2016 WHO CLASSIFICATION OF TUMOURS OF THE PROSTATE

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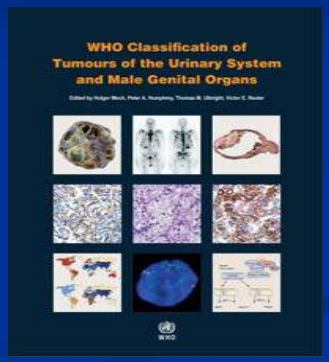
Disclosure

Dr. Peter Humphrey has nothing to disclose

WHO "BLUE BOOKS" ON PATHOLOGY AND GENETICS

- Standard classifications worldwide for all malignancies
- Last WHO book on classification of Tumors of the Urinary System and Male Genital Organs published in 2004
- Many evidence-based changes in the 2016 volume

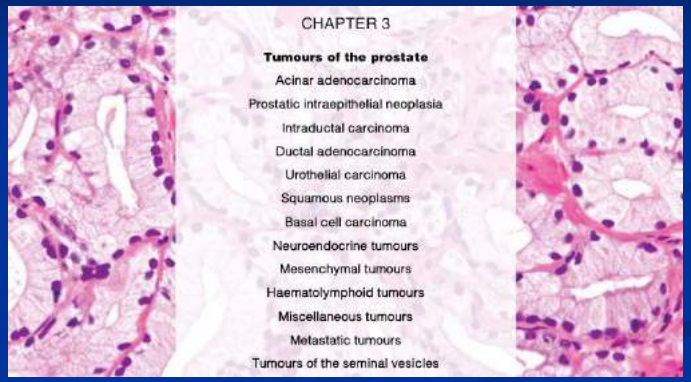


WHO Blue Books : History

- "In 1956 the WHO passed a resolution to explore the possibility that the WHO might organize centers … whose main purpose was to develop ***histological definitions of cancer types and to facilitate wide adoption of uniform nomenclature***."

Mostofi FK, Sesterhenn IA, Davis CJ Jr. Histological Typing of Prostate Tumors, 2002.

2016 WHO CLASSIFICATION OF TUMOURS OF THE PROSTATE



AUTHORS : PROSTATE CHAPTER

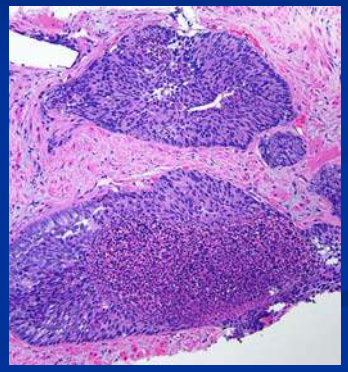
- Algaba F, Amin MB, Berney DM, Billis A, Bostwick DG, ***Cao D***, Cheng L, Cheville J, Comperat E, Delahunt B, ***Egevad L***, ***Epstein JI***, Evans AJ, Ferry JA, ***Fine SW***, Grignon DJ, Hameed O, Huang J, Iczkowski KA, ***Kristiansen G***, Lopez-Beltran A, Magi-Galluzzi C, Montironi R, Netto GJ, Osunkoya AO, Oxley J, Pan C-C, Ro JY, Rubin MA, ***Samaratunga H***, Srigley JR, Tan P-H, True LD, Tsuzuki T, van der Kwast T, Zhou M
- 36 authors from 16 countries

OUTLINE

- New Entity : Intraductal Carcinoma
- New Variants of Acinar Adenocarcinoma of the Prostate
- New Variant of Neuroendocrine Tumors of the Prostate : Large Cell Neuroendocrine Carcinoma
- Immunophenotype of Acinar Adenocarcinoma
- Grading of Adenocarcinoma
- Risk Stratification and Active Surveillance
- Genetic Profile and Molecular Classification

INTRADUCTAL CARCINOMA OF THE PROSTATE

- An intra-acinar and/or intraductal neoplastic proliferation that has some features of high-grade prostatic intraepithelial neoplasia but exhibits much greater architectural and/or cytological atypia



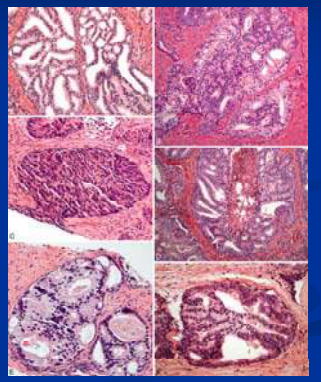
HISTOLOGICAL FEATURES OF INTRADUCTAL CARCINOMA OF THE PROSTATE

- Malignant cells filling large acini and prostatic ducts, with preservation of basal cells, and either:
- A solid or dense cribriform pattern or
- A loose cribriform pattern with either:
  - Marked nuclear atypia (nuclear size 6x normal or larger) or
  - Comedonecrosis

Mod Pathol 19:1528, 2006

Intraductal Carcinoma of Prostate : Spectrum of Presentation

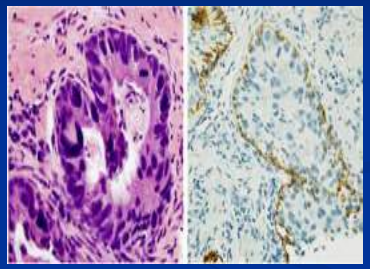
- A. Loose cribriform
- B. Dense cribriform
- C. Solid
- D. Comedonecrosis
- E,F. Nuclear pleomorphism



