New concepts in PCa pathology

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Dpt Pathology

Vienna/Paris

Conflicts of interest

- Receipt of honoraria or consultation fees: Jansen, BMS

WHO 2022

- Subtype (acinar ADK)
  - Variant reserved for genomic rather than morphologic alterations
- Neuroendocrine, mesenchymal, hematolymphoid, melanocytic, metastatic and genetic-related tumors → separate chapters
  - Exceptions
    - Mesenchymal tumors coming from prostatic tissue
    - Treatment related NEC
- Focus on BRCA1/2, ATM, MSI,….
- HGPIN, IDC-P
- Ductal ADK
- Basal cell carcinoma → adenoid cystic PCa

WHO 2022

1.) Glandular neoplasms of the prostate
- HG PIN
- IDC
- Acinar→ atypical histologies and subtypes +++
- Ductal
- Treatment related NE PCa

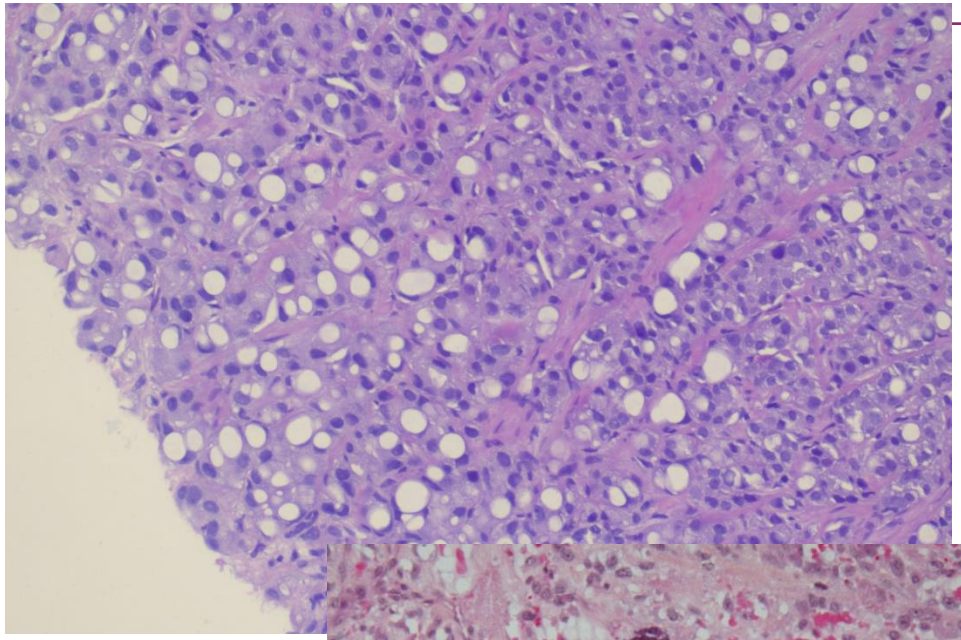
2.) Squamous neoplasms of the prostate
- Adenosquamour Pca
- SCC
  - Adenoid cystic, basal cell PCa

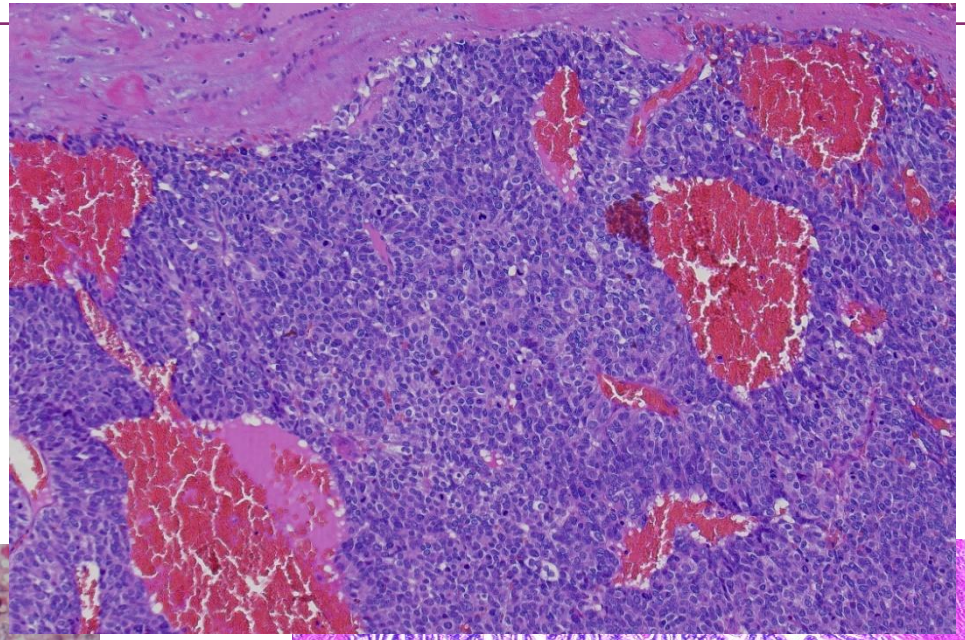
3.) Mesenchymatous…….

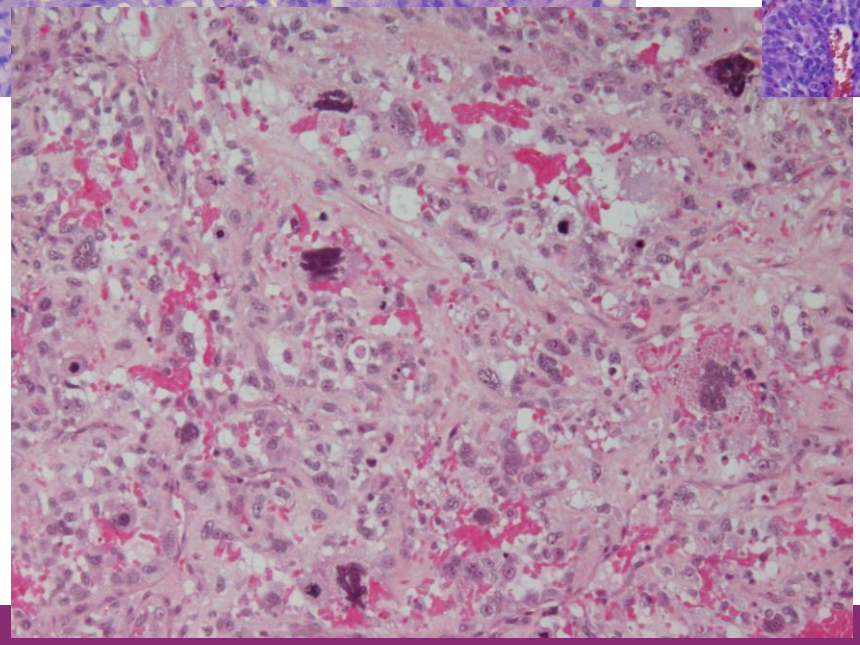
Different histological patterns
- Atrophic acinar adenocarcinoma (ADK)
- Foamy gland acinar ADK
- Pseudohyperplastic PCa

