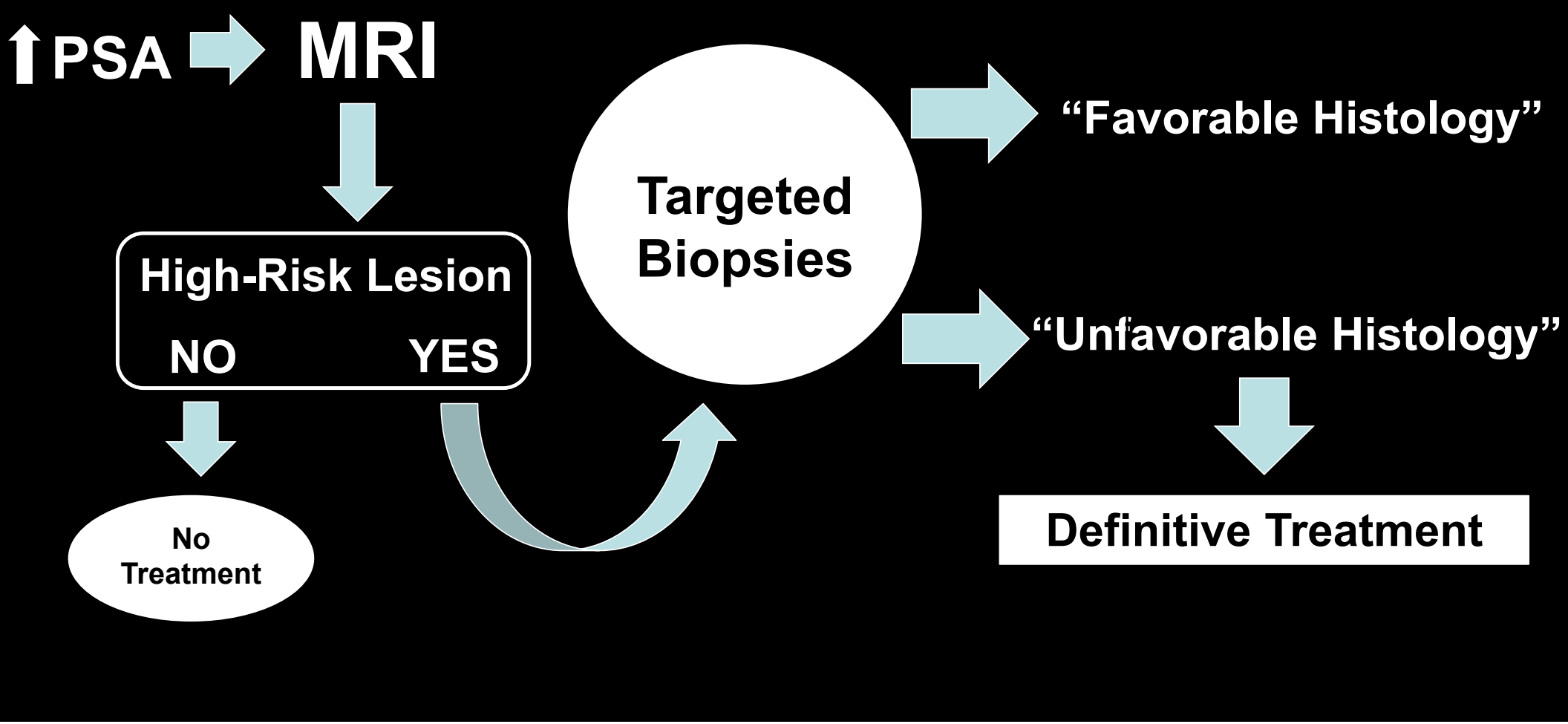
Future Treatment Algorithms?



Future Treatment Algorithms?



Future Treatment Algorithms?