Robinson B, et al. Arch Pathol Lab Med 136:481, 2012

INTRADUCTAL CARCINOMA OF THE PROSTATE

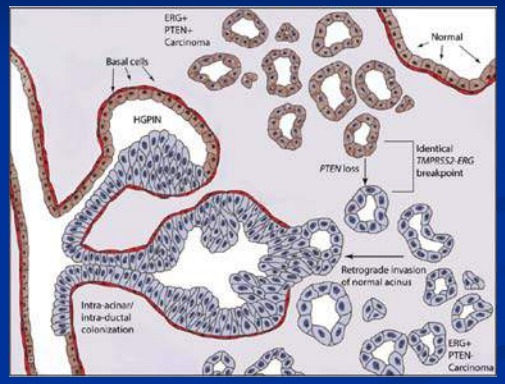
- In 17% of radical prostatectomy cases
- 2.8% of needle biopsies cases, typically with high-grade (mean Gleason score 8) invasive adenocarcinoma
- 0.1% to 0.3% of prostate biopsies without associated invasive adenocarcinoma



GENETIC PROFILE OF INTRADUCTAL CARCINOMA OF THE PROSTATE

- Intraductal carcinoma in most cases represents a late event in prostate cancer evolution.
- Genetically, intraductal carcinoma is different from high grade PIN with greater loss of heterozygosity, including loss of heterozygosity of *TP53* and *RB1*, and with a greater frequency of *ERG* rearrangement.
- Cytoplasmic PTEN loss is common in intraductal carcinoma, but not high grade PIN.

Proposed Model of Retrograde Glandular Colonization



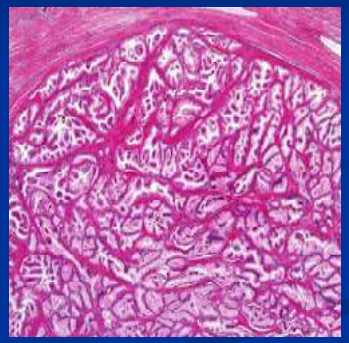
Haffner MC, et al. J Pathol 238:31, 2016

INTRADUCTAL CARCINOMA OF THE PROSTATE : OUTCOME

- Associated with high-grade and high-volume prostate cancer at radical prostatectomy
- Independent predictor of clinical outcome
- Isolated intraductal carcinoma in prostate needle biopsy : Definitive therapy may be indicated although 10% of patients will have intraductal carcinoma at radical prostatectomy so repeat biopsy is also an option.

VARIANTS OF ACINAR ADENOCARCINOMA OF THE PROSTATE

- Variants of acinar adenocarcinoma of the prostate may be of significance due to difficulty in diagnosis and due to prognostic and/or therapeutic differences compared to usual acinar adenocarinoma of the prostate.



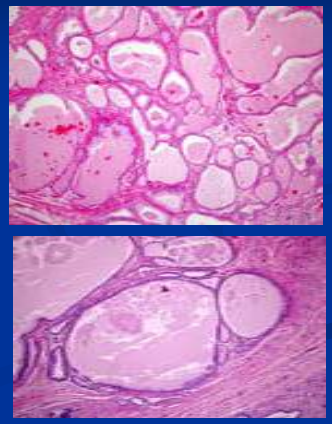
Pseudohyperplastic adenocarcinoma

HISTOLOGICAL VARIANTS OF ACINAR ADENOCARCINOMA

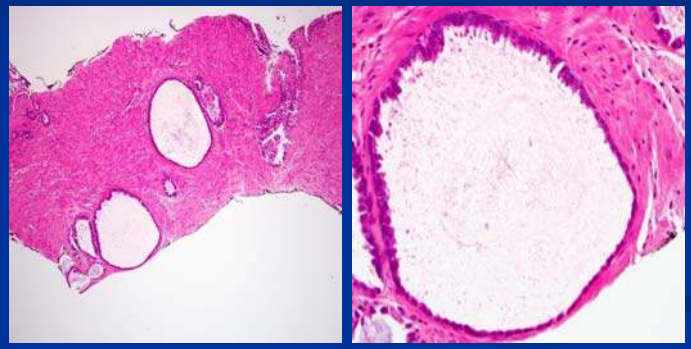
- Atrophic variant
- Pseudohyperplastic variant
- ***Microcystic variant : NEW***
- Foamy gland variant
- Mucinous variant
- Signet ring-like variant
- ***Pleomorphic giant cell variant : NEW***
- Sarcomatoid variant

MICROCYSTIC VARIANT OF ACINAR ADENOCARCINOMA

- Cystic change in prostatic adenocarcinoma glands seen in 11% of RP cases; may be confused with cystic change in benign glands, which is common
- Dilated glands 10-fold larger diameter compared to usual small gland adenocarcinoma



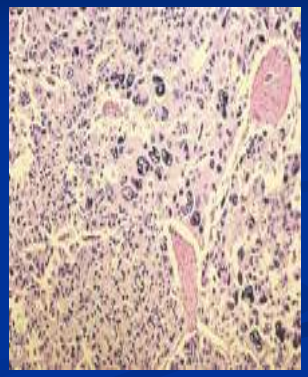
MICROCYSTIC ADENOCARCINOMA IN NEEDLE BIOPSY