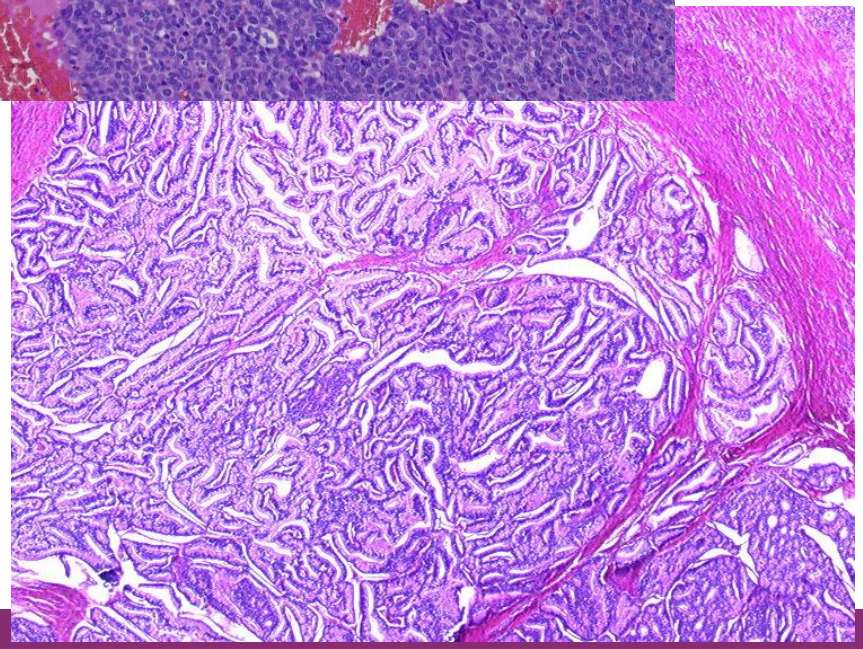
Subtypes
- PIN-like carcinoma
- Signet ring–like cell acinar ADK
- Pleomorphic PCa