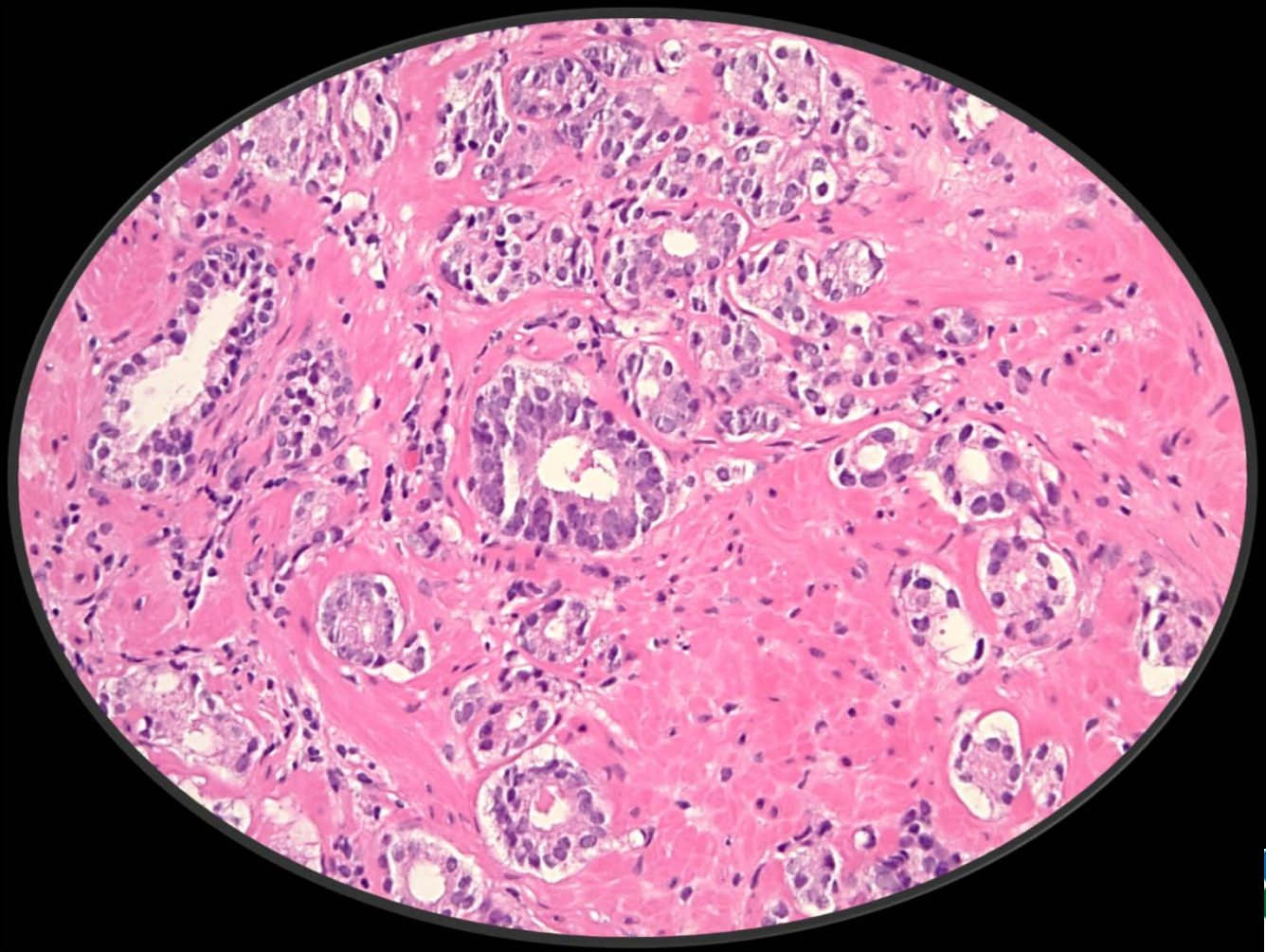


Summary

- Histologic classification
  - Strong prognostic factor in prostatic adenocarcinoma
  - Can be studied in a methodologically sound way
  - Specific histologic patterns grouped as “unfavorable” represent a very sensitive test for metastatic potential
    - Outperforms AJCC stage and current Grade Groups
    - Suggests that “unfavorable” may be the best marker for “adverse pathology”

Summary

- This classification is still in the “experimental phase”
- Validation studies by other groups will be critical
  - Reproducibility
  - MRI detection of “unfavorable”
  - Biopsy studies
    - Comparison of other adjunctive markers to detect “unfavorable”
    - Active surveillance cohort
      - Canary Prostate Active Surveillance Study (PASS)



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Laboratory Medicine Institute