Am J Surg Pathol 34:556, 2010

PLEOMORPHIC GIANT CELL ADENOCARCINOMA

- Rare
- Admixed with high Gleason score (9 to 10)
- Some cases emerge after hormonal or radiation treatment of acinar adenocarcinoma
- Outcome poor

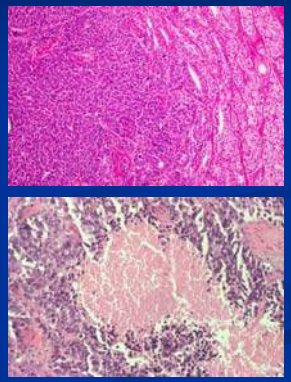


NEUROENDOCRINE TUMOR CLASSIFICATION

- Adenocarcinoma with neuroendocrine differentiation
- Well-differentiated neuroendocrine tumour (carcinoid tumor)
- Small cell neuroendocrine carcinoma
- ***Large cell neuroendocrine carcinoma : NEW***

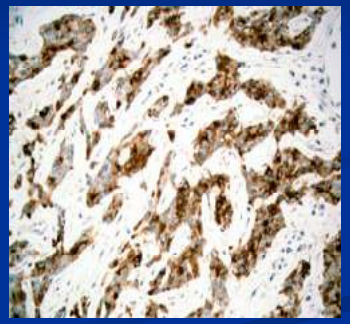
LARGE CELL NEUROENDOCRINE CARCINOMA OF THE PROSTATE

- Rare; largest series = 7 cases (Evans AJ, et al. AJSP 30:684, 2006)
- In 6/7 cases there was a history of prior hormonal therapy of adenocarcinoma
- Large cells, low N/C ratio, coarse chromatin, prominent nucleoli, high mitotic activity, necrosis, and immunohistochemical or EM evidence of neuroendocrine differentiation
- Outcome poor, even after chemotherapy : 7 months survival



IMMUNOPHENOTYPE OF ACINAR ADENOCARCINOMA

- 2004 Blue Book : Commonly utilized markers in immunohistochemistry :
- PSA
- PSAP
- High molecular weight cytokeratins
- p63
- AMACR (P504S)



PSA Immunostain in Metastasis to Bone

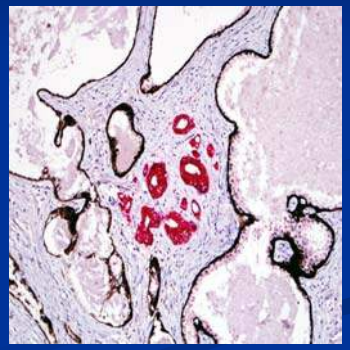
IMMUNOPHENOTYPING IN SPECIFC DIAGNOSTIC SCENARIOS

- Diagnosis of limited (minimal) adenocarcinoma on needle biopsy
- Poorly-differentiated prostatic adenocarcinoma versus urothelial carcinoma
- High-grade adenocarcinoma of the prostate versus granulomatous prostatitis/xanthoma
- High-grade adenocarcinoma of the prostate versus urinary bladder adenocarcinoma
- Diagnosis of metastatic adenocarcinoma of the prostate

DIAGNOSIS OF LIMITED (MINIMAL) ADENOCARCINOMA ON NEEDLE BIOPSY

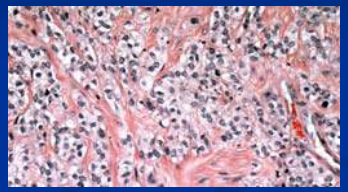
- p63
- High molecular weight cytokeratins (using 34betaE12)
- AMACR
- ERG not recommended

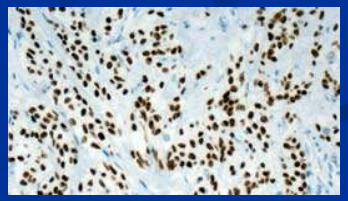
ISUP recommendations :
AJSP 38: e6, 2014



POORLY-DIFFERENTIATED PROSTATIC ADENOCACINOMA VERSUS UROTHELIAL CARCINOMA

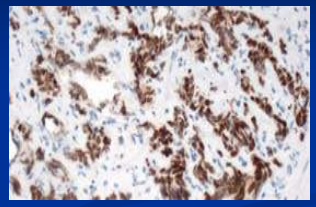
- ISUP recommendation : PSA and GATA3 (right) to start
- 2nd line urothelial markers : p63 and high molecular weight cytokeratins
- 2nd line prostatic markers : NKX3.1 and prostein (P501S)

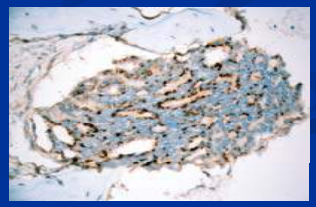




Diagnosis of metastatic adenocarcinoma of the prostate

- New prostatic markers since 2004 :
- ***NKX3.1*** (top right) – a homeobox containing transcription factor
- ***Prostein*** (P501S) (below right) – distinctive granular Golgi-type signal
- Can provide added value beyond PSA and PSAP