Subtypes

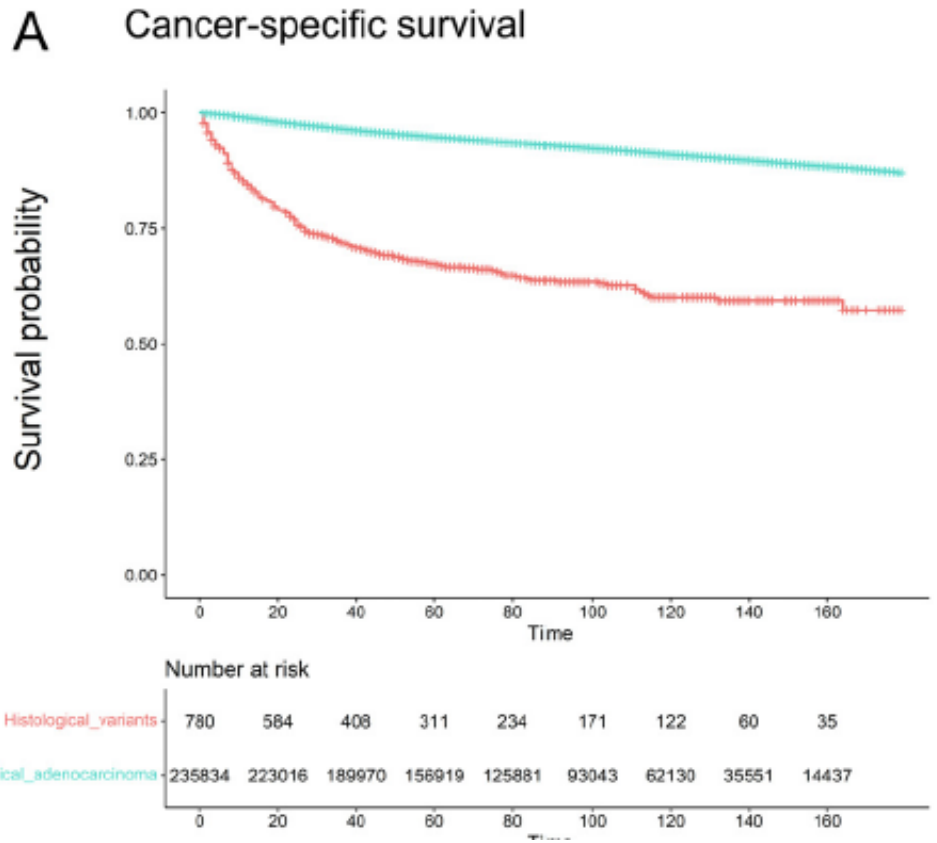


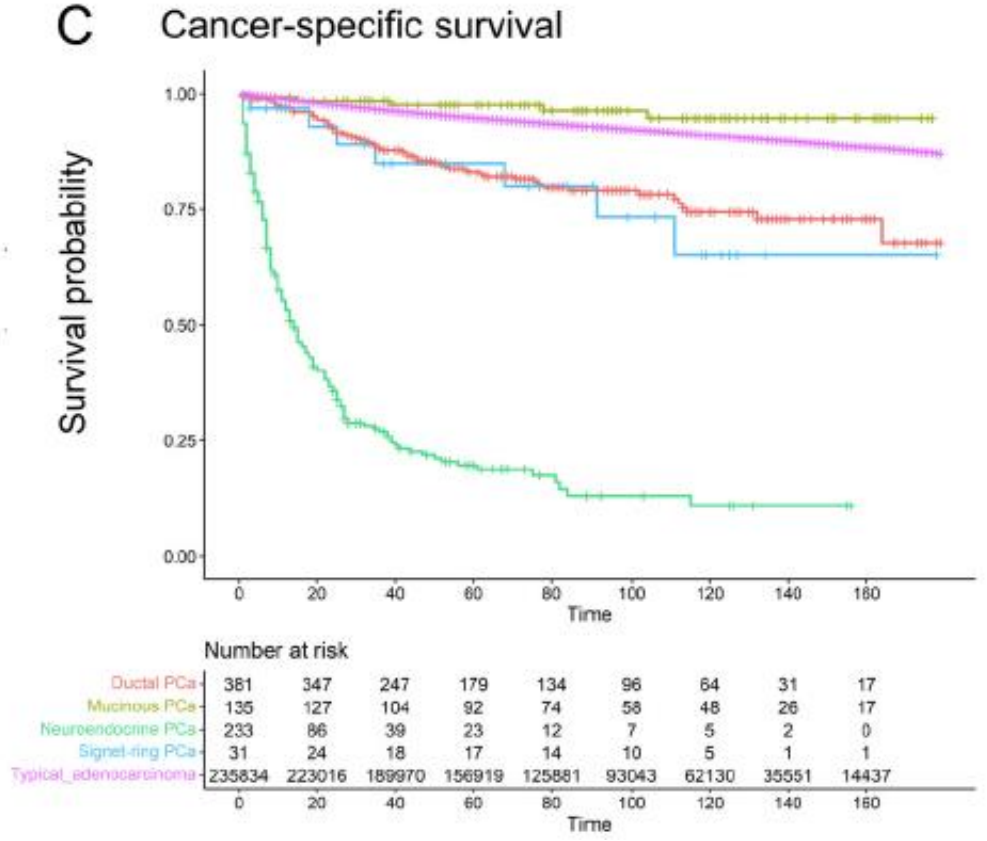






Different aspects must be recognized



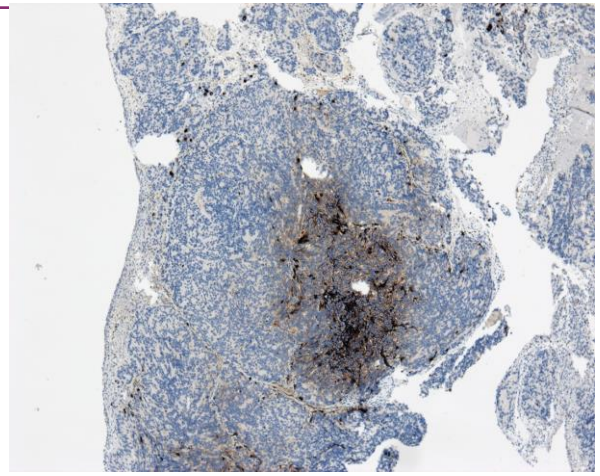


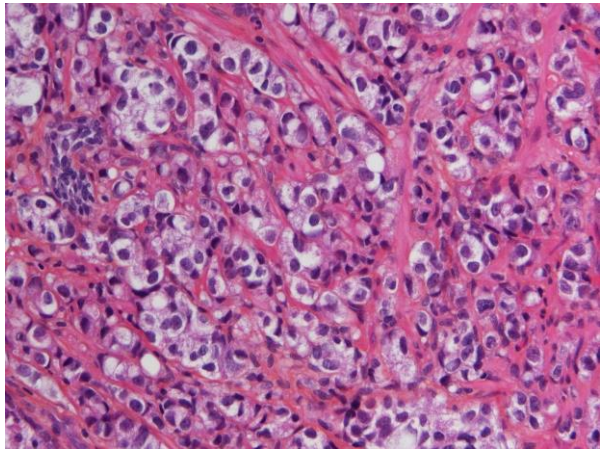
Zhou Eur Urol 2022

t-NEPC (treatment related NE Pca)

- Almost all PCa some degree of NE
- About 50% of tumours with an SCNEC component represent mixed NET
- If pure SCNEC → no Gleason grading
- NEPC is probably a separate clinical entity if pure
  - Mixed tumors with poorly differentiated ADK component
- Develops less than 24 months under ADT
  - Survival after transdifferentiation to t-NEPC is +/- 7 months
  - Pure SCNEC associated with worse overall survival than mixed histology
    - 8.9 months from NEPC diagnosis versus 26.1 months, $P < 0.001$

- Treated PCa no GS
  - Pseudo GG4 or 5!!!





Ductal ADK

WHO Classification of Tumours fifth edition: evolving issues in the classification, diagnosis, and prognostication of prostate cancer

James G Kench,[1,2] Mahul B Amin,[3] Daniel M Berney,[4] Eva M Compérat,[5] Ian A Cree,[6] Anthony J Gill,[2,7] Arndt Hartmann,[8] Santosh Menon,[9] Holger Moch,[10] George J Netto,[11] Maria R Raspollini,[12] Mark A Rubin,[13] Puay Hoon Tan,[14] Toyonori Tsuzuki,[15] Samra Turjalic,[16,17] Theo H van der Kwast,[18] Ming Zhou[19] & John R Srigley[18]

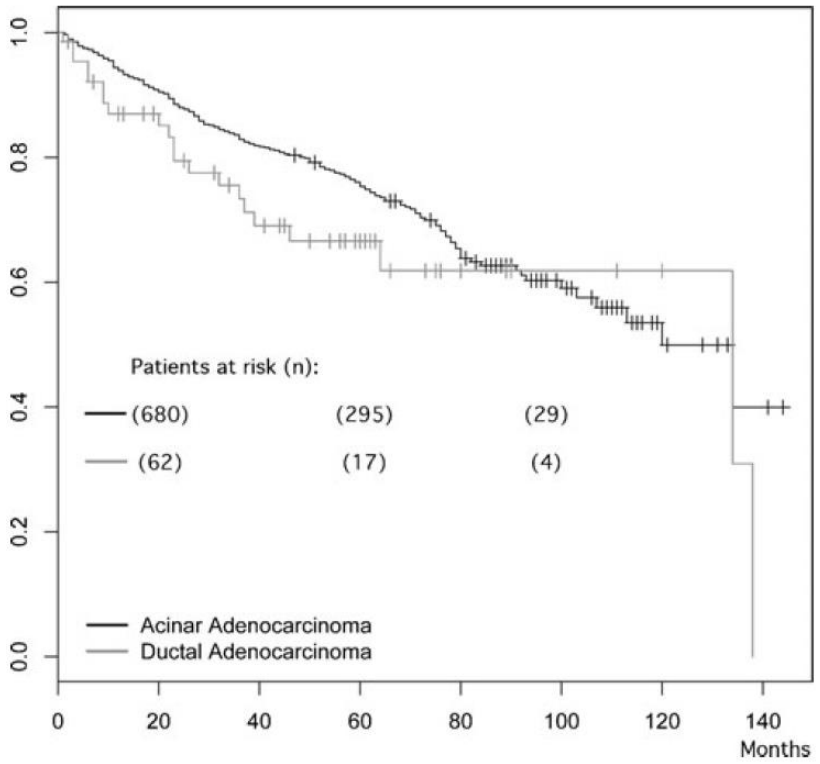
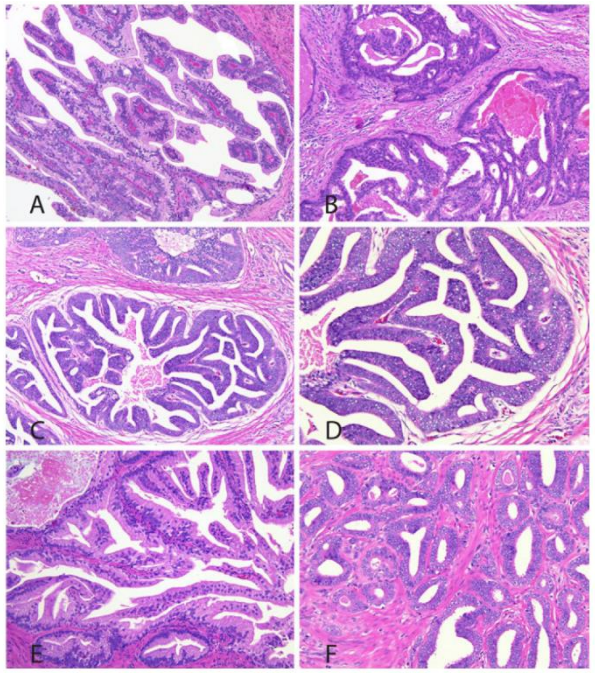