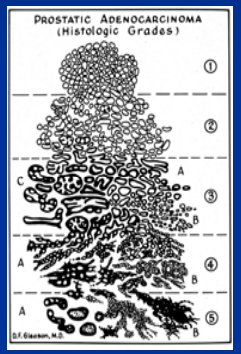




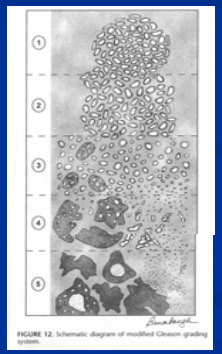
PROSTATE CANCER GRADING

- Gleason grading system remains the standard approach : Most of the text and all images are devoted to ISUP modified Gleason grading.
- The 2014 ISUP modified system is described (AJSP 40: 244, 2016) and the new 2015 ISUP modified Gleason grading schematic diagram is presented.
- Recommendation : Report % Gleason pattern 4 when the highest grade is Gleason score 7
- Grade groups introduced

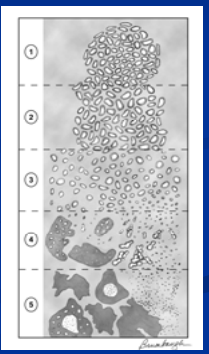
EVOLUTION OF GLEASON GRADING



Original Gleason scheme

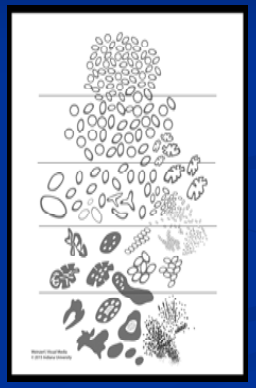


ISUP modified 2005



AFIP modified 2011

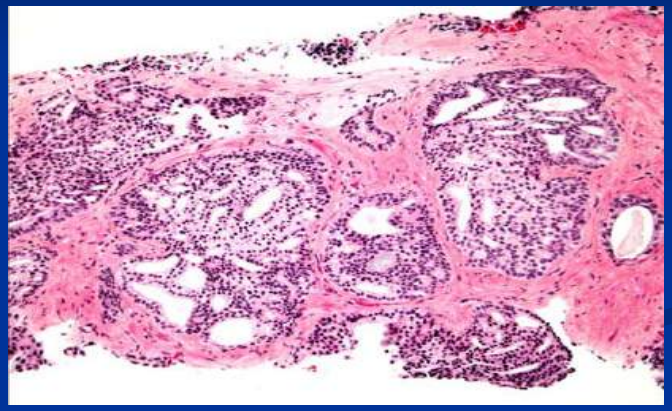
NEW 2015 ISUP MODIFIED GLEASON GRADING DIAGRAM IN WHO 2016



2014 INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGY (ISUP) GLEASON GRADE MODIFICATIONS INCORPORATED INTO WHO 2016

- All cribriform adenocarcinomas are high-grade pattern 4
- Glomeruloid carcinoma is high-grade pattern 4
- Mucinous adenocarcinoma may be 3 or 4
- Do not grade intraductal carcinoma
- Additional details on morphologies within Gleason patterns

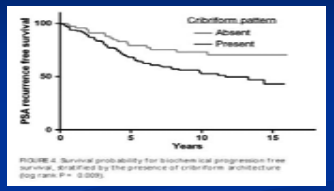
GLEASON GRADE PATTERN 4 : ALL CRIBRIFORM GLANDS

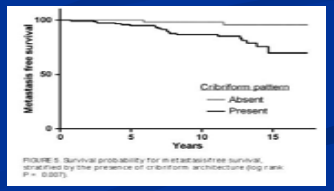


CRIBRIFORM ADENOCARCINOMA

- Outcome : independently associated with biochemical failure after radical prostatectomy, with metastasis after radical prostatectomy, and with metastasis-free and disease-specific survival.

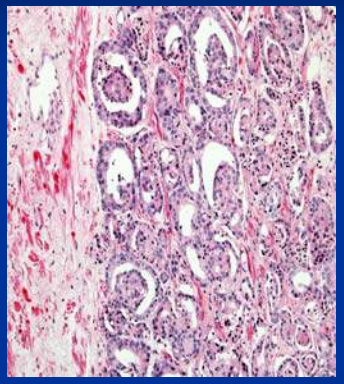
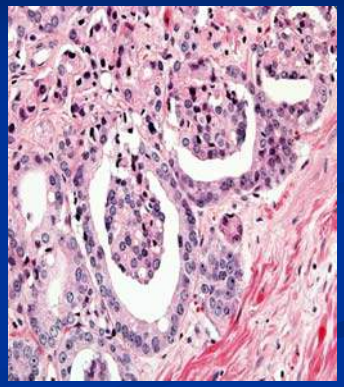
Am J Clin Pathol 136:98, 2011
Am J Surg Pathol 37:1855, 2013
Pathol Res Prac 210:640, 2014
Mod Pathol 28:457, 2015





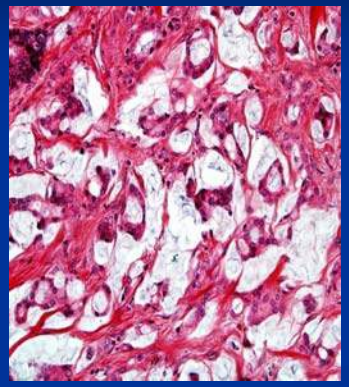
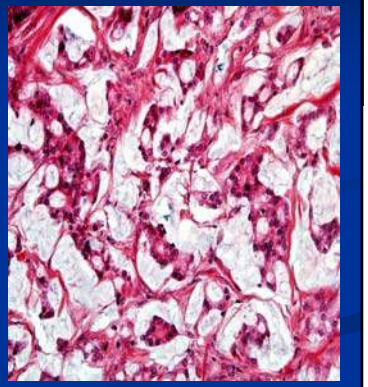
Dong FP, et al. Am J Surg Pathol Dec. 2013