Fig. 3 Kaplan–Meier curve showing survival probability for patients with DAC vs. acinar adenocarcinoma, the former group having a larger number of patients with biochemical recurrence



acinar adenocarcinomas.[12,15] The behaviour of ductal adenocarcinoma is clinically distinctive, with a higher rate of biochemical recurrence (BCR), worse metastasis-free survival (MFS), and overall survival (OS), lower salvage-free survival, and lower response rate to androgen deprivation therapy than high-grade acinar adenocarcinoma.[16–18] Moreover, ductal adeno-

Seipel, Virchow 2013 and 2016
Kench Histopathology 2022

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‖*

Gleason Score 1 + 1 = 2

It was the consensus that a Gleason score of 1 + 1 = 2 is a grade that should not be diagnosed regardless of the type of specimen, with extremely rare exception (Table 3). Most cases

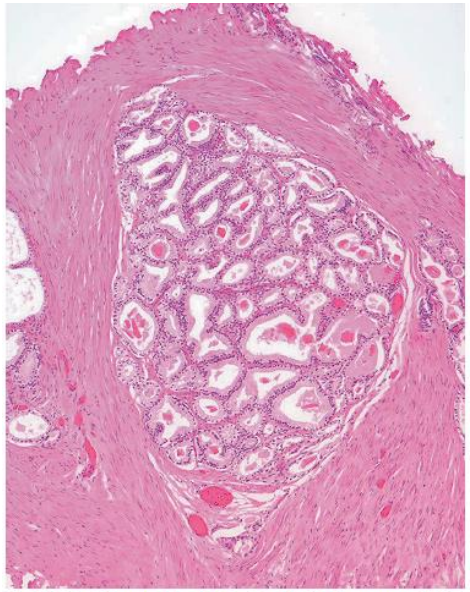


FIGURE 2. Gleason score 1 + 2 = 3 nodule of cancer on TURP, verified immunohistochemically with negative stains for basal cells.

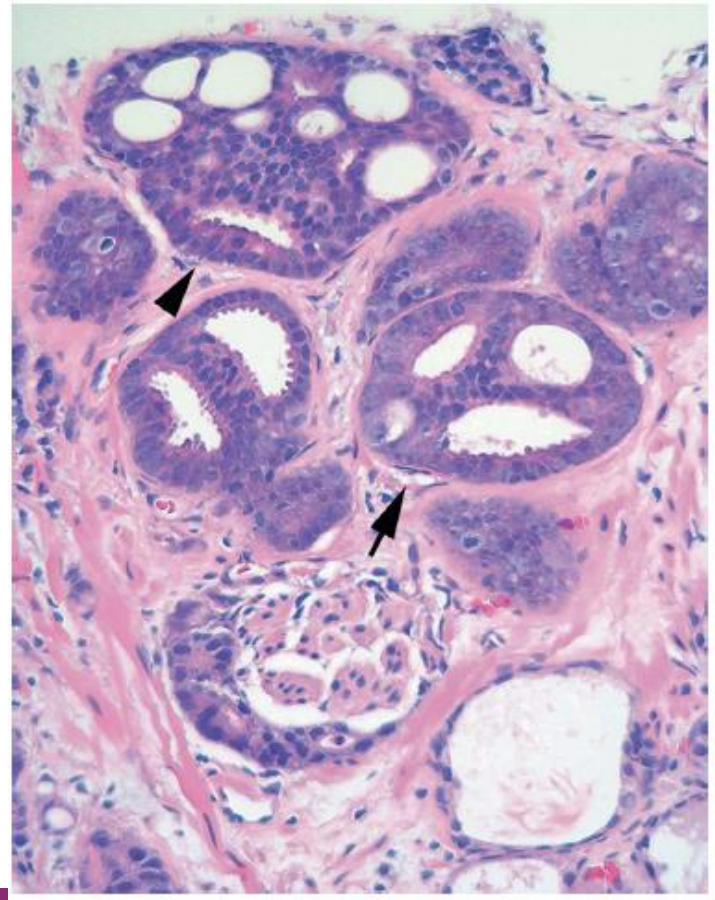


TABLE 3. 2005 ISUP Modified Gleason System

Pattern 1:
- Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)

Pattern 2:
- Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration
- Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

Pattern 3:
- Discrete glandular units
- Typically smaller glands than seen in Gleason pattern 1 or 2
- Infiltrates in and amongst nonneoplastic prostate acini
- Marked variation in size and shape
- Smoothly circumscribed small cribriform nodules of tumor

Pattern 4:
- Fused microacinar glands
- Ill-defined glands with poorly formed glandular lumina
- Large cribriform glands
- Cribriform glands with an irregular border
- Hypernephromatoid

Pattern 5:
- Essentially no glandular differentiation, composed of solid sheets, cords, or single cells
- Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

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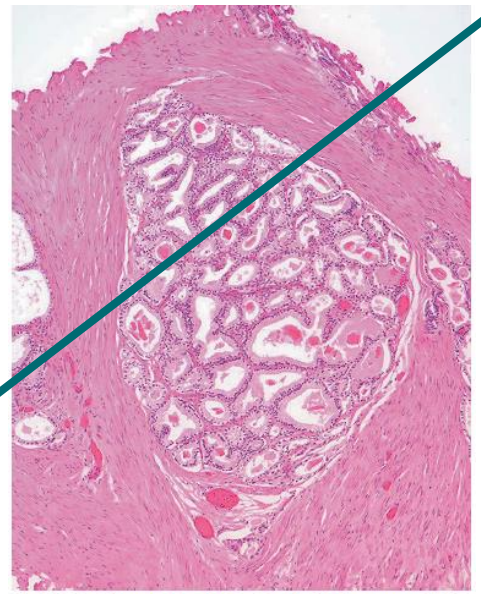

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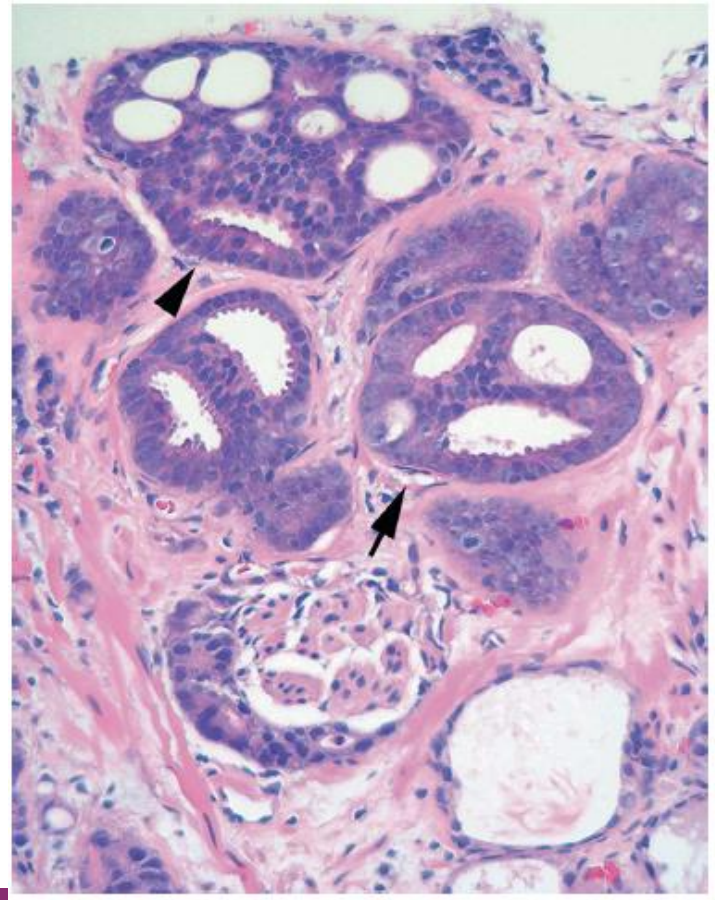

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Original Article

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]

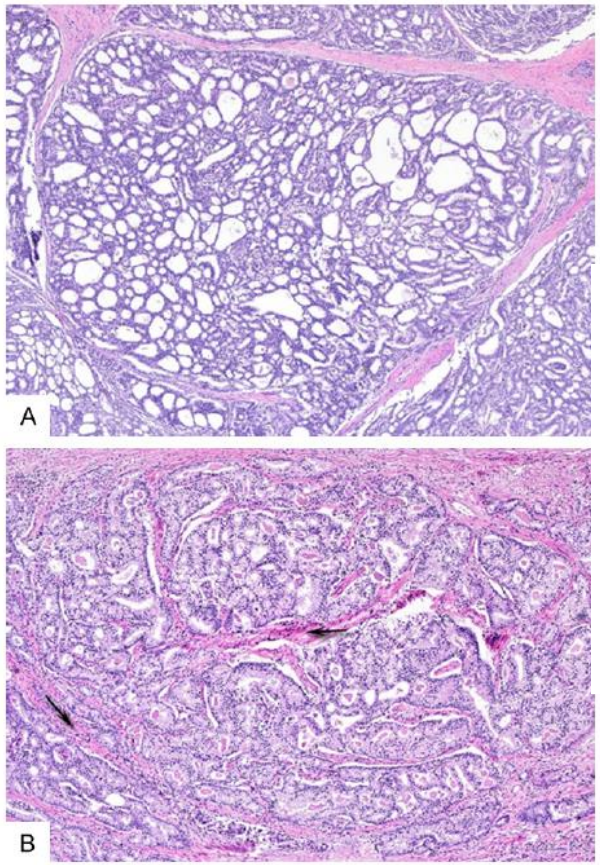
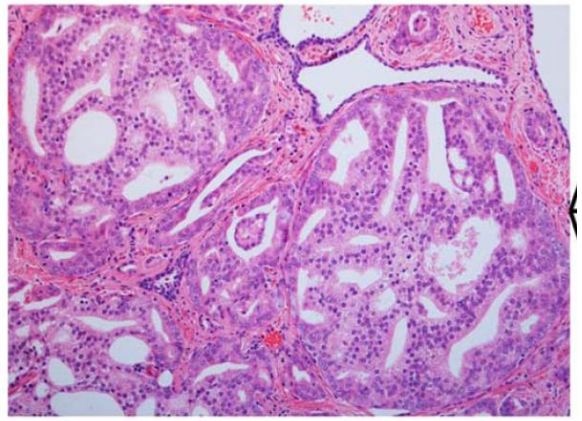


Table 1. Consensus classification of 60 images among 27 participants

Consensus diagnosis	Consensus/total number (%)
For Cribriform	24/60 (40%)
100% agreement	5
≥75% agreement	24
Against cribriform	12/60 (20%)
100% agreement	2
>75% agreement	12
No consensus	24/60 (40%)

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¶¶*



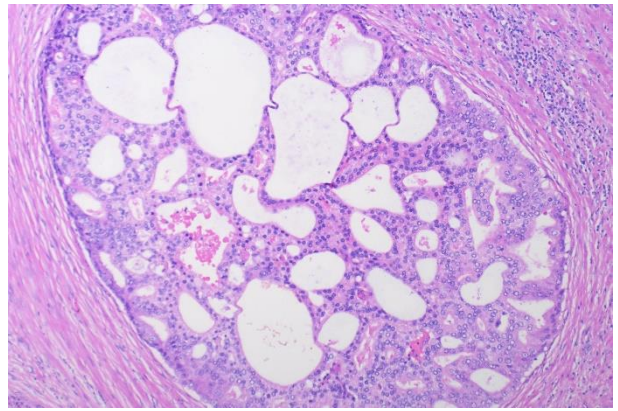
Definition of cribriform pattern: A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina easily visible at low power (objective magnification 10X). There should be no intervening stroma or mucin separating individual or fused glandular structures.