GLEASON GRADE PATTERN 4 : GLOMERULOID STRUCTURES

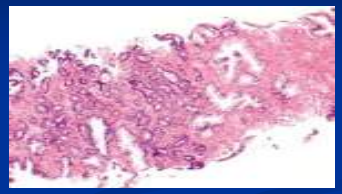
In the past : Some have graded as 3. Now : 4 uniformly

GLEASON GRADING OF MUCINOUS ADENOCARCINOMA OF PROSTATE

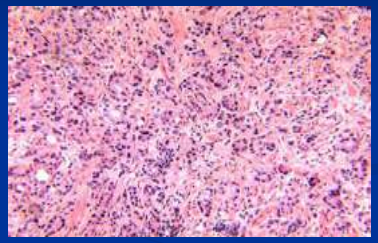
GLEASON PATTERN ARCHITECTURAL ARRANGEMENTS SPECIFIED

- ***Gleason pattern 3*** : Discrete, well-formed, variably sized glands
- Variably sized glands include microcystic and pseudohyperplastic glands
- vs. WHO 2004 : No cribriform glands




GLEASON PATTERN ARCHITECTURAL ARRANGEMENTS : PATTERN 4

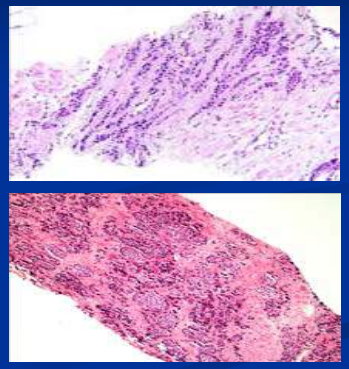
- ***Gleason pattern 4*** : Cribriform, poorly-formed, fused, or glomeruloid glands
- Poorly-formed glands were not recognized in the WHO 2004 book, but were in the 2005 ISUP paper



Need "cluster of poorly formed glands" to be certain of pattern 4 rather than tangentially sectioned pattern 3

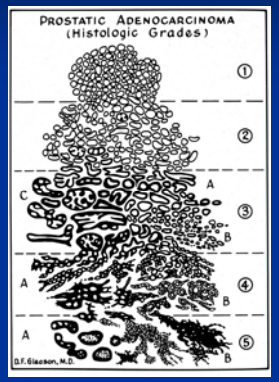
GLEASON PATTERN ARCHITECTURAL ARRANGEMENTS : PATTERN 5

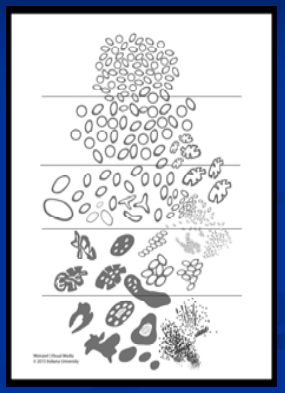
- ***Gleason pattern 5*** : Sheets, individual cells, cords, linear arrays, and solid nests
- Linear arrays and solid nests not recognized in WHO 2004 blue book or 2005 ISUP paper.



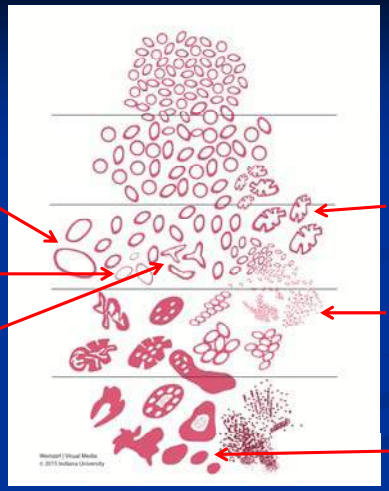
Gleason 5 : Linear arrays (top) and solid nests (bottom)

GLEASON GRADING DIAGRAM WHO 2004 VS. ISUP/WHO 2016





2015 ISUP/2016 WHO Revised Gleason Diagram

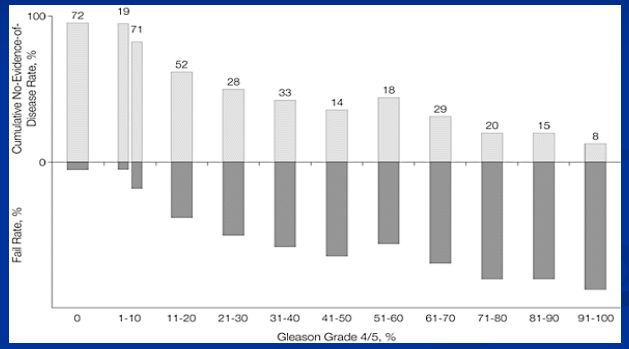


Courtesy
Dr. David Grignon

WHO 2016 RECOMMENDATION : REPORT % GLEASON GRADE PATTERN 4

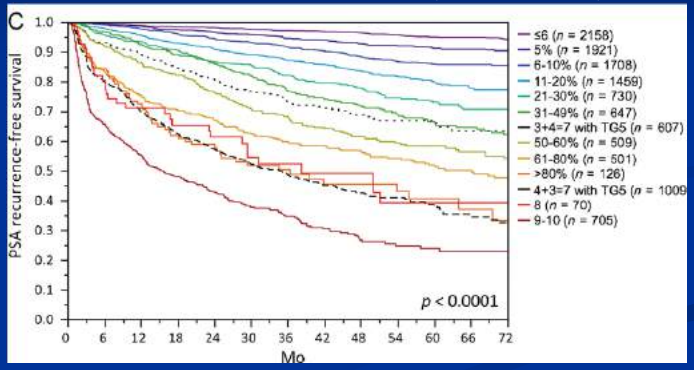
- Percentage of high-grade pattern 4/5 proposed as a significant prognosticator (JAMA 281;1395, 1999)
- Mainly tested in radical prostatectomy cases
- Not established : increments to use
- Previously viewed as experimental, with optional reporting
- May have implications for active surveillance and radiation therapy

% 4/5 GLEASON GRADE IN RELATION TO FAILURE AFTER SURGERY



JAMA 281:1395, 1999

IMPACT OF % GLEASON PATTERN 4 ON OUTCOME AFTER RADICAL PROSTATECTOMY (n =12, 823)



Eur Urol 69:599, 2016

% GLEASON PATTERN 4 IN NEEDLE BIOPSY TISSUE

- Prognostic value of percent **Gleason grade** 4 at prostate biopsy on predicting prostatectomy pathology and recurrence. Cole AI et al. J Urol. 2016 Feb 23. [Epub ahead of print]
- G4% in multivariate analysis was a significant predictor of adverse pathology and time to biochemical recurrence.
- Can improve risk assessment even in 3+4 versus 4+3 subsets of Gleason score 7.

IMPACT OF LOW % GLEASON GRADE 4 IN 3 +4 = SCORE OF 7 PROSTATE CANCERS IN NEEDLE BIOPSY

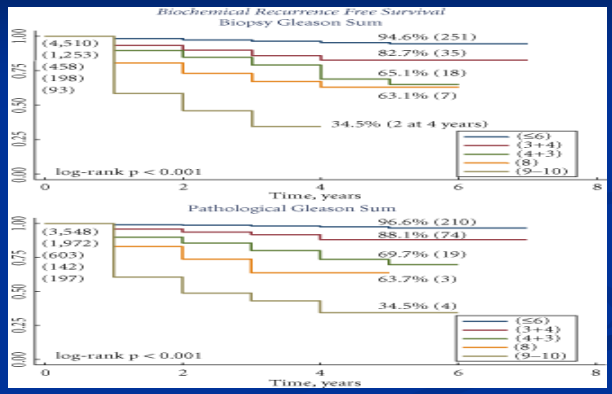
- Several studies suggest no/minimal impact of less than 5% or 10% Gleason grade 4 in 7s:
- Lack of significant risk of adverse pathology among Gleason 7 patients when G4% is 5% or 10%; however it is markedly different when G4% reaches 20% (J Urol Feb 2016)
- 3 + 3= 6 vs. 3 + 4 = 7 with 5% or less Gleason grade 4 : No difference in pathologic findings in radical prostatectomy tissue (AJSP 38:1096, 2014) and biochemical recurrence (Ann Diagn Pathol 20:48, 2016)

PROGNOSTIC GRADE GROUPS

- GROUP I : Gleason score < 7
- GROUP II : Gleason score 3 + 4 = 7
- GROUP III : Gleason score 4 + 3 = 7
- GROUP IV : Gleason score 8
- GROUP V : Gleason score 9-10

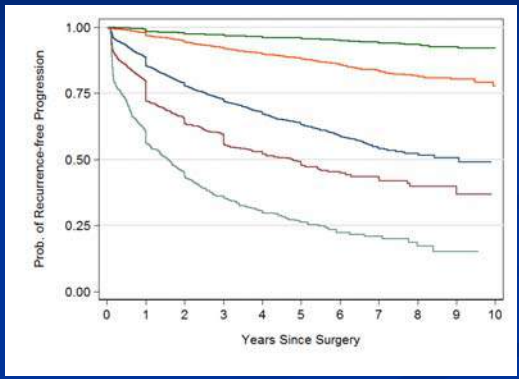
J Clin Oncol 30:4294-4296, 2012
BJU Int 111:753-760, 2013

PROGNOSTIC GRADE GROUPS : INITIAL DATA FOR NEEDLE BIOPSY AND RADICAL PROSTATECTOMY



BJU International
Volume 111, Issue 5, pages 753-760, 6 MAR 2013 DOI: 10.1111/j.1464-410X.2012.11611.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2012.11611.x/full#bju11611-fig-0001

OUTCOME FOR 20,845 MEN BASED ON GRADE GROUPS



Epstein JI, et al. Eur Urol 69:428, 2016

GRADE GROUPS

- "These grade groups should be reported in conjuction with the 2014 WHO/International Society of Urological Pathology (ISUP) modified Gleason scores."
- Reporting Example : Adenocarcinoma, Gleason grade 3 + 3 = score of 6 (grade group 1)