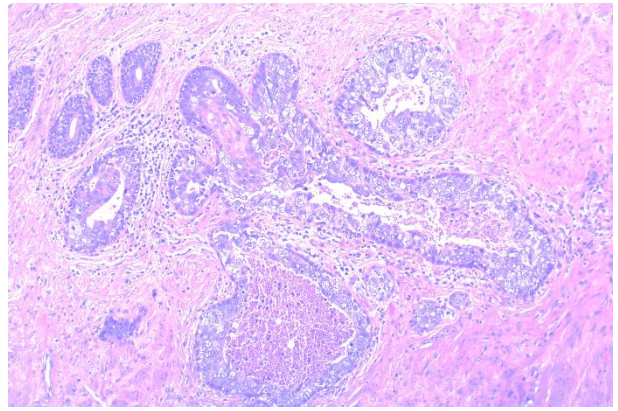
Association between *BRCA2* alterations and intraductal and cribriform histologies in prostate cancer

Rebeca Lozano [a,b,1], Daniela C. Salles [c,1], Shahneen Sandhu [d], Isabel M. Aragón [a,b], Heather Thorne [d], Fernando López-Campos [a,e], José Rubio-Briones [f], Ana M. Gutierrez-Pecharroman [a,g], Laneisha Maldonado [c], Tomas di Domenico [h], Alejandro Sanz [a], Juan D. Prieto [i], Isabel García [i], María I. Pacheco [a], Teresa Garcés [a,b], Casilda Llacer [b,j], Nuria Romero-Laorden [k], Francisco Zambrana [l], Pedro P. López-Casas [a], David Lorente [a,m], Joaquin Mateo [n], Colin C. Pritchard [o], Emmanuel S. Antonarakis [p], David Olmos [a,b], Tamara L. Lotan [c,**], Elena Castro [a,b,j,*]

Abstract ***Background:*** Intraductal (IDC) and cribriform (CRIB) histologies in prostate cancer have been associated with germline *BRCA2 (gBRCA2)* mutations in small retrospective series, leading to the recommendation of genetic testing for patients with IDC in the primary tumour.

Results: No significant differences between *gBRCA2* carriers and non-carriers were observed in the prevalence of IDC (36% *gBRCA2* versus 50% non-carriers, p = 0.085) or CRIB (53% *gBRCA2* versus 43% non-carriers p = 0.197) patterns. However, IDC histology was independently associated with bi-allelic *BRCA2* alterations (OR 4.3, 95%CI 1.1−16.2) and *PTEN* homozygous loss (OR 5.2, 95%CI 2.1−13.1). CRIB morphology was also independently associated with bi-allelic *BRCA2* alterations (OR 5.6, 95%CI 1.7−19.3).

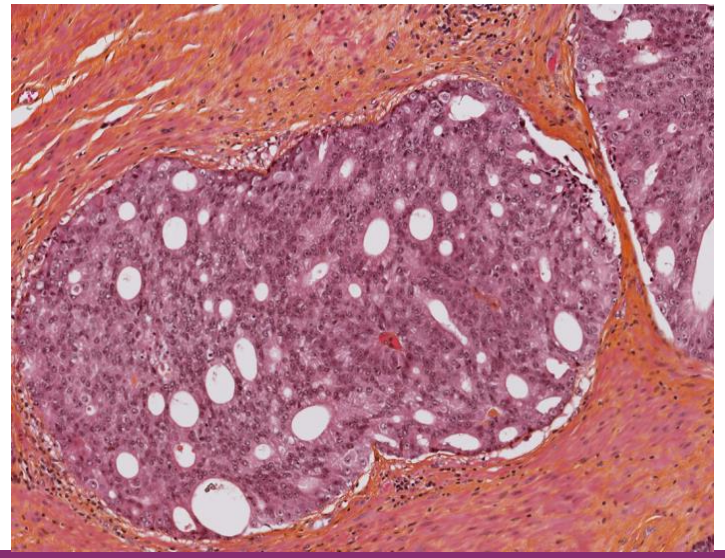




Shall we test all patients with IDC and cribriform PCa?

WHO 2022

- Cribriform pattern
  - Biochemical relapse
    - OR -5.87 , p<0,0001
  - EPE (extraprostatic extension), margins +, **M+,** DOD



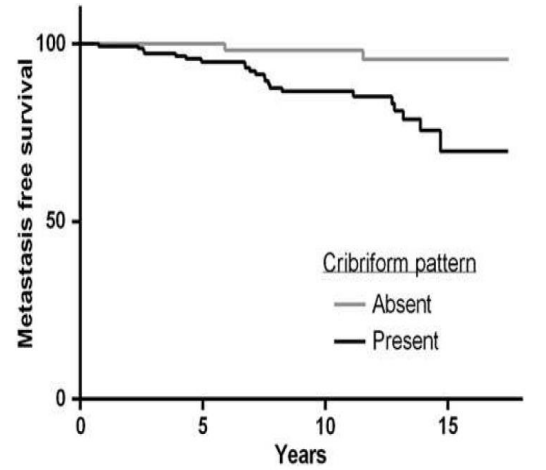


FIGURE 5. Survival probability for metastasis-free survival, stratified by the presence of cribriform architecture (log rank $P=0.007$).

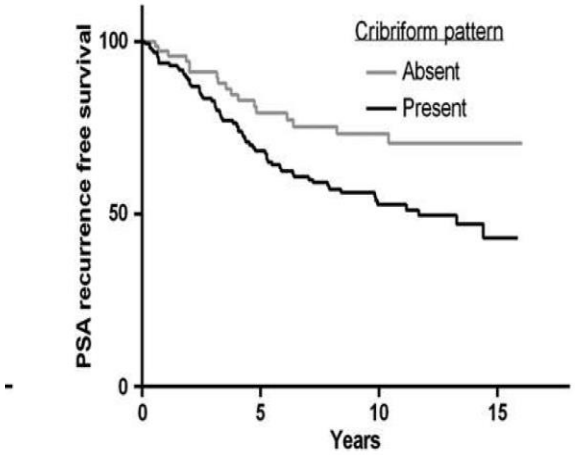


FIGURE 4. Survival probability for biochemical progression-free survival, stratified by the presence of cribriform architecture (log rank $P=0.009$).

Table 7. Summary of Recommendations on Cribriform Glands	
1	**Report the presence or absence of cribriform glands in biopsy and radical prostatectomy specimens with Gleason pattern 4 carcinoma**

Bold item reflects first time recommendations by the Genitourinary Pathology Society.

Dong AJSP 2013
Epstein AJSP 2021

WHO 2022 cribriform

ISUP Consensus Definition of Cribriform Pattern Prostate Cancer

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- If in PB before treatment
  - Predicitve for more advanced clinical stage at RP
  - Upgrading
  - Poorer survival for outcomes
- More commonly loss of PTEN and p27
- Higher genomic instability
- More frequent SPOP and ATM mutations
- ↑ Expression of SChLAP1
- Role of BRCA1/2?