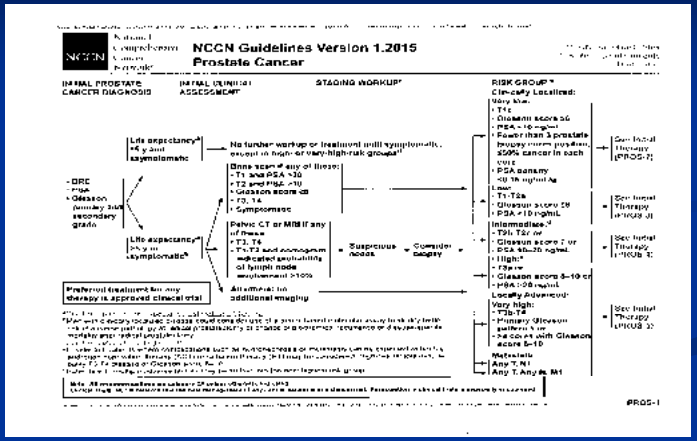
RISK STRATIFICATION AND ACTIVE SURVEILLANCE FOR ACINAR ADENOCARCINOMA

- The vital importance of risk stratification is highlighted in a section on prognosis and predictive factors.
- Details on pathologic prognostic factors provided for different types of tissue samples – needle biopsy, transurethral resection, and radical prostatectomy tissues

RISK CATEGORIES

- Tables or nomograms that utilize patient age, clinical stage, measures of serum PSA, number of cores with cancer, linear extent of cancer, and Gleason score
- Table in WHO 2016 blue book : National Comprehensive Cancer Network (NCCN) risk groups

NCCN GUIDELINES 2015


NCCN Guidelines Version 1.2015
Prostate Cancer

NCCN LOW RISK GROUPS

VERY LOW RISK

- cT1c (non-palpable)
- Gleason score ≤ 6
- Serum PSA < 10 ng/ml
- Fewer than 3 prostate biopsy cores positive, less than or equal to 50% cancer in each core

LOW RISK

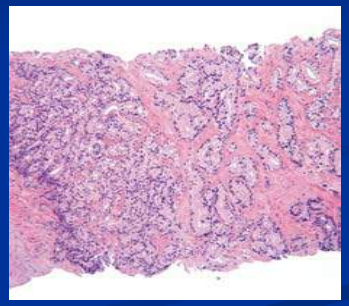
- cT1 to cT2a
- Gleason score ≤ 6
- PSA < 10 ng/ml

INTERMEDIATE RISK ALLOWED IN SOME ACTIVE SURVEILLANCE COHORTS

- cT2b – cT2c
- Gleason score of 7

(usually 3+4=7)

- PSA 10 -20 ng/ml



GLEASON GRADE 3 + 4 = SCORE OF 7

INCLUSION CRITERIA FOR ACTIVE SURVEILLANCE

Study No. Patients	Clinical stage	PSA	Gleason score	Cancer extent	Other
Cooperberg and Glass 640	≤ T2	≤ 10	≤ 6	≤ 33% cores ≤ 50% any one core	
Klotz et al 453		≤ 15	≤ 7 (3+4)		
Selvadurai 471	≤ T2a	≤ 15	≤ 7 (3+4)	≤ 50% cores positive	
Bul et al 2494	≤ T2	≤ 10	≤ 6	≤ 2 cores positive	PSAD ≤ 0.2
Patel et al 870	T1c		≤ 6	≤ 2 cores + ≤ 50% core any core	PSAD ≤ 0.15

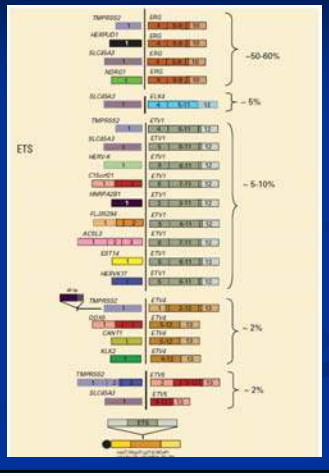
Arch Pathol Lab Med 138 : 1390, 2014

GENETIC PROFILE OF PROSTATE CANCER

- Since 2004 there has been a remarkable expansion of knowledge on the genetics of prostate cancer.
- *ETS* gene fusions and the *TMPRSS2-ERG* fusion described in 2005 (Science 310:644, 2005).
- Next-generation sequencing technologies have revolutionized our understanding of the molecular basis of prostate cancer and its significant genetic heterogeneity.

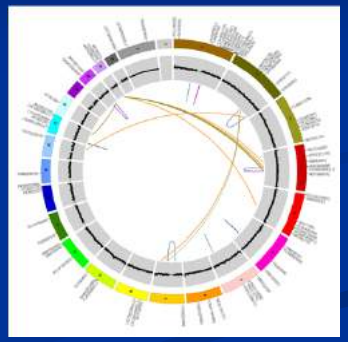
ETS Gene Fusions Discovered in 2005 :

- The most common mutations in both primary and metastatic prostate cancer are fusions of the androgen-regualted promoters with *ERG* and other members of the *ETS* family, particularly *TMPRSS2-ERG*.
- Tomlins SA, et al. Science 310:644, 2005

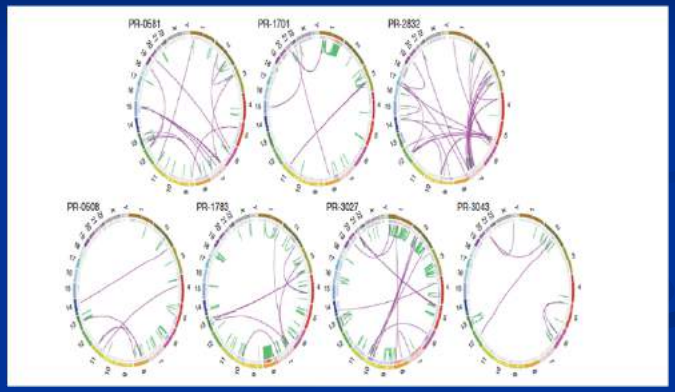


The Prostate Cancer Genome Undergoes Frequent Large-scale Genomic Rearrangements Detected by Whole Genome Sequencing

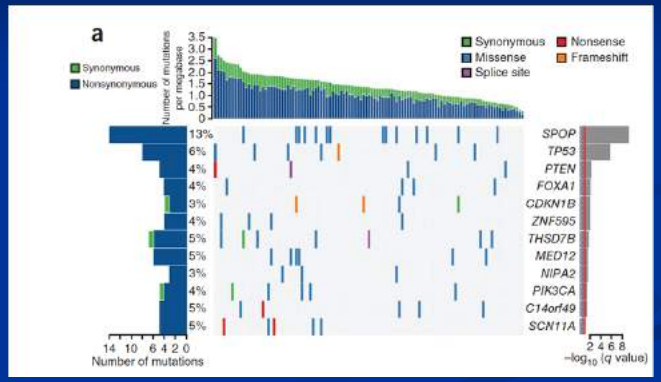
- Median of 90 rearrangements per genome (range 43-213). 7 cases of high-grade prostate cancer characterized. (*Nature* 470:214, 2011.).
- Rearrangements, not single base pair substitutions, as in colon and breast cancer, are dominant.
- Abundant DNA translocations and deletions that arise in a highly interdependent manner = chromoplexy, a process that commonly disrupts cancer genes. (*Cell* 153:666, 2013).



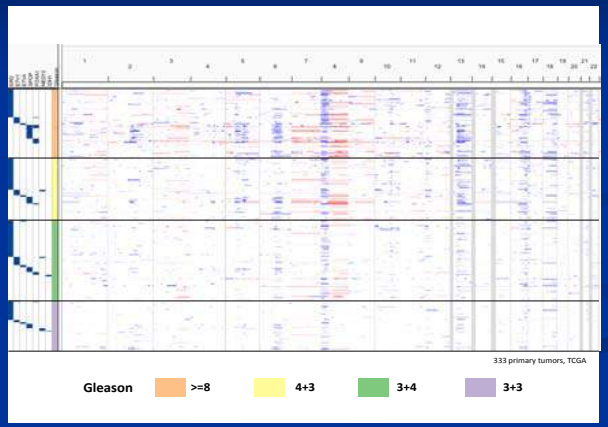
Landscape of Prostate Cancer Mutations : Rearrangements



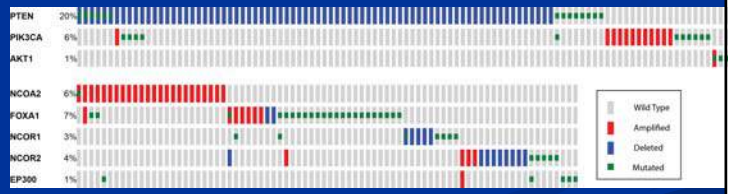
Landscape of Prostate Cancer Mutations : Significantly Mutated Genes in Primary Prostate Cancer



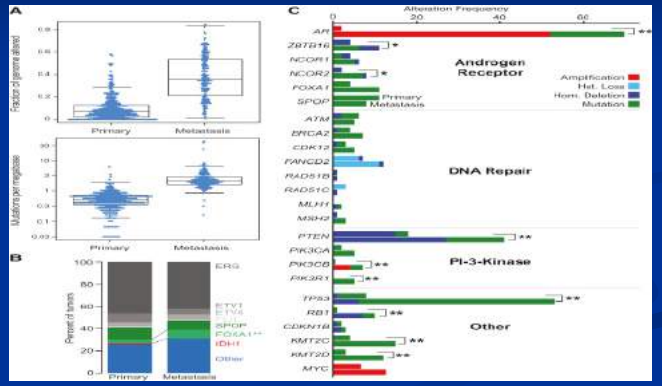
Genomic Copy Number Alterations Increase with Gleason Scores



Mutations in Genes in the PI3K/PTEN/AKT and AR Pathways are Common



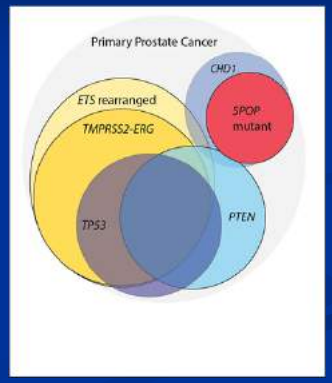
MUTATIONAL PROFILES : PRIMARY VS. METASTATIC PROSTATE CANCER



TCGA : Cell 163: 1011, 2015

MOLECULAR CLASSIFICATION OF PROSTATE CANCER

- Major advances have been made in cataloguing the genomic alterations in prostatic carcinoma
- Objective is subclassification of acinar adenocarcinoma
- Not currently used



ONE FUTURE

- Integration of whole genome or whole exome or targeted gene sequence data, into predictions of prostate cancer outcome and response to treatment