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WHO 2022 cribriform

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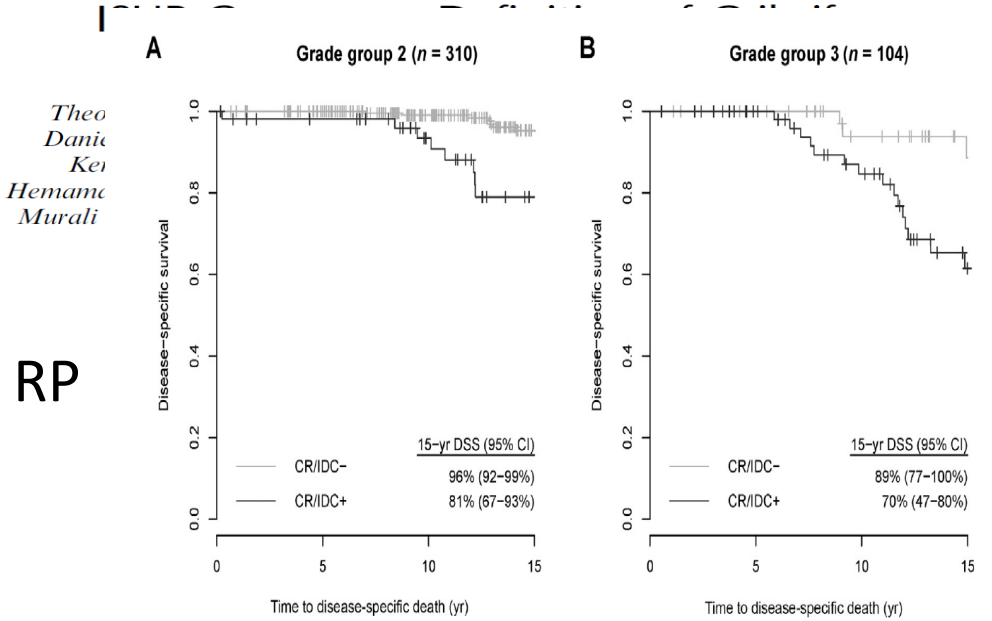
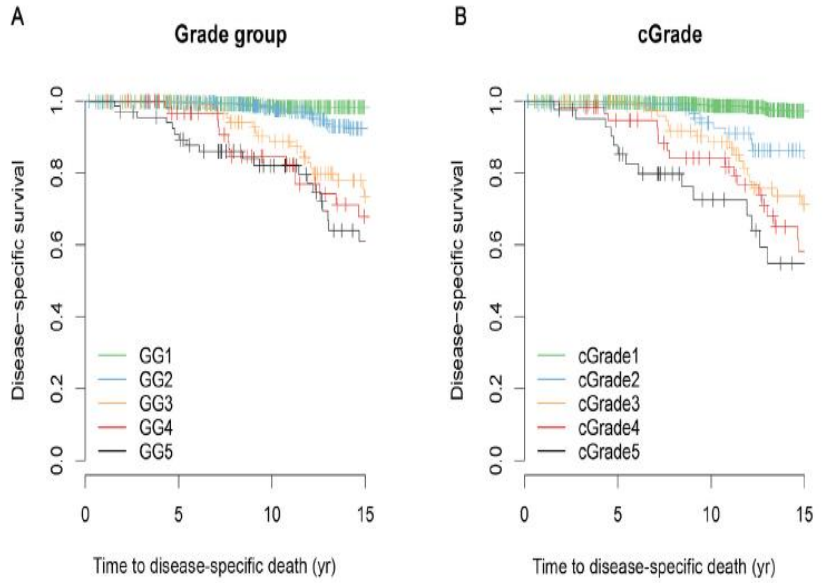




Eur Urol 2020

Intraductal carcinoma

- DD
  - HGPIN
  - Urothelial carcinoma
  - Not enough reported
- Mostly together with invasive PCa

TABLE I. Diagnostic Criteria of Intraductal Cancer of the Prostate (IDC-P) and Distinction From High Grade Prostatic Intraepithelial Neoplasia (HGPIN)

Diagnostic criteria	IDC-P	HGPIN
Basal cells (34βE12, p63)	Always present	Always present
Cytological malignant cells	Always present	Always present
Intraluminal bridging	Always present	Never present
Solid growth pattern	Frequent	Never present
Dense cribriform pattern	Frequent	Never present
Loose cribriform pattern	Less frequent	Rare
Complex papillary pattern	Less frequent	Never present
Comedonecrosis	Frequent	Never present
Markedly enlarged nuclei	Less frequent	Never present
Two population of cells	Frequent	Never present

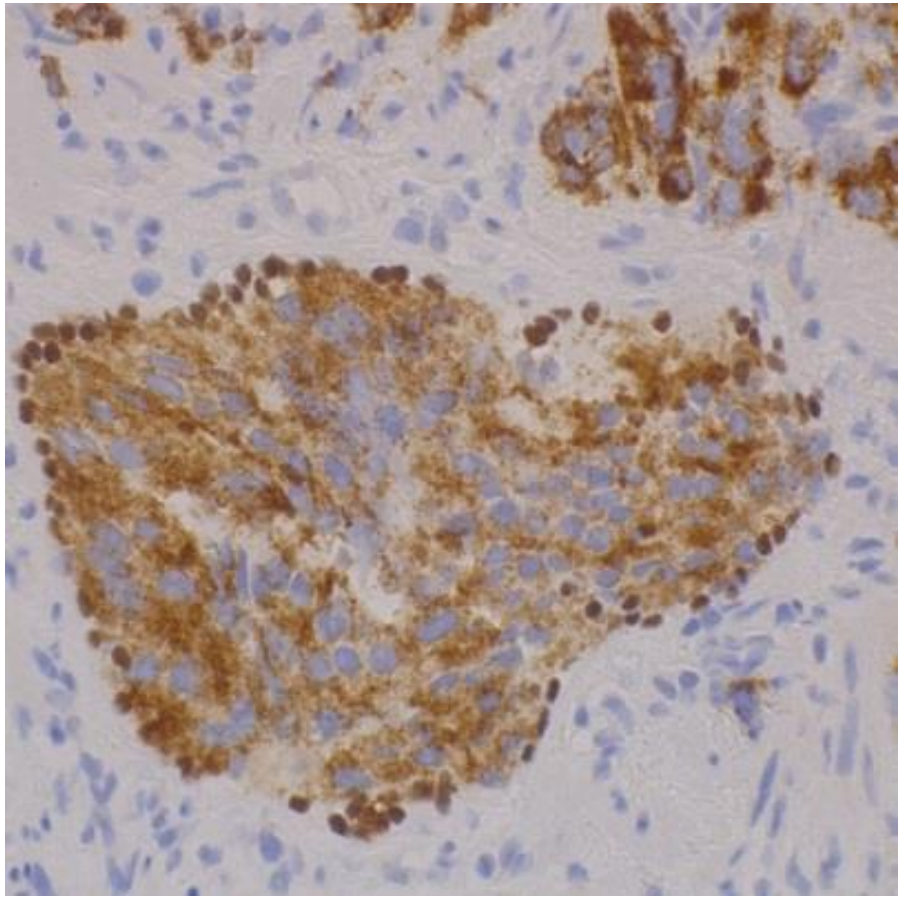
Bonkhoff 2012, The Prostate

WHO 2022

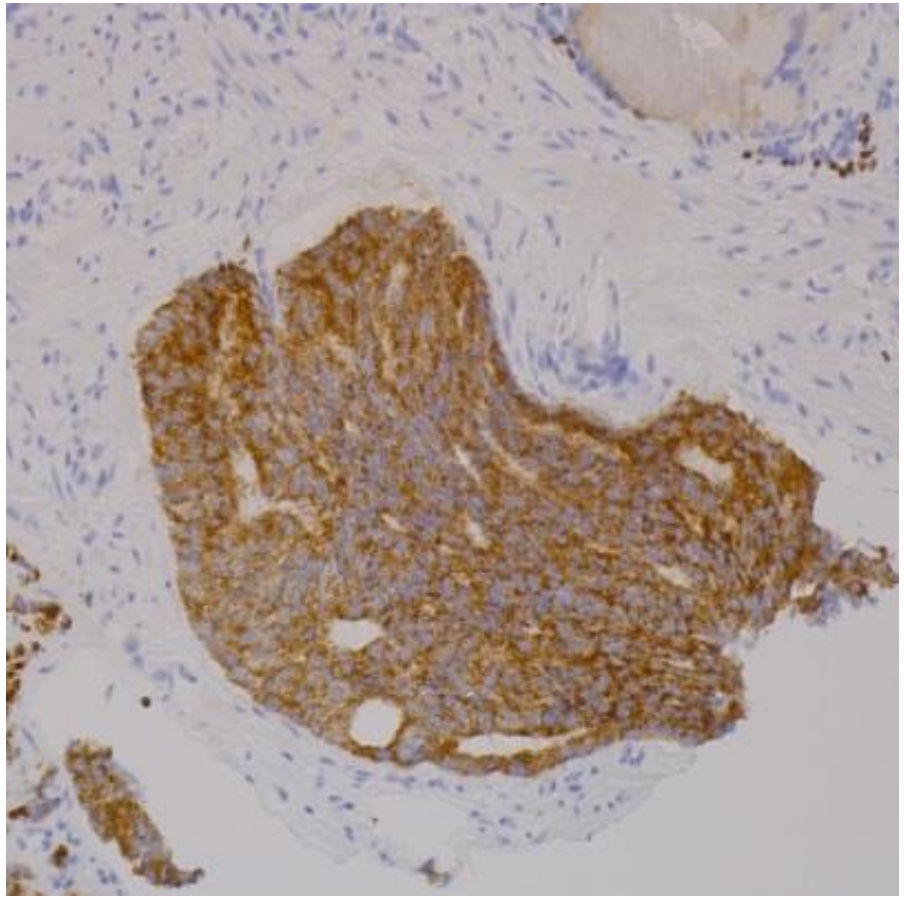
- IDC-P: better understanding
  - 2 forms
    - De novo
    - In situ
    - Most are late events →colonisation of preexisting ducts and acini of prostate
- Grading of IDC-P?
  - No grading of pure lesions
  - If with invasive PCa → controversial (ISUP-GUPS)

IDC-P versus GG 4

ICD-P

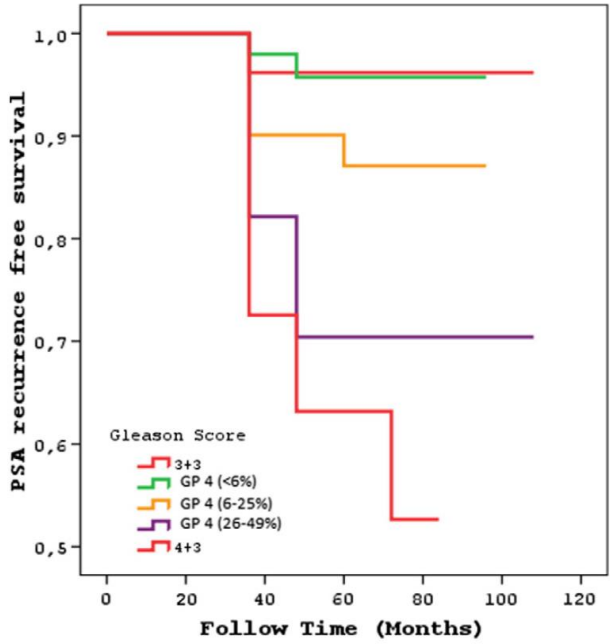


GG4 PCa



Subgroups of favourable GS 7 ?

- Distinguish **very low** and **low** risk disease on biopsy
- Extent on samples ?→ MRI
- % GG 4 must be reported
  - If < 5-10% GG4 + GG3 → risk same as GS6
  - Helpful for decision making → AS
  - ! GG 4 can range from <5%- 49% (difference to 7 (4+3)) !
- Cribriform PCa GG 4 and ICD-P
  - Adverse clinical outcome and molecular features like in advanced disease
  - No AS!!



BRCA1/2

Germline or somatic mutations

- BRCA1/2 are key genes in homologus reparation
- DDR genes→ key role in PCa development
- BRCA2> ATM >MSH2> BRCA1>HOXB13> RAD51
- BRCA/RAD51→ PARPi sensitive

- More aggressive clinical features (BRCA2) and worse outcomes
- mCRPCa 46% Mutations in DNA repair factors (localised PCa 27%)
- mPCa 8% germline and 23% somatic DDR alterations

- ~ 23% of mPCa
- Testing if mPCa (germline and tumor genetic)?

Grasso, 2012 Nature
Castro J Clin Res 2019

Guidelines and testing

- **EAU guidelines**
- Genetic sequencing of the primary tumor, ctDNA, or fresh tissue biospsies of mets consider early in particular as soon as the patient becomes CR
- **NCCN guidelines**
- Germline testing with or without pretest genetic counseling, for patients with PCa and any of the following:
- A positive family history of cancer (eg, prostate, breast) High-risk, very-high-risk, regional or metastatic PCa regardless of family history
- Intermediate and low risk if intraducatal and /or suspicious family history
- **ESMO guidelines**
- **Somatic** testing for homologous recombination repair defects and mismatch repair defects (or microsatellite instability) in patients with mCRPC.
- **Germline** testing in all men with mPCa
- Localised PCa tissue-based molecular assays may be used in conjunction with clinicopathological factors knowledge of *BRCA*-status may have a role in active surveillance discussions.

Testing evidences and uncertainities

- Known mutations in a cancer- susceptibility gene within the family
- Familiy history suggestive of
- Lynch syndrome, hereditary breast, ovarian, PCa
- Deficiency of DNA MMR
- mPCa
- High-risk PCa
- Localised PCa (Grade group 4/5, PSA ≥ 20ng/ml, WHO group ≥ 3)
- Young age at PCa detection

- Test primary? Lynode? Distant M+?
- FFPE? Fresh tissue?
- Liquid biopsy?

Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019

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Take home

- Pathology refinement→ allows preciser reports
- Be careful when reading report (subtypes, IDC-P, cribriform…)
- Testing will NOT replace pathology, but complementary